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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AXSOME THERAPEUTICS, INC. and ANTECIP BIOVENTURES II LLC, **Plaintiffs,** **v.** **TEVA PHARMACEUTICALS, INC.,** **Defendant.**	**Civil Action No. _____** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Axsome Therapeutics, Inc. ("Axsome") and Antecip Bioventures II LLC ("Antecip" and, collectively with Axsome, "Plaintiffs"), by their undersigned attorneys, for their Complaint against defendant Teva Pharmaceuticals, Inc. ("Teva" or "Defendant"), allege as follows:

Nature of the Action

1. This is an action for patent infringement under the patent laws of the United States, 35 U.S.C. §100, *et seq.*, arising from the Defendant's filing of its Abbreviated New Drug Application ("ANDA") No. 218147 ("Teva's ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market a generic version of

Plaintiffs' dextromethorphan hydrobromide and bupropion hydrochloride extended-release tablets prior to the expiration of United States Patent Nos. 11,839,612 ("the '612 patent"), 11,844,797 ("the '797 patent"), 11,883,373 ("the '373 patent"), 11,896,563 ("the '563 patent"), 11,925,636 ("the '636 patent"), and 11,969,421 ("the '421 patent") (collectively, "the patents-in-suit"), all owned by Antecip and exclusively licensed to Axsome.

The Parties

2. Axsome is a biopharmaceutical company focused on discovering, developing, and commercializing novel therapeutics for central nervous system ("CNS") conditions that have limited treatment options.

3. Axsome is a corporation existing under the laws of Delaware, having a principal place of business at One World Trade Center, 22nd Floor, New York, NY 10007.

4. Antecip is a limited liability corporation existing under the laws of Delaware, having a principal place of business at 630 Fifth Avenue, Suite 200, New York, NY 10111.

5. On information and belief, Teva is a corporation organized and existing under the laws of Delaware, having a principal place of business at 400 Interpace Parkway, Suite A1, Parsippany, New Jersey 07054.

The Patents-in-Suit

6. On December 12, 2023, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '612 patent, entitled, "Compounds and Combinations Thereof For Treating Neurological and Psychiatric Conditions." The face of the '612 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '612 patent; the assignment is recorded with the USPTO at Reel: 063524, Frame: 0142. Axsome is the exclusive licensee of the '612 patent. A copy of the '612 patent is attached hereto as Exhibit A.

7. On December 19, 2023, the USPTO duly and lawfully issued the '797 patent, entitled, "Combination of Dextromethorphan and Bupropion for Treating Depression." The face of the '797 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '797 patent; the assignment is recorded with the USPTO at Reel: 063524, Frame: 0142. Axsome is the exclusive licensee of the '797 patent. A copy of the '797 patent is attached hereto as Exhibit B.

8. On January 30, 2024, the USPTO duly and lawfully issued the '373 patent, entitled, "Treatment of Depression in Certain Patient Populations." The face of the '373 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '373 patent; the assignment is recorded with the USPTO at Reel: 064043, Frame: 0032; Reel: 064894, Frame: 0543. Axsome is the exclusive licensee of the '373 patent. A copy of the '373 patent is attached hereto as Exhibit C.

9. On February 13, 2024, the USPTO duly and lawfully issued the '563 patent, entitled, "Bupropion and Dextromethorphan for Reduction of Suicide Risk in Depression Patients." The face of the '563 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '563 patent; the assignment is recorded with the USPTO at Reel: 064043, Frame: 0505. Axsome is the exclusive licensee of the '563 patent. A copy of the '563 patent is attached hereto as Exhibit D.

10. On March 12, 2024, the USPTO duly and lawfully issued the '636 patent, entitled, "Bupropion Dosage Forms with Reduced Food and Alcohol Dosing Effects." The face of the '636 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '636 patent; the assignment is recorded with the USPTO at Reel: 064894, Frame: 0543.

Axsome is the exclusive licensee of the '636 patent. A copy of the '636 patent is attached hereto as Exhibit E.

11. On April 30, 2024, the USPTO duly and lawfully issued the '421 patent, entitled, "Bupropion as a Modulator of Drug Activity." The face of the '421 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '421 patent; the assignment is recorded with the USPTO at Reel: 060888, Frame: 0241. Axsome is the exclusive licensee of the '421 patent. A copy of the '421 patent is attached hereto as Exhibit F.

The Auvelity® Drug Product

12. Axsome holds an approved New Drug Application ("NDA") under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for dextromethorphan hydrobromide and bupropion hydrochloride extended-release tablets ("NDA No. 215430"), which is sold under the trade name Auvelity®. Auvelity® is a combination of dextromethorphan, an uncompetitive *N*-methyl *D*-aspartate ("NMDA") receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, approved in adult patients for the treatment of major depressive disorder ("MDD"). The claims of the patents-in-suit cover, *inter alia*, methods of using dextromethorphan and bupropion to treat MDD.

13. Pursuant to 21 U.S.C. § 355(b)(1) and attendant FDA regulations, the patents-in-suit are listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to Auvelity®.

Jurisdiction and Venue

14. This Court has jurisdiction over the subject matter of Counts I through VI against Teva pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

15. As set forth in Paragraphs 16-20 below, the Court has personal jurisdiction over Teva by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

16. On information and belief, Teva purposefully has conducted and continues to conduct business in this Judicial District.

17. On information and belief, Teva is in the business of, among other things, manufacturing, marketing, importing, offering for sale, and selling pharmaceutical products, including generic drug products, throughout the United States, including in this Judicial District.

18. On information and belief, this Judicial District will be a destination for the generic version of Plaintiffs' dextromethorphan hydrobromide and bupropion hydrochloride extended-release tablets for which Teva seeks FDA approval to manufacture, market, import, offer for sale, and/or sell pursuant to ANDA No. 218147 ("Teva's Proposed Product").

19. On information and belief, Teva maintains a physical place of business in this Judicial District, in at least Parsippany, New Jersey. Teva's website states that its "US Headquarters" is located in Parsippany, New Jersey. *See* https://www.tevausa.com/contact-us/ (last visited, May 28, 2024). Teva has admitted that it has a "a principal place of business" in Parsippany, New Jersey in related action *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 23-1695 (MEF)(LDW) (D.N.J) (consolidated).

20. On information and belief, Teva is registered with the State of New Jersey's Division of Revenue and Enterprise Services as a business operating in New Jersey under Business ID No. 0450614134.

21. For at least the foregoing reasons set forth above in Paragraphs 16-20 above, venue is proper in this Judicial District with respect to Teva pursuant to 28 U.S.C. § 1400(b).

Acts Giving Rise To Counts I-VI

22. Pursuant to Section 505 of the FFDCA, Teva filed ANDA No. 218147 seeking approval to engage in the commercial manufacture, use, sale, offer for sale, or importation of Teva's Proposed Product, before the patents-in-suit expire.

23. No earlier than February 9, 2023, Teva sent written notice of its first Paragraph IV Certification ("Teva's First Notice Letter") to Axsome. According to Teva's First Notice Letter, Teva filed an ANDA pursuant to Section 505 of the FFDCA seeking approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product before expiration of United States Patent Nos. 10,780,064 (the "'064 patent"), 10,925,842 (the "'842 patent"), 10,940,124 (the "'124 patent"), and 10,966,942 (the "'942 patent").[1] Teva's First Notice Letter alleged that the claims of '064, '842, '124, and '942 patents are invalid, unenforceable and/or will not be infringed by the activities described in Teva's ANDA.

24. No earlier than November 2, 2023, Teva sent written notice of its second Paragraph IV Certification ("Teva's Second Notice Letter") to Axsome. According to Teva's Second Notice Letter, Teva seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product before expiration of the United States Patent Nos. 11,717,518 (the "'518 patent"), 11,730,706 (the

[1] The '064, '842, '124, and '942 patents are subject to an existing lawsuit, *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 23-1695 (MEF)(LDW) (D.N.J.) (consolidated).

"'706 patent"), and 11,752,144 (the "'144 patent").[2] Teva's Second Notice Letter alleged that the claims of the '518, '706, and '144 patents are invalid, unenforceable and/or will not be infringed by the activities described in Teva's ANDA.

25. No earlier than April 10, 2024, Teva sent written notice of its third Paragraph IV Certification ("Teva's Third Notice Letter") to Axsome. According to Teva's Third Notice Letter, Teva seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product before expiration of the '612 and '373 patents. Teva's Third Notice Letter alleged that the claims of the '612 and '373 patents are invalid, unenforceable and/or will not be infringed by the activities described in Teva's ANDA.

26. No earlier than May 1, 2024, Teva sent written notice of its fourth Paragraph IV Certification ("Teva's Fourth Notice Letter") to Axsome. According to Teva's Fourth Notice Letter, Teva seeks approval to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product before expiration of the '797, '563, and '636 patents. Teva's Fourth Notice Letter alleged that the claims of the '797, '563, and '636 patents are invalid, unenforceable and/or will not be infringed by the activities described in Teva's ANDA.

27. On information and belief, in connection with the filing of its ANDA as described above, Teva provided written certifications to the FDA, as called for by Section 505 of the FFDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Teva's Paragraph IV Certifications"), alleging that the claims of the '064, '842, '124, '942, '518, '706, '144, '612, '797, '373, '563,

[2] The '518, '706, and '144 patents are subject to an existing lawsuit, *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 23-1695 (MEF)(LDW) (D.N.J.) (consolidated).

'636, and '421 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Teva's ANDA.

28. On information and belief, following FDA approval of Teva's ANDA, unless enjoined by the Court, Teva will make, use, offer to sell, or sell Teva's Proposed Product throughout the United States, or import such a generic product into the United States.

Count I: Infringement of the '612 Patent by Teva

29. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

30. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '612 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

31. A justiciable controversy exists between the parties hereto as to the infringement of the '612 patent.

32. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '612 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

33. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '612 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, upon FDA approval of

Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '612 patent and knowledge that its acts are encouraging infringement.

34. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '612 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva knew and knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '612 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

35. Failure to enjoin Teva's infringement of the '612 patent will substantially and irreparably damage Plaintiffs.

36. Plaintiffs do not have an adequate remedy at law.

37. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

Count II: Infringement of the '797 Patent by Teva

38. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

39. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '797 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

40. A justiciable controversy exists between the parties hereto as to the infringement of the '797 patent.

41. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '797 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

42. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '797 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '797 patent and knowledge that its acts are encouraging infringement.

43. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '797 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva knew and knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '797 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

44. Failure to enjoin Teva's infringement of the '797 patent will substantially and irreparably damage Plaintiffs.

45. Plaintiffs do not have an adequate remedy at law.

46. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

Count III: Infringement of the '373 Patent by Teva

47. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

48. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '373 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claims 1 and 10.

49. A justiciable controversy exists between the parties hereto as to the infringement of the '373 patent.

50. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '373 patent under 35 U.S.C. § 271(a), including at least claims 1 and 10, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

51. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '373 patent under 35 U.S.C. § 271(b), including at least claims 1 and 10, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '373 patent and knowledge that its acts are encouraging infringement.

52. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '373 patent under 35 U.S.C. § 271(c), including at least claims 1 and 10, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva knew and

knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '373 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

53. Failure to enjoin Teva's infringement of the '373 patent will substantially and irreparably damage Plaintiffs.

54. Plaintiffs do not have an adequate remedy at law.

55. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

Count IV: Infringement of the '563 Patent by Teva

56. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

57. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '563 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claim 1.

58. A justiciable controversy exists between the parties hereto as to the infringement of the '563 patent.

59. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '563 patent under 35 U.S.C. § 271(a), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

60. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '563 patent under 35 U.S.C. § 271(b), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's

Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '563 patent and knowledge that its acts are encouraging infringement.

61. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '563 patent under 35 U.S.C. § 271(c), including at least claim 1, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva knew and knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '563 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

62. Failure to enjoin Teva's infringement of the '563 patent will substantially and irreparably damage Plaintiffs.

63. Plaintiffs do not have an adequate remedy at law.

64. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

Count V: Infringement of the '636 Patent by Teva

65. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

66. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '636 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claims 1, 6, and 11.

67. A justiciable controversy exists between the parties hereto as to the infringement of the '636 patent.

68. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '636 patent under 35 U.S.C. § 271(a), including at least claims 1, 6, and 11, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

69. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '636 patent under 35 U.S.C. § 271(b), including at least claims 1, 6, and 11, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '636 patent and knowledge that its acts are encouraging infringement.

70. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '636 patent under 35 U.S.C. § 271(c), including at least claims 1, 6, and 11, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva knew and knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '636 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

71. Failure to enjoin Teva's infringement of the '636 patent will substantially and irreparably damage Plaintiffs.

72. Plaintiffs do not have an adequate remedy at law.

73. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

Count VI: Infringement of the '421 Patent by Teva

74. Plaintiffs repeat and reallege the allegations of the preceding paragraphs as if fully set forth herein.

75. Teva's submission of its ANDA to engage in the commercial manufacture, use, offer for sale, sale, or importation into the United States of Teva's Proposed Product, prior to the expiration of the '421 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including at least claims 1, 28, and 29.

76. A justiciable controversy exists between the parties hereto as to the infringement of the '421 patent.

77. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '421 patent under 35 U.S.C. § 271(a), including at least claims 1, 28, and 29, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

78. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '421 patent under 35 U.S.C. § 271(b), including at least claims 1, 28, and 29, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, upon FDA approval of Teva's ANDA, Teva will intentionally encourage acts of direct infringement with knowledge of the '421 patent and knowledge that its acts are encouraging infringement.

79. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '421 patent under 35 U.S.C. § 271(c), including at least claims 1, 28, and 29, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States. On information and belief, Teva

knew and knows that Teva's Proposed Product is designed for a use that infringes one or more claims of the '421 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

80. Failure to enjoin Teva's infringement of the '421 patent will substantially and irreparably damage Plaintiffs.

81. Plaintiffs do not have an adequate remedy at law.

82. This case is an exceptional one, and Plaintiffs are entitled to an award of their reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request the following relief:

(A) A Judgment that Teva infringed one or more claims of each of the patents-in-suit by submitting ANDA No. 218147;

(B) A Judgment that Teva has infringed, and that Teva's making, using, offering to sell, selling, or importing Teva's Proposed Product will infringe one or more claims of each of the patents-in-suit;

(C) An Order, pursuant to 35 U.S.C. § 271(e)(4)(A), that the effective date of FDA approval of ANDA No. 218147 be a date no earlier than the later of the expiration of each of the patents-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(D) Preliminary and permanent injunctions enjoining Teva and its officers, agents, attorneys, and employees, and those acting in privity or concert with them, from making, using, offering to sell, selling, or importing Teva's Proposed Product until after the expiration of each of the patents-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(E) A permanent injunction, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Teva, its officers, agents, attorneys, and employees, and those acting in privity or

concert with them, from practicing any method claimed in the patents-in-suit, or from actively inducing or contributing to the infringement of any claim of the patents-in-suit, until after the expiration of each such patent-in-suit, or any later expiration of exclusivity to which Plaintiffs are or become entitled;

(F) A Judgment that the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Teva's Proposed Product will directly infringe, induce and/or contribute to infringement of one or more claims of each of the patents-in-suit;

(G) To the extent that Teva has committed any acts with respect to the methods claimed in the patents-in-suit, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), a Judgment awarding Plaintiffs damages for such acts;

(H) If Teva engages in the commercial manufacture, use, importation into the United States, offer for sale, and/or sale of Teva's Proposed Product prior to the expiration of the patents-in-suit, a Judgment awarding damages to Plaintiffs resulting from such infringement, together with interest;

(I) A Judgment declaring that each of the patents-in-suit remains valid and enforceable;

(J) A Judgment that this is an exceptional case pursuant to 35 U.S.C. § 285 and awarding Plaintiffs their attorneys' fees, costs, and expenses incurred in this action; and

(K) Such further and other relief as this Court may deem just and proper.

Dated: May 28, 2024

By: s/ Charles M. Lizza

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CERTIFICATION PURSUANT TO L. CIV. R. 11.2 & 40.1

Pursuant to Local Civil Rules 11.2 and 40.1, I hereby certify that the matter captioned *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 23-1695 (MEF)(LDW) (D.N.J.) (consolidated) is related to the matter in controversy because the matter in controversy involves the same plaintiffs and the same defendant, and because Defendant is seeking FDA approval to market a generic version of the same pharmaceutical product.

Dated: May 28, 2024

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EXHIBIT A

US011839612B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,839,612 B1**
(45) **Date of Patent: Dec. 12, 2023**

(54) **COMPOUNDS AND COMBINATIONS THEREOF FOR TREATING NEUROLOGICAL AND PSYCHIATRIC CONDITIONS**

(71) Applicant: **ANTECIP BIOVENTURES II LLC**, New York, NY (US)

(72) Inventor: **Herriot Tabuteau**, New York, NY (US)

(73) Assignee: **ANTECIP BIOVENTURES II LLC**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **18/177,585**

(22) Filed: **Mar. 2, 2023**

Related U.S. Application Data

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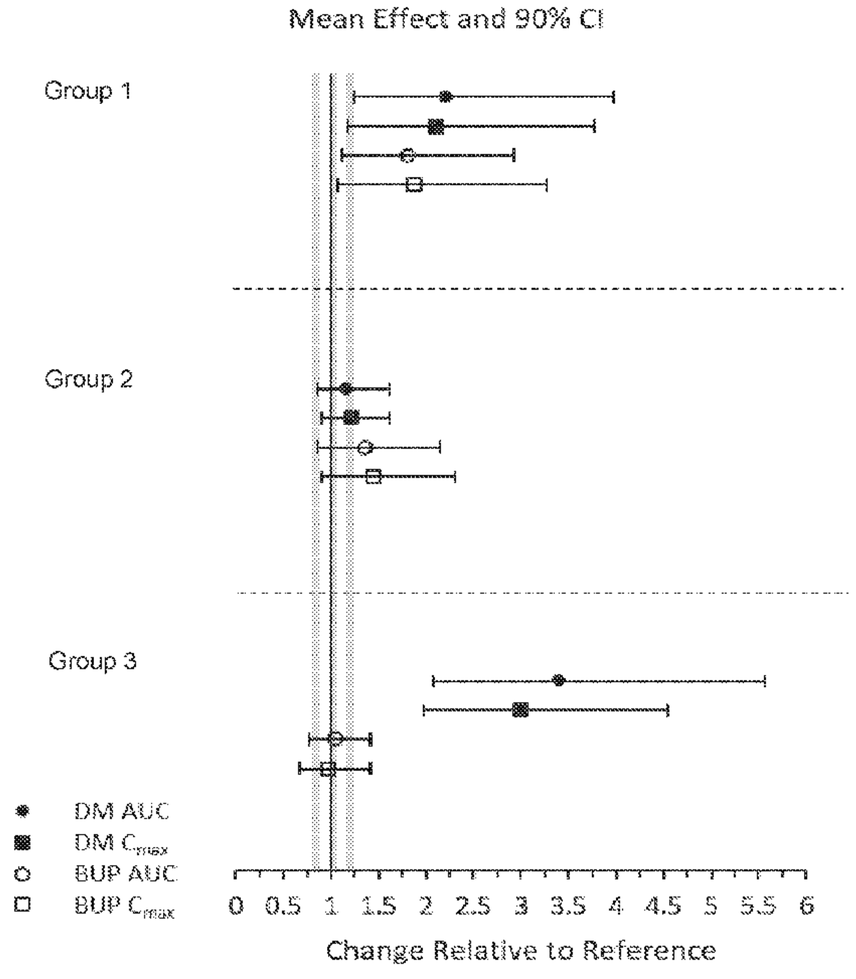
(57) **ABSTRACT**

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of bupropion; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations, such as patients having moderate renal impairment, patients receiving a concomitant strong CYP2D6 inhibitor, patients who are known CYP2D6 poor metabolizers, those in need of an NMDA antagonist that does not cause dissociation, and those at risk of QT prolongation.

18 Claims, 1 Drawing Sheet



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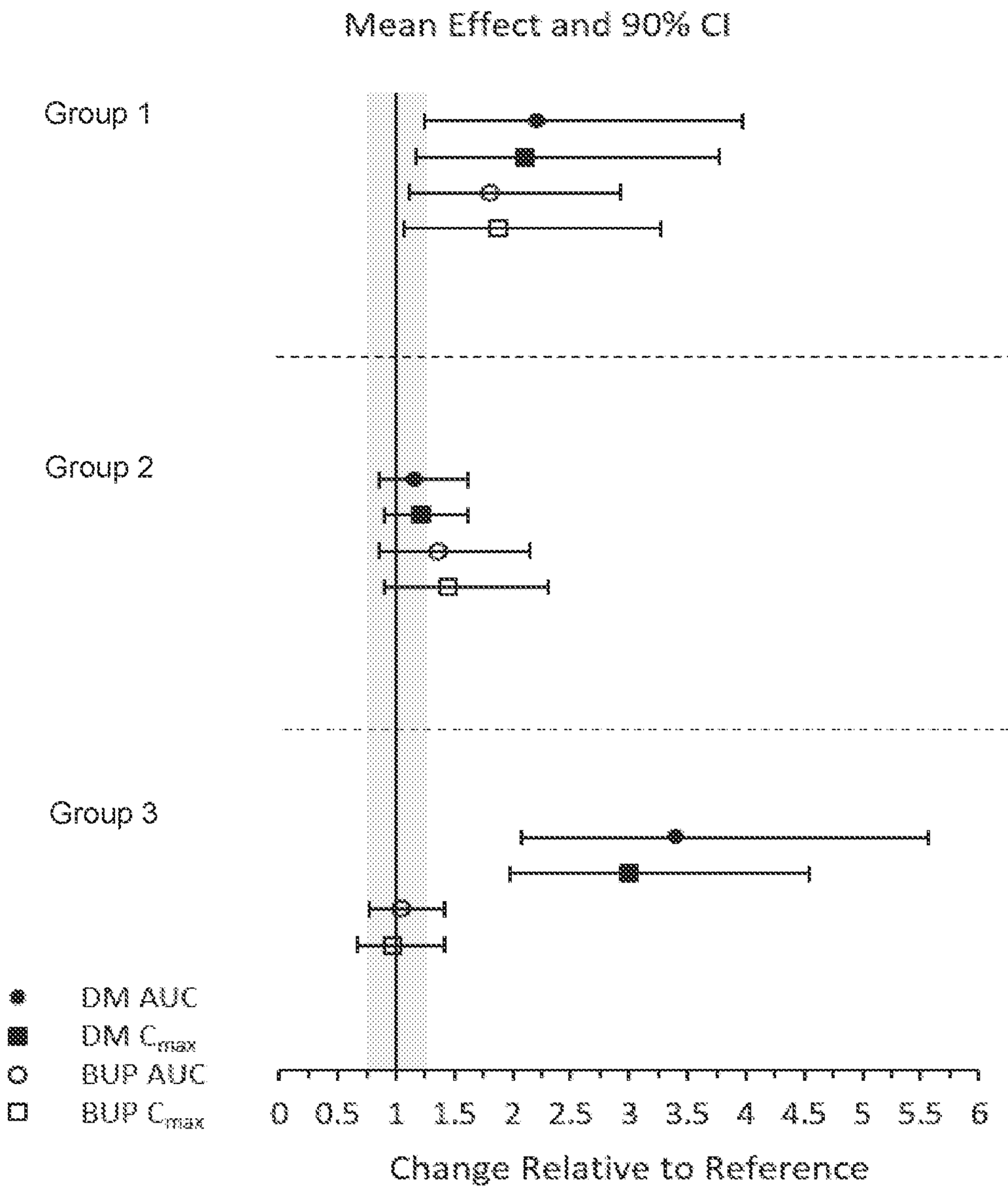
Mean Effect and 90% CI
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COMPOUNDS AND COMBINATIONS THEREOF FOR TREATING NEUROLOGICAL AND PSYCHIATRIC CONDITIONS

SUMMARY

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations.

Some embodiments include a method of treating major depressive disorder in a patient having moderate renal impairment, comprising administering a daily dose of: (i) about 105 mg of bupropion hydrochloride and (ii) about 45 mg of dextromethorphan hydrobromide to a human patient who has moderate renal impairment and is experiencing major depressive disorder.

Some embodiments include a method of treating a patient having a nervous system condition by administering a combination of dextromethorphan and bupropion, the method comprising:

orally administering to the patient, once a day, a dosage form comprising: 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan in the dosage form is about the ratio of the molar amount bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

wherein the patient is selected for: 1) having the nervous system condition and 2) having moderate renal impairment, wherein the patient is determined to have moderate renal impairment by an assay on a biological sample from the patient; and

wherein a risk of somnolence or dizziness for the patient who has moderate renal impairment is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

determining whether the patient has moderate renal impairment by:

obtaining or having obtained a biological sample from the patient; and

performing or having performed an assay on the biological sample to determine if the patient has moderate renal impairment; and

if the patient has moderate renal impairment, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

if the patient does not have renal impairment, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan;

wherein a risk of somnolence or dizziness for a patient who has moderate renal impairment is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

Some embodiments include a method of treating a patient who is experiencing a nervous system condition, the method comprising the steps of:

a) determining whether the patient is at risk of an adverse event associated with overexposure to dextromethorphan by:

obtaining or having obtained a biological sample from the patient; and performing or having performed an assay on the biological sample to determine if the patient has moderate renal impairment, wherein a result that the patient has moderate renal impairment indicates that the patient is at risk of an adverse event associated with overexposure to dextromethorphan; and

b) if the patient is at risk of an adverse event associated with overexposure to dextromethorphan, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide; and

c) if the patient is not at risk of an adverse event associated with overexposure to dextromethorphan, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.

Some embodiments include a method of treating a nervous system condition with a combination of dextromethorphan and bupropion, comprising:

orally administering to a patient, once a day, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount

of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of bupropion to dextromethorphan in the dosage form is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide; and

wherein the patient is selected for: 1) having the nervous system condition and 2) having moderate renal impairment, wherein the patient is determined to have moderate renal impairment by an assay on a biological sample from the patient; and

wherein the patient has a reduced risk of an adverse event as compared with the risk of the adverse event that the patient would have if the dosage form were administered twice daily to the patient.

Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

determining whether the patient has moderate renal impairment by:

obtaining or having obtained a biological sample from the patient; and

performing or having performed an assay on the biological sample to determine if the patient has moderate renal impairment; and

if the patient has moderate renal impairment, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of bupropion to dextromethorphan in the dosage form is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide; and

if the patient does not have renal impairment, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.

Some embodiments include a method of treating a patient having a nervous system condition by administering a combination of dextromethorphan and bupropion, the method comprising:

orally administering to the patient, once a day, a dosage form comprising: 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan in the dosage form is about the ratio of the molar amount bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

wherein the patient is selected for: 1) having the nervous system condition and 2) having moderate renal impairment, wherein the patient is determined to have moderate renal impairment by an assay on a biological sample from the patient; and wherein a risk of somnolence and dizziness for the patient who has moderate renal impairment is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

determining whether the patient has moderate renal impairment by:

obtaining or having obtained a biological sample from the patient; and

performing or having performed an assay on the biological sample to determine if the patient has moderate renal impairment; and

if the patient has moderate renal impairment, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

if the patient does not have renal impairment, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan;

wherein a risk of somnolence and dizziness for a patient who has moderate renal impairment is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

Some embodiments include a method of treating major depressive disorder in a human patient who requires concomitant treatment with a strong CYP2D6 inhibitor, comprising administering, once daily to the human patient, a combination of about 105 mg of bupropion hydrochloride and about 45 mg of dextromethorphan hydrobromide, wherein the human patient is experiencing major depressive disorder and is receiving concomitant treatment with the strong CYP2D6 inhibitor. In some embodiments, the strong CYP2D6 inhibitor is paroxetine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** depicts the effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the

pharmacokinetics of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride.

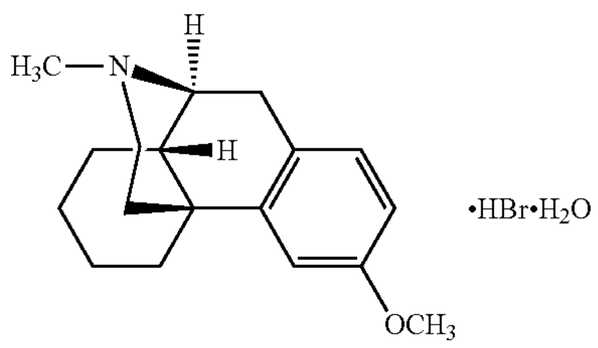
DETAILED DESCRIPTION

As mentioned above, this disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan. This combination is referred to for convenience herein as the "subject combination." In every instance where the subject combination is referred to herein, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is specifically contemplated.

Strong CYP2D6 inhibitors include, but are not limited to, compounds such as fluoxetine, propafenone, quinidine, and paroxetine.

Dextromethorphan hydrobromide is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist.

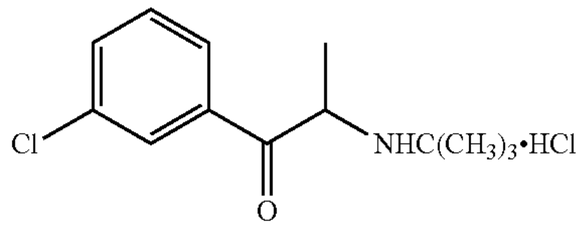
The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9a, 13a, 14a), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and a molecular weight of 370.33. The structural formula is:



Dextromethorphan hydrobromide powder is white or almost white, crystalline, and sparingly soluble in water.

Bupropion hydrochloride is an aminoketone and CYP450 2D6 inhibitor.

The chemical name of bupropion hydrochloride is: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Bupropion hydrochloride has the empirical formula $C_{13}H_{18}ClNO \cdot HCl$ and a molecular weight of 276.2. The structural formula is:



Bupropion hydrochloride powder is white and highly soluble in water.

The subject combination may be contained in an oral dosage form, including a tablet, such as an extended-release tablet. In some embodiments, the subject combination is contained in a dosage form for oral administration and is available as round bilayer tablets.

In some embodiments, each tablet containing the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation. In some embodiments, each tablet of the subject combination contains 105 mg of bupropion hydrochloride in an extended-release formulation. In some embodiments, each tablet of the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation and 105 mg of bupropion hydrochloride in an extended-release formulation.

In some embodiments, a tablet containing the subject combination contains L-cysteine hydrochloride monohydrate. In some embodiments, a tablet containing the subject combination contains carbomer homopolymer. In some embodiments, a tablet containing the subject combination contains microcrystalline cellulose. In some embodiments, a tablet containing the subject combination contains colloidal silicon dioxide. In some embodiments, a tablet containing the subject combination contains crospovidone. In some embodiments, a tablet containing the subject combination contains stearic acid. In some embodiments, a tablet containing the subject combination contains magnesium stearate.

In some embodiments, a tablet containing the subject combination contains the following inactive ingredients: L-cysteine hydrochloride monohydrate, carbomer homopolymer, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, stearic acid, and magnesium stearate.

In some embodiments, the starting dosage of the subject combination is 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride in one tablet that is administered once daily in the morning. In some embodiments, after 3 days, the dosage is increased to one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) twice daily, e.g., given at least 8 hours apart. In some embodiments, no more than two doses containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are administered in the same day.

The subject combination may be administered orally with or without food. In some embodiments, the tablets are swallowed whole, and not crushed, divided, or chewed.

Patients having renal impairment may require special dosing. In some embodiments, the recommended dosage of the subject combination for patients with moderate renal impairment (estimated glomerular filtration rate (eGFR) or glomerular filtration rate (GFR) of 30 to 59 mL/minute/1.73 m2) is a daily dose of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride, or a molar equivalent amount of another form of dextromethorphan and/or bupropion, such as administration of one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning, or twice daily oral administration of a combination of 52.5 mg of bupropion hydrochloride and about 22.5 mg of dextromethorphan hydrobromide. In some embodiments, the patients are monitored for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Moderate renal impairment may be determined by an assay, such as an assay that determines creatine levels, on a biological sample from the patient, such as a blood sample. Creatine levels from a blood sample can be used to estimate GFR.

Patients who are concomitantly using the subject combination with strong CYP2D6 inhibitors may require special

dosing. Concomitant use of the subject combination with a strong CYP2D6 inhibitor increases plasma concentrations of dextromethorphan. In some embodiments, the recommended dosage of the subject combination when coadministered with a strong CYP2D6 inhibitor is one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning. In some embodiments, the patients are monitored for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Patients who are known CYP2D6 poor metabolizers (PMs) may require special dosing. In some embodiments, the recommended dosage for patients known to be poor CYP2D6 metabolizers is one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning.

Special precautions may be required when switching a patient to or from a monoamine oxidase inhibitor (MAOI) antidepressant to the subject combination. In some embodiments, at least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with the subject combination. Conversely, in some embodiments, at least 14 days must be allowed after stopping the subject combination before starting an MAOI antidepressant.

In the subject combination, bupropion inhibits the metabolism of dextromethorphan via CYP2D6. Dextromethorphan, when co-administered with bupropion, displays nonlinear pharmacokinetics at steady state, with greater than dose-proportional changes in AUC and C_{max} for varying doses of dextromethorphan (30 to 60 mg) and less than dose-proportional changes for varying doses of bupropion (75 to 150 mg).

Steady state plasma concentrations of dextromethorphan and bupropion when given as the subject combination are achieved within 8 days. The accumulation ratios for dextromethorphan at steady state are about 20 and about 32, respectively based on C_{max} and AUC_{0_12}. The accumulation ratios for bupropion at steady state are 1.1 and 1.5, respectively based on C_{max} and $AUC_{0\text{-}12}$.

After administration of the subject combination, the median T_{max} of dextromethorphan is about 3 hours and the median T_{max} of bupropion is about 2 hours. The C_{max} of hydroxybupropion metabolite occurs approximately 3 hours post-dose and is approximately 14 times the peak level of bupropion. The $AUC_{0\text{-}2}$ hydroxybupropion is about 19 times that of bupropion. The C_{max} of the erythrohydroxybupropion and threohydroxybupropion metabolites occurs approximately 4 hours post-dose and is approximately equal to and about 5 times that of bupropion, respectively. The $AUC_{0\text{-}12}$ values of erythrohydroxybupropion and threohydroxybupropion are about 1.2 and about 7 times that of bupropion, respectively.

The subject combination can be taken with or without food. Dextromethorphan C_{max} and $AUC_{0\text{-}2}$ were unchanged and decreased by 14%, respectively, and bupropion C_{max} and $AUC_{0\text{-}2}$ were increased by 3% and 6%, respectively, when the subject combination was administered with food.

The plasma protein binding of dextromethorphan is approximately 60-70% and bupropion is 84%. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas the extent of protein binding of the threohydroxybupropion metabolite is about half that seen with bupropion.

Following 8 days of administration of the subject combination in extensive metabolizers, the mean elimination half-life of dextromethorphan was increased approximately 3-fold to about 22 hours, as compared to dextromethorphan given without bupropion.

The mean elimination half-life of dextromethorphan and bupropion was 22 hours and 15 hours, respectively. The apparent elimination half-life of hydroxybupropion, erythrohydroxybuporpion and threohydroxybupropion metabolites were approximately 35, 44 and 33 hours, respectively.

Esketamine is a non-competitive NMDA receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults. Treatment of treatment-resistant depression carries a risk of dissociation. The label for esketamine states that because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paranesthesia; paranesthesia oral; pharyngeal paranesthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment.

The subject combination is a combination of dextromethorphan, an uncompetitive N-methyl D-aspartate (NDMA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for the treatment of major depressive disorder (MDD) in adults. Unlike esketamine, the subject combination can be administered as a without dissociation or dissociative events. In some embodiments, the patient is not monitored for dissociation after the subject combination is administered.

Unlike the combination of quinidine and dextromethorphan, at a dose of a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide given twice a day, the subject combination does not prolong the QT interval to any clinically relevant extent. Thus, for a human patient who is experiencing major depressive disorder and is at risk of QT prolongation and torsades de pointer, electrocardiographic evaluation of QT interval is not typically conducted on the human patient.

The subject combination may be used for adjunctive treatment of major depressive disorder or depression.

In addition to major depressive disorder, the subject combination may be used to treat other diseases in conditions in the patient populations or circumstances described herein. For example, the subject combination may be used to treat pain or a neurological disorder. Examples of neurological disorders that may be treated with the subject combination include, but are not limited to: affective disorders, psychiatric disorders, cerebral function disorders, movement disorders, dementias, motor neuron diseases, neurodegenerative diseases, seizure disorders, and headaches.

Affective disorders that may be treated by the subject combination include, but are not limited to, depression, major depression, treatment resistant depression, treatment resistant bipolar depression, bipolar disorders including cyclothymia, seasonal affective disorder, mood disorders, chronic depression (dysthymia), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, atypical depression, mania,

anxiety disorders, attention deficit disorder (ADD), attention deficit disorder with hyperactivity (ADDH), and attention deficit/hyperactivity disorder (AD/HD), bipolar and manic conditions, obsessive-compulsive disorder, bulimia, obesity or weight-gain, narcolepsy, chronic fatigue syndrome, pre-menstrual syndrome, substance addiction or abuse, nicotine addiction, psycho-sexual dysfunction, pseudobulbar affect, and emotional lability.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts, or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restlessness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Psychiatric disorders that may be treated by the subject combination, include, but are not limited to, anxiety disorders, including but not limited to, phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD); mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, somatoform disorders, personality disorders, psychosis, schizophrenia, delusional disorder, schizoaffective disorder, schizotypy, aggression, aggression in Alzheimer's disease, agitation, and agitation in Alzheimer's disease. Alzheimer's disease may also be referred to as dementia of the Alzheimer's type. Other neurobehavioral symptoms of Alzheimer's disease that may be treated include disinhibition and apathy.

Agitation in Alzheimer's disease occurs as the disease progresses. Agitation may present itself as inappropriate verbal, emotional, and/or physical behaviors. Inappropriate behaviors may include, but are not limited to, incoherent babbling, inappropriate emotional response, demands for attention, threats, irritability, frustration, screaming, repetitive questions, mood swings, cursing, abusive language, physical outbursts, emotional distress, restlessness, shredding, sleeping disturbances, delusions, hallucinations, pacing, wandering, searching, rummaging, repetitive body motions, hoarding, shadowing, hitting, scratching, biting, combativeness, hyperactivity, and/or kicking.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Managing agitation is a priority in AD. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality. There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Neurobehavioral symptoms have been known to appear during dementia and may be treated by the combination. Caregivers or families may feel more overwhelmed by patients' behavioral/psychological symptoms than by their cognitive impairment. Common forms of the syndrome are Alzheimer's disease, vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The symptoms that dementia patients have are similar to those of psychiatric disorders, but some are slightly different from each other. Neurobehavioral symptoms associated with dementia include depression, apathy, agitation, disinhibition, hallucinations, delusions, psychosis, impulsiveness, aggressiveness, compulsion, excessive sex drive, and personality disorders. Neurobehavioral symptoms such as disinhibition may also be found in other conditions such as traumatic brain injury.

Agitation in patients with Alzheimer's disease may be assessed using the Cohen Mansfield Agitation Inventory or CMAI. The CMAI assesses various behaviors including, Hitting (including self), Kicking, Grabbing onto people, Pushing, Throwing things, Biting, Scratching, Spitting, Hurting self or others, Tearing things or destroying property, Making physical sexual advances, Pacing, aimless wandering, Inappropriate dress or disrobing, Trying to get to a different place, Intentional falling, Eating/drinking inappropriate substances, Handling things inappropriately, Hiding things, Hoarding things, Performing repetitive mannerisms, General restlessness, Screaming, Making verbal sexual advances, Cursing or verbal aggression, Repetitive sentences or questions, Strange noises (weird laughter or crying), Complaining, Negativism, Constant unwarranted request for attention or help.

Schizophrenia may treated by the combination including positive symptoms and/or negative symptoms of schizophrenia, or residual symptoms of schizophrenia. Other conditions that may treated include intermittent explosive disorder.

Cerebral function disorders that may be treated by the subject combination include, but are not limited to, disorders involving intellectual deficits such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, voice spasms, Parkinson's disease, Lennox-Gastaut syndrome, autism, hyperkinetic syndrome, and schizophrenia. Cerebral function disorders also include disorders caused by cerebrovascular diseases including, but not limited to, stroke, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like where symptoms include disturbance of consciousness, senile dementia, coma, lowering of attention, and speech disorders.

Substance addiction abuse that may be treated by the subject combination includes, but is not limited to, drug dependence, addiction to cocaine, psychostimulants (e.g., crack, cocaine, speed, meth), nicotine, alcohol, opioids, anxiolytic and hypnotic drugs, cannabis (marijuana), amphetamines, hallucinogens, phencyclidine, volatile solvents, and volatile nitrites. Nicotine addiction includes nicotine addiction of all known forms, such as smoking cigarettes, cigars and/or pipes, e-cigarettes or vaping, and addiction to chewing tobacco.

Movement disorders that may be treated by the subject combination include, but are not limited to, akathisia, akinesia, associated movements, athetosis, ataxia, ballismus, hemiballismus, bradykinesia, cerebral palsy, chorea, Huntington's disease, Huntington's disease chorea, rheumatic chorea, Sydenham's chorea, dyskinesia, tardive dyskinesia, dystonia, blepharospasm, spasmodic torticollis, dopamine-responsive dystonia, Parkinson's disease, restless legs syndrome (RLS), tremor, essential tremor, and Tourette's syndrome, and Wilson's disease.

Dementias that may be treated by the subject combination include, but are not limited to, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, fronto-temporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, Wernicke-Korsakoff Syndrome, and Pick's disease.

Motor neuron diseases that may be treated by the subject combination include, but are not limited to, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, post-polio syndrome (PPS), spinal muscular atrophy (SMA), spinal motor atrophies, Tay-Sach's disease, Sandhoff disease, and hereditary spastic paraplegia.

Neurodegenerative diseases that may be treated the subject combination include, but are not limited to, Alzheimer's disease, prion-related diseases, cerebellar ataxia, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), bulbar muscular atrophy, Friedrich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis (MS), multiple system atrophy, Shy-Drager syndrome, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, Menkes disease, adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), muscular dystrophies, Charcot-Marie-Tooth disease (CMT), familial spastic paraparesis, neurofibromatosis, olivopontine cerebellar atrophy or degeneration, striatonigral degeneration, Guillain-Barré syndrome, and spastic paraplesia.

Seizure disorders that may be treated by the subject combination include, but are not limited to, epileptic seizures, nonepileptic seizures, epilepsy, febrile seizures; partial seizures including, but not limited to, simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua; generalized seizures including, but not limited to, generalized tonic-clonic seizures, absence seizures, atonic seizures, myoclonic seizures, juvenile myoclonic seizures, and infantile spasms; and status epilepticus.

Types of headaches that may be treated by the subject combination include, but are not limited to, migraine, tension, and cluster headaches.

Other neurological disorders that may be treated by the subject combination include, Rett Syndrome, autism, tinnitus, disturbances of consciousness disorders, sexual dysfunction, intractable coughing, narcolepsy, cataplexy; voice disorders due to uncontrolled laryngeal muscle spasms, including, but not limited to, abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; diabetic neuropathy, chemotherapy-induced neurotoxicity, such as methotrexate neurotoxicity; incontinence including, but not limited, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

In some embodiments, the subject combination may be used to treat pain, joint pain, pain associated with sickle cell disease, pseudobulbar affect, depression (including treatment resistant depression), disorders related to memory and cognition, schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Rhett's syndrome, seizures, cough (including chronic cough), etc.

In some embodiments, the subject combination may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

In some embodiments, the subject combination may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

In some embodiments, the subject combination is used to treat chronic musculoskeletal pain.

In some embodiments, the subject composition may be administered to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component. Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor, and sensory changes.

In some embodiments, the subject composition may be administered orally to relieve neuropathic pain.

Examples of neuropathic pain include pain due to diabetic peripheral neuropathy or diabetic peripheral neuropathic pain, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, central pain, pain due to multiple sclerosis, etc. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio- or chemotherapy associated neuropathy, etc.

In some embodiments, the subject composition may be administered to relieve fibromyalgia.

In some embodiments, the subject composition may be co-administered with one or more strong Inhibitors of CYP2D6. It has been found that the concomitant use of the subject combination with one or more strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan. It is thus recommended to monitor patients for adverse effects or adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

The dosage adjustment may be necessary when the subject composition is co-administered with one or more strong inhibitors of CYP2D6. Adjusting to a lower dose amount of the bupropion and/or the dextromethorphan in the subject combination or less frequent dosing of the subject combination may reduce adverse effects or adverse reactions, such as, but not limited to, somnolence, dizziness, or a combination thereof in a patient. For example, a recommended dosage of the subject combination when co-administered with one or more strong CYP2D6 inhibitors, is one tablet containing 45 mg or less of dextromethorphan hydrobromide and 105 mg or less of bupropion hydrochloride once daily, such as once daily in the morning.

Administration of the subject combination once a day to patients who are receiving a concomitant strong CYP2D6 may reduce the adverse effects, such as, but not limited to, somnolence, dizziness, or a combination thereof, as compared to administration of the subject combination twice a day for same number of days. In some embodiments,

reducing the dose amount or dose frequency of the subject combination may reduce somnolence. In some embodiments, reducing dose amount or dose frequency may reduce dizziness. As dizziness may link to falls, adjusting the dosage to lower amount or lower dose frequency of the subject combination may reduce the risk of falls for a patient taking the subject combination. For example, taking the subject combination once a day may reduce the risk of falls for a patient as compared to taking the subject combination twice a day for same number of days. This may be important, for example, to elderly patients or patients suffering from a dementia, such as Alzheimer's disease.

In some embodiments, the subject composition may be administered to a patient who has moderate renal impairment. As explained herein, it has been found that administering the subject composition to CYP2D6 poor metabolizers increases plasma concentrations of dextromethorphan as compared to patients who are not CYP2D6 poor metabolizers. It is thus recommended to monitor patients for adverse effects or adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Dosage adjustment may be necessary when the patient has moderate renal impairment. Adjusting to a lower dose amount of the bupropion and/or the dextromethorphan in the subject combination or less frequent dosing of the subject combination may reduce adverse effects or adverse reactions, or a risk of adverse effects or adverse reactions, such as, but not limited to, somnolence, dizziness, or a combination thereof in a patient. For example, a recommended dosage of the subject combination when administered to a patient who has moderate renal impairment, is one tablet containing 45 mg or less of dextromethorphan hydrobromide and 105 mg or less of bupropion hydrochloride once daily, such as once daily in the morning.

Administration of the subject combination once a day to patients who have moderate renal impairment may reduce the adverse effects, or the risk of adverse effects, such as, but not limited to, somnolence, dizziness, or a combination thereof, as compared to administration of the subject combination twice a day for same number of days. In some embodiments, reducing the dose amount or dose frequency of the subject combination may reduce somnolence. In some embodiments, reducing dose amount or dose frequency may reduce dizziness. As dizziness may link to falls, adjusting the dosage to lower amount or lower dose frequency of the subject combination may reduce the risk of falls for a patient taking the subject combination. For example, taking the subject combination once a day may reduce the risk of falls for a patient as compared to taking the subject combination twice a day for same number of days. This may be important, for example, to elderly patients or patients suffering from a dementia, such as Alzheimer's disease.

The term "treating" or "treatment" includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

A subject combination may be used to treat any disease or condition identified as treatable by the combination of bupropion and dextromethorphan in any of the following U.S. Pat. Nos. 8,569,328, 9,168,234, 9,189,905 9,205,083, 9,238,032, 9,278,095, 9,314,462, 9,370,513, 9,375,429, 9,408,815, 9,421,176, 9,457,023, 9,457,025, 9,474,731, 9,486,450, 9,700,528, 9,700,553, 9,707,191, 9,763,932, 9,861,595, 9,867,819, 9,968,568, 10,058,518, 10,064,857, 10,080,727, 10,092,560, 10,092,561, 10,105,327, 10,105,361, 10,251,879, 10,463,634, 10,512,643, 10,548,857,

10,596,167, 10,772,850, 10,780,064, 10,780,066, 10,786,469, 10,786,496, 10,799,497, 10,806,710, 10,864,209, 10,874,663, 10,874,664, 10,874,665, 10,881,624, 10,881,657, 10,894,046, 10,894,047, 10,898,453, all of which are incorporated by reference herein in their entireties for their disclosure of diseases that may be treated by a combination of bupropion and dextromethorphan, including specific embodiments and combinations described therein.

The following U.S. Provisional applications are also incorporated by reference herein in their entireties: Ser. No. 63/359,143, filed Jul. 7, 2022, Ser. No. 63/370,592, filed Aug. 5, 2022, Ser. No. 63/396,182, filed Aug. 8, 2022, Ser. No. 63/373,040, filed Aug. 19, 2022, and Ser. No. 63/401,541, filed Aug. 26, 2022.

Example 1

In a study of the subject combination in 7 subjects with moderate (GFR 30-60 mL/min) renal impairment compared to 6 matched controls with normal renal function (matched in gender, age, and weight range to impaired subjects), both dextromethorphan and bupropion exposures increased by approximately 2-fold and clearances were reduced by 50%.

Example 2

Approximately 7 to 10% of Caucasians and 3 to 8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. In 3 poor metabolizers the pharmacokinetics of the subject combination resulted in an approximate 3-fold and 3.4-fold increase in dextromethorphan C_{max} and AUC_{0-12}, respectively, compared to extensive metabolizers. An exploration of steady state pharmacokinetic data in 12 poor metabolizers treated with the subject combination in efficacy trials showed plasma concentrations of dextromethorphan that were generally higher than exposures for non-poor metabolizers.

Example 3

Co-administration of the SSRI paroxetine and the subject combination was studied in 29 healthy volunteers. Paroxetine increased the overall exposure of dextromethorphan by 2.5-fold and had no effect on bupropion. The overall exposure of paroxetine was increased by 1.2-fold when co-administered with the subject combination. Based on these results, when the subject combination is prescribed with drugs that inhibit CYP2D6, the subject combination should be dosed once daily. Use caution when administering the subject combination in conjunction with drugs which are extensively metabolized via CYP2D6.

Example 4

The properties of a tablet containing a combination of dextromethorphan hydrobromide, which is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, which is an aminoketone and CYP450 2D6 inhibitor, were studied.

The tablets are for oral administration and are round bilayer tablets. Each tablet contains 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg of the dextromethorphan free base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg of the bupropion free base) in an extended-release formulation. Each tablet contains the following inactive ingredients: carbomer homopolymer, colloidal silicon diox-

ide, crospovidone, glyceryl monocaprylocaprate, L-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and/or yellow iron oxide.

The effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the exposure to a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are summarized in Table 1 and FIG. **1**.

TABLE 1

Patients	Group	PK Parameter	Change relative to reference (90% CI)
Moderate Renal Impairment	1	DM AUC	2.21 (1.24, 3.97)
Moderate Renal Impairment	1	DM C_{max}	2.10 (1.17, 3.77)
Moderate Renal Impairment	1	BUP AUC	1.80 (1.12, 2.92)
Moderate Renal Impairment	1	BUP C_{max}	1.87 (1.07, 3.27)
Moderate Hepatic Impairment	2	DM AUC	1.17 (0.85, 1.61)
Moderate Hepatic Impairment	2	DM C_{max}	1.21 (0.90, 1.62)
Moderate Hepatic Impairment	2	BUP AUC	1.36 (0.86, 2.15)
Moderate Hepatic Impairment	2	BUP C_{max}	1.44 (0.90, 2.30)
CYP2D6 Poor Metabolizer	3	DM AUC	3.40 (2.08, 5.57)
CYP2D6 Poor Metabolizer	3	DM C_{max}	3.00 (1.98, 4.54)
CYP2D6 Poor Metabolizer	3	BUP AUC	1.04 (0.77, 1.41)
CYP2D6 Poor Metabolizer	3	BUP C_{max}	0.97 (0.67, 1.41)

Results depicted in FIG. **1** are based on plasma concentrations in human patients after 8 days of twice daily dosing of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride. Data are GMRs and 90% CIs. Reference used are the matched healthy subjects for renal and hepatic impairment studies, and extensive or ultra-extensive CYP2D6 metabolizers. AUC represents the area under the plasma concentration-time curve from zero to 12 hours; BUP represents bupropion; CI is confidence interval; C_{max} is maximum plasma concentration; DM represents dextromethorphan; GMRs represents geometric mean ratios; PK represents pharmacokinetics.

For patients having moderate renal impairment, a 2.21-fold increase in dextromethorphan AUC_{0-2}, a 2.10-fold increase in dextromethorphan C_{max}, a 1.80-fold increase in bupropion AUC_{0-2}, and a 1.87-fold increase in bupropion C_{max} were observed.

Based upon these results, dosage adjustment is recommended in patients known to have moderate renal impairment because these patients have higher dextromethorphan and bupropion concentrations than patients with healthy renal function. The recommended total daily dose for patients known to have moderate renal impairment is about 45 mg of dextromethorphan hydrobromide and about 105 mg of bupropion hydrochloride (e.g. one tablet containing about 45 mg of dextromethorphan hydrobromide and about 105 mg of bupropion hydrochloride for administration once daily, such as in the morning), or an equivalent dose of another form dextromethorphan and/or bupropion.

Example 5

The properties of a tablet containing a combination of dextromethorphan hydrobromide, which is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, which is an aminoketone and CYP450 2D6 inhibitor, were studied.

The tablets are for oral administration and are round bilayer tablets. Each tablet contains 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg of the dextromethorphan free base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg of the bupropion free base) in an extended-release formulation. Each tablet contains the following inactive ingredients: carbomer homopolymer, colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, L-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and/or yellow iron oxide.

The effect of concomitantly administered 20 mg of paroxetine on the dextromethorphan exposure to patients taking, twice daily, a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride was determined. Dextromethorphan AUC_{0-2} was increased 2.69-fold and dextromethorphan C_{max} was increased 2.38-fold as compared to patients taking the tablet twice daily without paroxetine.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as amounts, percentage, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Use of the term "comprising" or "comprises" herein also contemplates that use of "consisting essentially of," "consists essentially of," "consisting of," or "consists of" in its place.

Affirmative recitation of an element anywhere herein should be understood to contemplate both including and excluding that element.

The terms "a," "an," "the" and similar referents used in the context of describing the embodiments (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claims.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from a group, for reasons of convenience and/or to expedite prosecution. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups if used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the

claimed embodiments. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the claimed embodiments to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

The invention claimed is:

1. A method of treating major depressive disorder in a human patient who requires concomitant treatment with paroxetine, comprising administering, once daily to the human patient, a combination of about 105 mg of bupropion hydrochloride and about 45 mg of dextromethorphan hydrobromide, wherein the human patient is experiencing major depressive disorder and is receiving concomitant treatment with paroxetine, wherein the combination is present in a solid dosage form, wherein the solid dosage form is orally administered in the morning, wherein the dextromethorphan is in an immediate-release formulation, wherein the bupropion is in an extended-release formulation, and wherein the solid dosage form further contains L-cysteine hydrochloride monohydrate.

2. The method of claim **1**, wherein the once-daily administration avoids the human patient having an about 2.7-fold increase in AUC_{0-12} of dextromethorphan as compared to the AUC_{0-12} of dextromethorphan that would result after 8 days of twice daily administration of the solid dosage form to the human patient without the concomitant treatment with paroxetine.

3. The method of claim **1**, wherein the once-daily administration avoids the human patient having an about 2.4-fold increase in C_{max} of dextromethorphan as compared to the C_{max} of dextromethorphan that would result after 8 days of twice daily administration of the solid dosage form to the human patient without the concomitant treatment with paroxetine.

4. The method of claim **1**, wherein the solid dosage form further contains a carbomer homopolymer.

5. The method of claim **1**, wherein the solid dosage form further contains colloidal silicon dioxide.

6. The method of claim **1**, wherein the solid dosage form further contains crospovidone.

7. The method of claim **1**, wherein the solid dosage form further contains glyceryl monocaprylocaprate.

8. The method of claim **1**, wherein the solid dosage form further contains magnesium stearate.

9. The method of claim **1**, wherein the solid dosage form further contains microcrystalline cellulose.

10. The method of claim **1**, wherein the solid dosage form further contains polyvinyl alcohol.

11. The method of claim **1**, wherein the solid dosage form further contains red iron oxide.

12. The method of claim **1**, wherein the solid dosage form further contains sodium lauryl sulfate.

13. The method of claim **1**, wherein the solid dosage form further contains stearic acid.

14. The method of claim **1**, wherein the solid dosage form further contains talc.

15. The method of claim **1**, wherein the solid dosage form further contains titanium dioxide.

16. The method of claim **1**, wherein the solid dosage form further contains yellow iron oxide.

17. The method of claim **1**, wherein administration of the solid dosage form twice daily to the human patient for 8 days would result in the human patient having about the same AUC_{0-12} of bupropion as compared to the AUC_{0-12} of bupropion that would result after 8 days of twice daily administration of the solid dosage form to a human patient without the concomitant treatment with paroxetine.

18. The method of claim **1**, wherein administration of the solid dosage form twice daily to the human patient for 8 days would result in the human patient having about the same C_{max} of bupropion as compared to the C_{max} of bupropion that would result after 8 days of twice daily administration of the solid dosage form to a human patient without the concomitant treatment with paroxetine.

* * * * *

EXHIBIT B

US011844797B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,844,797 B1**
(45) **Date of Patent: Dec. 19, 2023**

(54) **COMBINATION OF DEXTROMETHORPHAN AND BUPROPION FOR TREATING DEPRESSION**

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(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of bupropion; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations, such as patients having moderate renal impairment, patients having mild or moderate hepatic impairment, patients receiving a concomitant strong CYP2D6 inhibitor, patients who are known CYP2D6 poor metabolizers, those in need of an NMDA antagonist that does not cause dissociation, and those at risk of QT prolongation.

14 Claims, 1 Drawing Sheet

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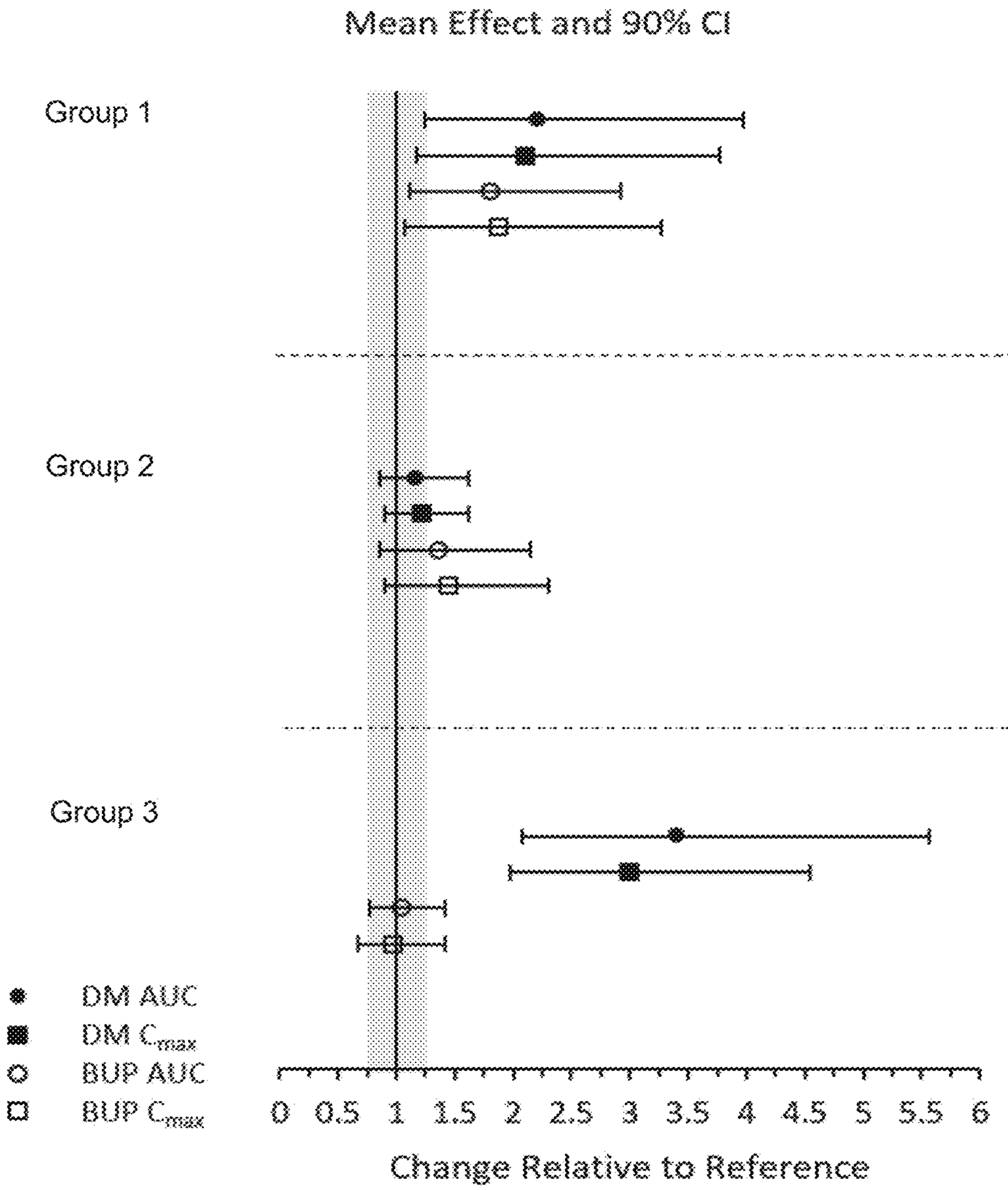

Mean Effect and 90% CI
Group 1
Group 2
Group 3
DM AUC
DM C_{max}
BUP AUC
BUP C_{max}
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6
Change Relative to Reference

COMBINATION OF DEXTROMETHORPHAN AND BUPROPION FOR TREATING DEPRESSION

SUMMARY

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations.

Some embodiments include a method of treating a patient with major depressive disorder, comprising: administering a therapeutically effective amount of a combination of a dextromethorphan and a bupropion, wherein the patient has mild hepatic impairment, defined as Child-Pugh A, or moderate hepatic impairment, defined as Child-Pugh B, and wherein the therapeutically effective amount is the same amount that would be administered to a patient with normal hepatic function.

Some embodiments include a method of treating major depressive disorder, comprising: determining whether a human patient has hepatic impairment; and

if the human patient has mild hepatic impairment, defined as Child-Pugh A, or moderate hepatic impairment, defined as Child-Pugh B, administering twice a day to the human patient, a combination of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride; and

if the human patient has severe hepatic impairment, defined as Child-Pugh C, avoiding use of the combination of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride on the human patient.

BRIEF DESCRIPTION OF THE DRAWINGS

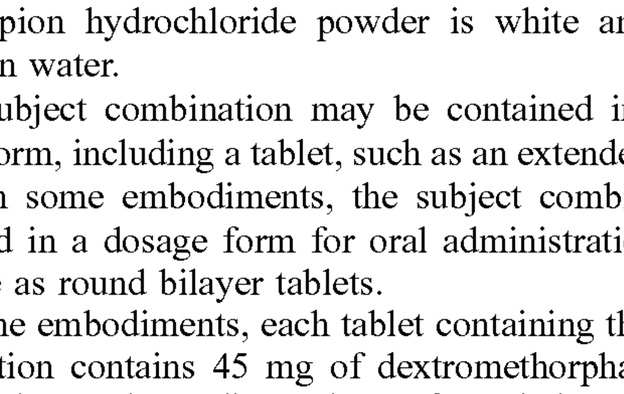
FIG. **1** depicts the effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the pharmacokinetics of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride.

DETAILED DESCRIPTION

As mentioned above, this disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations. This combination is referred to for convenience herein as the "subject combination." In every instance where the subject combination is referred to herein, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is specifically contemplated.

Dextromethorphan hydrobromide is an uncompetitive NMDA receptor antagonist and A sigma-1 receptor agonist.

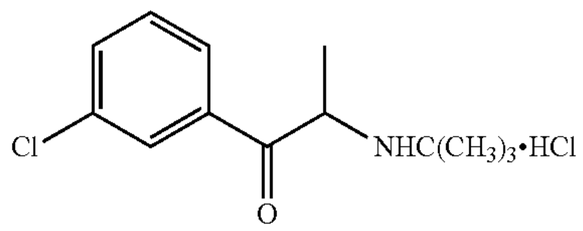
The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and a molecular weight of 370.33. The structural formula is:



Dextromethorphan hydrobromide powder is white or almost white, crystalline, and sparingly soluble in water.

Bupropion hydrochloride is an aminoketone and CYP450 2D6 inhibitor.

The chemical name of bupropion hydrochloride is: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Bupropion hydrochloride has the empirical formula $C_{13}H_{18}ClNO \cdot HCl$ and a molecular weight of 276.2. The structural formula is:



Bupropion hydrochloride powder is white and highly soluble in water.

The subject combination may be contained in an oral dosage form, including a tablet, such as an extended-release tablet. In some embodiments, the subject combination is contained in a dosage form for oral administration and is available as round bilayer tablets.

In some embodiments, each tablet containing the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation. In some embodiments, each tablet of the subject combination contains 105 mg of bupropion hydrochloride in an extended-release formulation. In some embodiments, each tablet of the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation and 105 mg of bupropion hydrochloride in an extended-release formulation.

In some embodiments, a tablet containing the subject combination contains l-cysteine hydrochloride monohydrate. In some embodiments, a tablet containing the subject combination contains carbomer homopolymer. In some embodiments, a tablet containing the subject combination contains microcrystalline cellulose. In some embodiments, a tablet containing the subject combination contains colloidal silicon dioxide. In some embodiments, a tablet containing the subject combination contains crospovidone. In some embodiments, a tablet containing the subject combination contains stearic acid. In some embodiments, a tablet containing the subject combination contains magnesium stearate.

In some embodiments, a tablet containing the subject combination contains the following inactive ingredients: l-cysteine hydrochloride monohydrate, carbomer homopolymer, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, stearic acid, and magnesium stearate.

In some embodiments, the starting dosage of the subject combination is 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride in one tablet that is administered once daily in the morning. In some embodiments, after 3 days, the dosage is increased to one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) twice daily, e.g., given at least 8 hours apart. In some embodiments, no more than two doses containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are administered in the same day.

No dose adjustment is recommended in patients with mild (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B) as compared with the dose recommended to a patient with normal hepatic function.

The pharmacokinetics of the combination of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride have not been evaluated in patients with severe hepatic impairment (Child-Pugh C). Use of combination of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride is not recommended, or should be avoided, in patients with severe hepatic impairment.

The subject combination may be administered orally with or without food. In some embodiments, the tablets are swallowed whole, and not crushed, divided, or chewed.

Special precautions may be required when switching a patient to or from a monoamine oxidase inhibitor (MAOI) antidepressant to the subject combination. In some embodiments, at least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with the subject combination. Conversely, in some embodiments, at least 14 days must be allowed after stopping the subject combination before starting an MAOI antidepressant.

In the subject combination, bupropion inhibits the metabolism of dextromethorphan via CYP2D6. Dextromethorphan, when co-administered with bupropion, displays nonlinear pharmacokinetics at steady state, with greater than dose-proportional changes in AUC and C_{max} for varying doses of dextromethorphan (30 to 60 mg) and less than dose-proportional changes for varying doses of bupropion (75 to 150 mg).

Steady state plasma concentrations of dextromethorphan and bupropion when given as the subject combination are achieved within 8 days. The accumulation ratios for dextromethorphan at steady state are about 20 and about 32, respectively based on C_{max} and AUC_{0-12}. The accumulation ratios for bupropion at steady state are 1.1 and 1.5, respectively based on C_{max} and AUC_{0-12}.

After administration of the subject combination, the median T_{max} of dextromethorphan is about $_3$ hours and the median T_{max} of bupropion is about 2 hours. The C_{max} of hydroxybupropion metabolite occurs approximately 3 hours post-dose and is approximately 14 times the peak level of bupropion. The AUC_{0-12} hydroxybupropion is about 19 times that of bupropion. The C_{max} of the erythrohydroxybupropion and threohydroxybupropion metabolites occurs approximately 4 hours post-dose and is approximately equal to and about 5 times that of bupropion, respectively. The AUC_{0-12} values of erythrohydroxybupropion and threohydroxybupropion are about 1.2 and about 7 times that of bupropion, respectively.

The subject combination can be taken with or without food. Dextromethorphan C_{max} and AUC_{0-12} were unchanged and decreased by 14%, respectively, and bupropion C_{max} and AUC_{0-12} were increased by 3% and 6%, respectively, when the subject combination was administered with food.

The plasma protein binding of dextromethorphan is approximately 60-70% and bupropion is 84%. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Following 8 days of administration of the subject combination in extensive metabolizers, the mean elimination half-life of dextromethorphan was increased approximately 3-fold to about 22 hours, as compared to dextromethorphan given without bupropion.

The mean elimination half-life of dextromethorphan and bupropion was 22 hours and 15 hours, respectively. The apparent elimination half-life of hydroxybupropion, erythrohydroxybuporpion and threohydroxybupropion metabolites were approximately 35, 44 and 33 hours, respectively.

Esketamine is a non-competitive NMDA receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults. Treatment of treatment-resistant depression carries a risk of dissociation. The label for esketamine states that because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paranesthesia; paranesthesia oral; pharyngeal paranesthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment.

The subject combination is a combination of dextromethorphan, an uncompetitive N-methyl D-aspartate (NDMA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for the treatment of major depressive disorder (MDD) in adults. Unlike esketamine, the subject combination can be administered as a without dissociation or dissociative events. In some embodiments, the patient is not monitored for dissociation after the subject combination is administered.

Unlike the combination of quinidine and dextromethorphan, at a dose of a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide given twice a day, the subject combination does not prolong the QT interval to any clinically relevant extent. Thus, for a human patient who is experiencing major depressive disorder and is at risk of QT prolongation and torsades de pointer, electrocardiographic evaluation of QT interval is not typically conducted on the human patient.

The subject combination may be used for adjunctive treatment of major depressive disorder or depression.

In addition to major depressive disorder, the subject combination may be used to treat other diseases in conditions in the patient populations or circumstances described herein. For example, the subject combination may be used to treat pain or a neurological disorder. Examples of neurological disorders that may be treated with the subject combination include, but are not limited to: affective disorders, psychiatric disorders, cerebral function disorders, movement

disorders, dementias, motor neuron diseases, neurodegenerative diseases, seizure disorders, and headaches.

Affective disorders that may be treated by the subject combination include, but are not limited to, depression, major depression, treatment resistant depression, treatment resistant bipolar depression, bipolar disorders including cyclothymia, seasonal affective disorder, mood disorders, chronic depression (dysthymia), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, atypical depression, mania, anxiety disorders, attention deficit disorder (ADD), attention deficit disorder with hyperactivity (ADDH), and attention deficit/hyperactivity disorder (AD/HD), bipolar and manic conditions, obsessive-compulsive disorder, bulimia, obesity or weight-gain, narcolepsy, chronic fatigue syndrome, premenstrual syndrome, substance addiction or abuse, nicotine addiction, psycho-sexual dysfunction, pseudobulbar affect, and emotional lability.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts, or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restlessness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Psychiatric disorders that may be treated by the subject combination, include, but are not limited to, anxiety disorders, including but not limited to, phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD); mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, somatoform disorders, personality disorders, psychosis, schizophrenia, delusional disorder, schizoaffective disorder, schizotypy, aggression, aggression in Alzheimer's disease, agitation, and agitation in Alzheimer's disease. Alzheimer's disease may also be referred to as dementia of the Alzheimer's type. Other neurobehavioral symptoms of Alzheimer's disease that may be treated include disinhibition and apathy.

Agitation in Alzheimer's disease occurs as the disease progresses. Agitation may present itself as inappropriate verbal, emotional, and/or physical behaviors. Inappropriate behaviors may include, but are not limited to, incoherent babbling, inappropriate emotional response, demands for attention, threats, irritability, frustration, screaming, repetitive questions, mood swings, cursing, abusive language, physical outbursts, emotional distress, restlessness, shredding, sleeping disturbances, delusions, hallucinations, pacing, wandering, searching, rummaging, repetitive body motions, hoarding, shadowing, hitting, scratching, biting, combativeness, hyperactivity, and/or kicking.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Managing agitation is a priority in AD. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality. There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Neurobehavioral symptoms have been known to appear during dementia and may be treated by the combination. Caregivers or families may feel more overwhelmed by patients' behavioral/psychological symptoms than by their cognitive impairment. Common forms of the syndrome are Alzheimer's disease, vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The symptoms that dementia patients have are similar to those of psychiatric disorders, but some are slightly different from each other. Neurobehavioral symptoms associated with dementia include depression, apathy, agitation, disinhibition, hallucinations, delusions, psychosis, impulsiveness, aggressiveness, compulsion, excessive sex drive, and personality disorders. Neurobehavioral symptoms such as disinhibition may also be found in other conditions such as traumatic brain injury.

Agitation in patients with Alzheimer's disease may be assessed using the Cohen Mansfield Agitation Inventory or CMAI. The CMAI assesses various behaviors including, Hitting (including self), Kicking , Grabbing onto people, Pushing, Throwing things, Biting , Scratching, Spitting, Hurting self or others, Tearing things or destroying property, Making physical sexual advances, Pacing, aimless wandering, Inappropriate dress or disrobing, Trying to get to a different place, Intentional falling, Eating/drinking inappropriate substances, Handling things inappropriately, Hiding things, Hoarding things, Performing repetitive mannerisms, General restlessness, Screaming, Making verbal sexual advances, Cursing or verbal aggression, Repetitive sentences or questions, Strange noises (weird laughter or crying), Complaining, Negativism, Constant unwarranted request for attention or help.

Schizophrenia may treated by the combination including positive symptoms and/or negative symptoms of schizophrenia, or residual symptoms of schizophrenia. Other conditions that may treated include intermittent explosive disorder.

Cerebral function disorders that may be treated by the subject combination include, but are not limited to, disorders involving intellectual deficits such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, voice spasms, Parkinson's disease, Lennox-Gastaut syndrome, autism, hyperkinetic syndrome, and schizophrenia. Cerebral function disorders also include disorders caused by cerebrovascular diseases including, but not limited to, stroke, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like where symptoms include disturbance of consciousness, senile dementia, coma, lowering of attention, and speech disorders.

Substance addiction abuse that may be treated by the subject combination includes, but is not limited to, drug dependence, addiction to cocaine, psychostimulants (e.g., crack, cocaine, speed, meth), nicotine, alcohol, opioids, anxiolytic and hypnotic drugs, cannabis (marijuana), amphetamines, hallucinogens, phencyclidine, volatile solvents, and volatile nitrites. Nicotine addiction includes nicotine addiction of all known forms, such as smoking cigarettes, cigars and/or pipes, e-cigarettes or vaping, and addiction to chewing tobacco.

Movement disorders that may be treated by the subject combination include, but are not limited to, akathisia, akinesia, associated movements, athetosis, ataxia, ballismus, hemiballismus, bradykinesia, cerebral palsy, chorea, Huntington's disease, Huntington's disease chorea, rheumatic chorea, Sydenham's chorea, dyskinesia, tardive dyskinesia, dystonia, blepharospasm, spasmodic torticollis, dopamine-responsive dystonia, Parkinson's disease, restless legs syndrome (RLS), tremor, essential tremor, and Tourette's syndrome, and Wilson's disease.

Dementias that may be treated by the subject combination include, but are not limited to, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, fronto-temporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, Wernicke-Korsakoff Syndrome, and Pick's disease.

Motor neuron diseases that may be treated by the subject combination include, but are not limited to, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, post-polio syndrome (PPS), spinal muscular atrophy (SMA), spinal motor atrophies, Tay-Sach's disease, Sandhoff disease, and hereditary spastic paraplegia.

Neurodegenerative diseases that may be treated the subject combination include, but are not limited to, Alzheimer's disease, prion-related diseases, cerebellar ataxia, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), bulbar muscular atrophy, Friedrich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis (MS), multiple system atrophy, Shy-Drager syndrome, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, Menkes disease, adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), muscular dystrophies, Charcot-Marie-Tooth disease (CMT), familial spastic paraparesis, neurofibromatosis, olivopontine cerebellar atrophy or degeneration, striatonigral degeneration, Guillain-Barré syndrome, and spastic paraplesia.

Seizure disorders that may be treated by the subject combination include, but are not limited to, epileptic seizures, nonepileptic seizures, epilepsy, febrile seizures; partial seizures including, but not limited to, simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua; generalized seizures including, but not limited to, generalized tonic-clonic seizures, absence seizures, atonic seizures, myoclonic seizures, juvenile myoclonic seizures, and infantile spasms; and status epilepticus.

Types of headaches that may be treated by the subject combination include, but are not limited to, migraine, tension, and cluster headaches.

Other neurological disorders that may be treated by the subject combination include, Rett Syndrome, autism, tinnitus, disturbances of consciousness disorders, sexual dysfunction, intractable coughing, narcolepsy, cataplexy; voice disorders due to uncontrolled laryngeal muscle spasms, including, but not limited to, abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; diabetic neuropathy, chemotherapy-induced neurotoxicity, such as methotrexate neurotoxicity; incontinence including, but not limited, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

In some embodiments, the subject combination may be used to treat pain, joint pain, pain associated with sickle cell disease, pseudobulbar affect, depression (including treatment resistant depression), disorders related to memory and cognition, schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Rhett's syndrome, seizures, cough (including chronic cough), etc.

In some embodiments, the subject combination may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

In some embodiments, the subject combination may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

In some embodiments, the subject combination is used to treat chronic musculoskeletal pain.

In some embodiments, the subject composition may be administered to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component. Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor, and sensory changes.

In some embodiments, the subject composition may be administered orally to relieve neuropathic pain.

Examples of neuropathic pain include pain due to diabetic peripheral neuropathy or diabetic peripheral neuropathic pain, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, central pain, pain due to multiple sclerosis, etc. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio- or chemotherapy associated neuropathy, etc.

In some embodiments, the subject composition may be administered to relieve fibromyalgia.

In some embodiments, the subject composition may be administered to a patient who has moderate renal impairment. As explained herein, it has been found that administering the subject composition to CYP2D6 poor metabolizers increases plasma concentrations of dextromethorphan as compared to patients who are not CYP2D6 poor metabolizers. It is, thus, recommended to monitor patients for adverse effects or adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Dosage adjustment may be necessary when the patient has moderate renal impairment. Adjusting to a lower dose amount of the bupropion and/or the dextromethorphan in the subject combination or less frequent dosing of the subject combination may reduce adverse effects or adverse reactions, or a risk of adverse effects or adverse reactions, such as, but not limited to, somnolence, dizziness, or a combination thereof in a patient. For example, a recommended

dosage of the subject combination when administered to a patient who has moderate renal impairment, is one tablet containing 45 mg or less of dextromethorphan hydrobromide and 105 mg or less of bupropion hydrochloride once daily, such as once daily in the morning.

Administration of the subject combination once a day to patients who have moderate renal impairment may reduce the adverse effects, or the risk of adverse effects, such as, but not limited to, somnolence, dizziness, or a combination thereof, as compared to administration of the subject combination twice a day for same number of days. In some embodiments, reducing the dose amount or dose frequency of the subject combination may reduce somnolence. In some embodiments, reducing dose amount or dose frequency may reduce dizziness. As dizziness may link to falls, adjusting the dosage to lower amount or lower dose frequency of the subject combination may reduce the risk of falls for a patient taking the subject combination. For example, taking the subject combination once a day may reduce the risk of falls for a patient as compared to taking the subject combination twice a day for same number of days. This may be important, for example, to elderly patients or patients suffering from a dementia, such as Alzheimer's disease.

The term "treating" or "treatment" includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

A subject combination may be used to treat any disease or condition identified as treatable by the combination of bupropion and dextromethorphan in any of the following U.S. Pat. No.: 8,569,328, 9,168,234, 9,189,905 9,205,083, 9,238,032, 9,278,095, 9,314,462, 9,370,513, 9,375,429, 9,408,815, 9,421,176, 9,457,023, 9,457,025, 9,474,731, 9,486,450, 9,700,528, 9,700,553, 9,707,191, 9,763,932, 9,861,595, 9,867,819, 9,968,568, 10,058,518, 10,064,857, 10,080,727, 10,092,560, 10,092,561, 10,105,327, 10,105, 361, 10,251,879, 10,463,634, 10,512,643, 10,548,857, 10,596,167, 10,772,850, 10,780,064, 10,780,066, 10,786, 469, 15 10,786,496, 10,799,497, 10,806,710, 10,864,209, 10,874,663, 10,874,664, 10,874,665, 10,881,624, 10,881, 657, 10,894,046, 10,894,047, 10,898,453, all of which are incorporated by reference herein in their entireties for their disclosure of diseases that may be treated by a combination of bupropion and dextromethorphan, including specific embodiments and combinations described therein.

The following U.S. provisional applications are also incorporated by reference herein in their entireties: Ser. No. 63/359,143, filed Jul. 7, 2022, Ser. No. 63/370,592, filed Aug. 5, 2022, Ser. No. 63/396,182, filed Aug. 8, 2022, Ser. No. 63/373,040, filed Aug. 19, 2022, and Ser. No. 63/401, 541, filed Aug. 26, 2022.

Example 1

The properties of a tablet containing a combination of dextromethorphan hydrobromide, which is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, which is an aminoketone and CYP450 2D6 inhibitor, were studied.

The tablets are for oral administration and are round bilayer tablets. Each tablet contains 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg of the dextromethorphan free base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg of the bupropion free base) in an extended-release formulation. Each tablet contains the following inactive ingredients: carbomer homopolymer, colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, L-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and/or yellow iron oxide.

The effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the exposure to a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are summarized in FIG. **1**.

Results depicted in FIG. **1** are based on plasma concentrations in human patients after 8 days of twice daily dosing of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride. Data are GMRs and 90% Cls. References used are the matched healthy subjects for renal (Group 1) and hepatic impairment (Group 2) studies, and extensive or ultra-extensive CYP2D6 metabolizers (Group 3) respectively. AUC represents the area under the plasma concentration-time curve from zero to 12 hours; BUP represents bupropion; CI is confidence interval; C_{max} is maximum plasma concentration; DM represents dextromethorphan; GMRs represents geometric mean ratios; PK represents pharmacokinetics.

In FIG. **1**, the results for patients with moderate Renal Impairment are identified as "Group 1," the results for patients with Moderate Hepatic Impairment are identified as "Group 2," and the results for patients who are CYP2D6 Poor Metabolizers are identified as "Group 3." The results are summarized in Table 1 below.

TABLE 1

Patients	PK Group	Parameter	Change Relative to Reference (90% CI)
Moderate Renal Impairment	1	DM AUC	2.21 (1.24, 3.97)
Moderate Renal Impairment	1	DM C_{max}	2.10 (1.17, 3.77)
Moderate Renal Impairment	1	BUP AUC	1.80 (1.12, 2.92)
Moderate Renal Impairment	1	BUP C_{max}	1.87 (1.07, 3.27)
Moderate Hepatic Impairment	2	DM AUC	1.17 (0.85, 1.61)
Moderate Hepatic Impairment	2	DM C_{max}	1.21 (0.90, 1.62)
Moderate Hepatic Impairment	2	BUP AUC	1.36 (0.86, 2.15)
Moderate Hepatic Impairment	2	BUP C_{max}	1.44 (0.90, 2.30)
CYP2D6 Poor Metabolizer	3	DM AUC	3.40 (2.08, 5.57)
CYP2D6 Poor Metabolizer	3	DM C_{max}	3.00 (1.98, 4.54)
CYP2D6 Poor Metabolizer	3	BUP AUC	1.04 (0.77, 1.41)
CYP2D6 Poor Metabolizer	3	BUP C_{max}	0.97 (0.67, 1.41)

For example, for patients having moderate hepatic impairment (Group 2), the AUC_{0-12} and C_{max} of dextromethorphan and bupropion were not significantly different from that for healthy patients.

The mean ratio of AUC_{0-12} of dextromethorphan for patients with moderate hepatic impairment as compared to healthy patients was 1.17, with a 90% confidence interval of 0.85-1.61.

The mean ratio of C_{max} of dextromethorphan for patients with moderate hepatic impairment as compared to healthy patients was 1.21, with a 90% confidence interval of 0.90-1.62.

The mean ratio of AUC_{0-12} of bupropion for patients with moderate hepatic impairment as compared to healthy patients was 1.36, with a 90% confidence interval of 0.86-2.15.

The mean ratio of C_{max} of bupropion for patients with moderate hepatic impairment as compared to healthy patients was 1.44, with a 90% confidence interval of 0.90-2.30.

Based upon these results, no dosage adjustment is recommended in patients known to have mild or moderate hepatic impairment.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as amounts, percentage, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Use of the term "comprising" or "comprises" herein also contemplates that use of "consisting essentially of," "consists essentially of," "consisting of," or "consists of" in its place.

Affirmative recitation of an element anywhere herein should be understood to contemplate both including and excluding that element.

The terms "a," "an," "the" and similar referents used in the context of describing the embodiments (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claims.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from a group, for reasons of convenience and/or to expedite prosecution. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups if used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the claimed embodiments. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the claimed embodiments to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

The invention claimed is:

1. A method of treating major depressive disorder in a human patient who has moderate hepatic impairment comprising administering twice daily, by mouth, one tablet containing about 105 mg of bupropion hydrochloride and about 45 mg of dextromethorphan hydrobromide to the human patient who has moderate hepatic impairment, defined as Child-Pugh B, and is experiencing major depressive disorder, wherein the dextromethorphan hydrobromide is in an immediate-release formulation, wherein the bupropion hydrochloride is in an extended-release formulation, and wherein the tablet is a bilayer tablet.

2. The method of claim **1**, wherein the tablet further contains a carbomer homopolymer.

3. The method of claim **1**, wherein the tablet further contains colloidal silicon dioxide.

4. The method of claim **1**, wherein the tablet further contains crospovidone.

5. The method of claim **1**, wherein the tablet further contains glyceryl monocaprylocaprate.

6. The method of claim **1**, wherein the tablet further contains magnesium stearate.

7. The method of claim **1**, wherein the tablet further contains microcrystalline cellulose.

8. The method of claim **1**, wherein the tablet further contains polyvinyl alcohol.

9. The method of claim **1**, wherein the tablet further contains red iron oxide.

10. The method of claim **1**, wherein the tablet further contains sodium lauryl sulfate.

11. The method of claim **1**, wherein the tablet further contains stearic acid.

12. The method of claim **1**, wherein the tablet further contains talc.

13. The method of claim **1**, wherein the tablet further contains titanium dioxide.

14. The method of claim **1**, wherein the tablet further contains yellow iron oxide.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,844,797 B1
APPLICATION NO. : 18/304246
DATED : December 19, 2023
INVENTOR(S) : Herriot Tabuteau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Add:
--Related U.S. Application Data:
Provisional application No. 63/359,143, filed on Jul. 7, 2022, provisional application no. 63/370,592 filed on Aug. 5, 2022, provisional application no. 63/396,182 filed on Aug. 8, 2022, provisional application no. 63/373,040 filed on Aug. 19, 2022, provisional application no. 63/401,541 filed on Aug. 26, 2022.--

Signed and Sealed this
Thirtieth Day of January, 2024

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

EXHIBIT C

US011883373B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,883,373 B1**
(45) **Date of Patent: *Jan. 30, 2024**

(54) **TREATMENT OF DEPRESSION IN CERTAIN PATIENT POPULATIONS**

(71) Applicant: **ANTECIP BIOVENTURES II LLC**, New York, NY (US)

(72) Inventor: **Herriot Tabuteau**, New York, NY (US)

(73) Assignee: **ANTECIP BIOVENTURES II LLC**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18/333,944**

(22) Filed: **Jun. 13, 2023**

Related U.S. Application Data

(63) Continuation of application No. 18/158,268, filed on Jan. 23, 2023, now Pat. No. 11,730,706.

(60) Provisional application No. 63/359,143, filed on Jul. 7, 2022, provisional application No. 63/370,592, filed on Aug. 5, 2022, provisional application No. 63/396,182, filed on Aug. 8, 2022, provisional application No. 63/373,040, filed on Aug. 19, 2022, provisional application No. 63/401,541, filed on Aug. 26, 2022.

(51) **Int. Cl.**

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A61K 9/20	(2006.01)
A61P 25/24	(2006.01)
A61K 31/485	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 31/137*** (2013.01); ***A61K 9/2086*** (2013.01); ***A61K 31/485*** (2013.01); ***A61P 25/24*** (2018.01)

(58) **Field of Classification Search**
CPC A61K 31/137; A61K 31/485; A61P 25/24
See application file for complete search history.

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(57) **ABSTRACT**

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of bupropion; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations, such as patients having moderate renal impairment, patients receiving a concomitant strong CYP2D6 inhibitor, patients who are known CYP2D6 poor metabolizers, those in need of an NMDA antagonist that does not cause dissociation, and those at risk of QT prologation.

19 Claims, 1 Drawing Sheet

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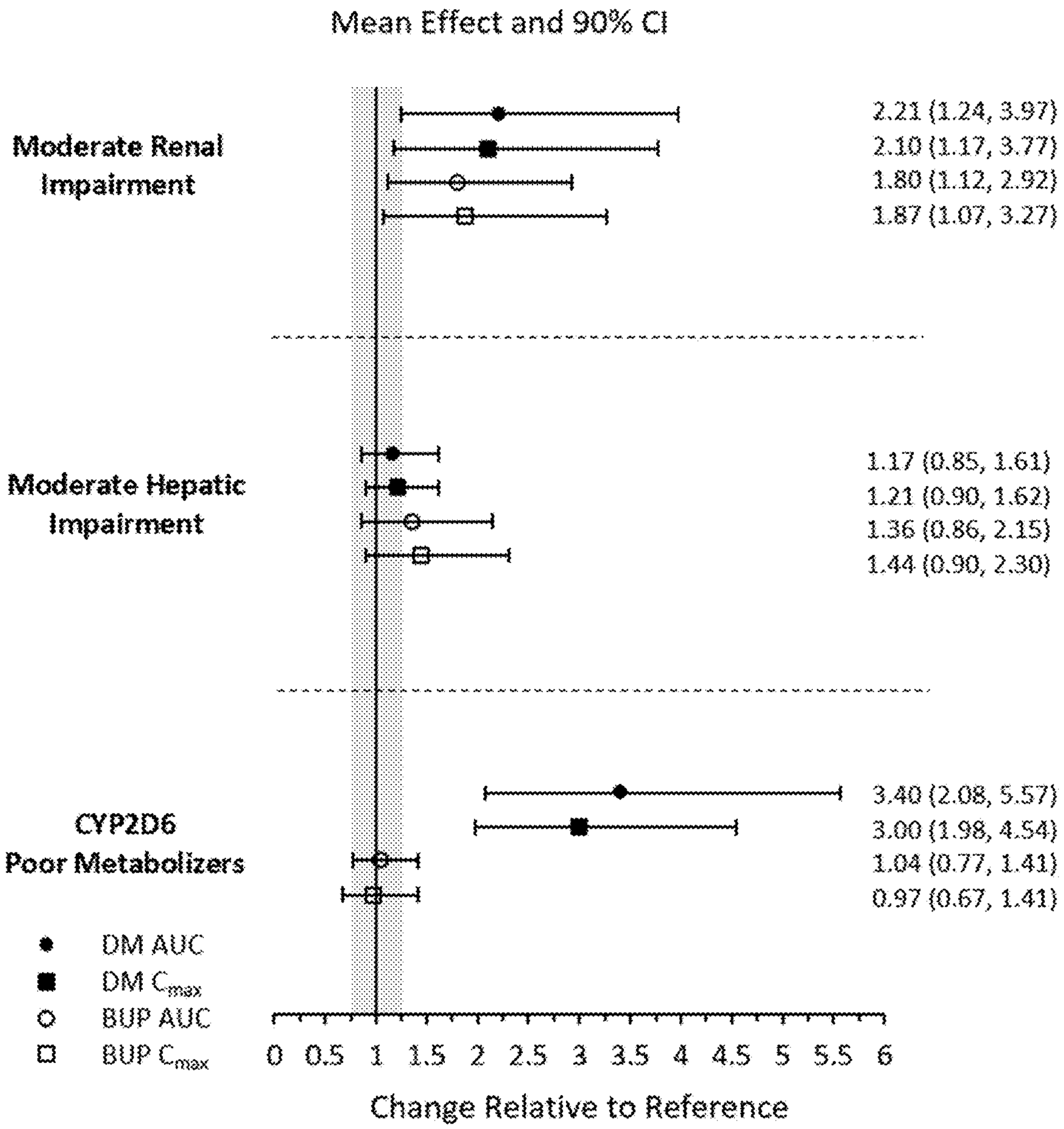


Effects of Renal Impairment, Hepatic Impairment, and CYP2D6 Poor Metabolizer Status on Dextromethorphan/Bupropion PK

TREATMENT OF DEPRESSION IN CERTAIN PATIENT POPULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is continuation of U.S. patent application Ser. No. 18/158,268, filed Jan. 23, 2023; which claims priority to U.S. Provisional Patent Application No. 63/359,143, filed Jul. 7, 2022, U.S. Provisional Patent Application No. 63/370,592, filed Aug. 5, 2022, U.S. Provisional Patent Application No. 63/396,182, filed Aug. 8, 2022, U.S. Provisional Patent Application No. 63/373,040, filed Aug. 19, 2022, and U.S. Provisional Patent Application No. 63/401,541, filed Aug. 26, 2022; all of which are incorporated by reference herein in their entireties.

SUMMARY

This disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan in certain patient populations.

Some embodiments include a method of treating major depressive disorder in a patient having moderate renal impairment, comprising administering a daily dose of: (i) about 105 mg of bupropion hydrochloride and (ii) about 45 mg of dextromethorphan hydrobromide to a human patient who has moderate renal impairment and is experiencing major depressive disorder.

Some embodiments include a method of treating major depressive disorder in a patient receiving a concomitant strong CYP2D6 inhibitor, comprising administering a daily dose of: (i) about 105 mg of bupropion hydrochloride and (ii) about 45 mg of dextromethorphan hydrobromide to a human patient who has major depressive disorder and is receiving concomitant treatment with a strong CYP2D6 inhibitor.

Some embodiments include a method of treating major depressive disorder in a patient who is a known CYP2D6 poor metabolizer, comprising administering a daily dose of: (i) about 105 mg of bupropion hydrochloride and (ii) about 45 mg of dextromethorphan hydrobromide to a human patient who is experiencing major depressive disorder and is known to be a CYP2D6 poor metabolizer.

Some embodiments include a method of using an N-methyl D-aspartate (NMDA) receptor antagonist to treat major depressive disorder, comprising administering, no more than twice daily, a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide to a human patient who is experiencing major depressive disorder, wherein the dextromethorphan acts as an uncompetitive antagonist of the NMDA receptor and a sigma-1 receptor agonist, and the human patient does not experience dissociation.

Some embodiments include a method of treating major depressive disorder in a human patient at risk of QT prolongation, comprising administering, no more than twice daily, a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide to a human patient who is experiencing major depressive disorder and is at risk of QT prolongation and torsades de pointer, wherein electrocardiographic evaluation of QT interval is not conducted on the human patient.

BRIEF DESCRIPTION OF THE DRAWINGS

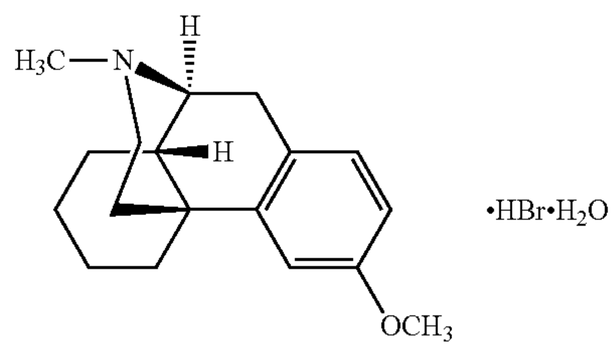
FIG. **1** depicts the effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the pharmacokinetics of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride.

DETAILED DESCRIPTION

As mentioned above, this disclosure relates to administration of a combination of: 1) about 100-110 mg, about 104-106 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of a free base form or another salt form of dextromethorphan; and 2) about mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of a free base form or another salt form of dextromethorphan. This combination is referred to for convenience herein as the "subject combination." In every instance where the subject combination is referred to herein, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is specifically contemplated.

Dextromethorphan hydrobromide is an uncompetitive NMDA receptor antagonist and A sigma-1 receptor agonist.

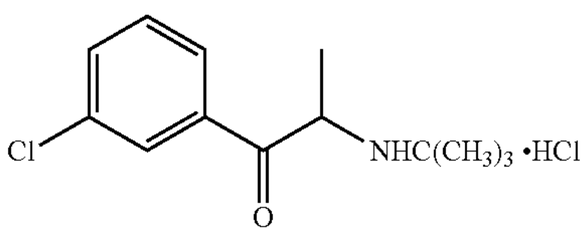
The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9α,13α,14α), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula $C_{18}H_{25}NO{\cdot}HBr{\cdot}H_2O$ and a molecular weight of 370.33. The structural formula is:



Dextromethorphan hydrobromide powder is white or almost white, crystalline, and sparingly soluble in water.

Bupropion hydrochloride is an aminoketone and CYP450 2D6 inhibitor.

The chemical name of bupropion hydrochloride is: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Bupropion hydrochloride has the empirical formula $C_{13}H_{18}ClNO{\cdot}HCl$ and a molecular weight of 276.2. The structural formula is:



Bupropion hydrochloride powder is white and highly soluble in water.

The subject combination may be contained in an oral dosage form, including a tablet, such as an extended-release tablet. In some embodiments, the subject combination is contained in a dosage form for oral administration and is available as round bilayer tablets.

In some embodiments, each tablet containing the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation. In some embodiments, each tablet of the subject combination contains 105 mg of bupropion hydrochloride in an extended-release formulation. In some embodiments, each tablet of the subject combination contains 45 mg of dextromethorphan hydrobromide in an immediate-release formulation and 105 mg of bupropion hydrochloride in an extended-release formulation.

In some embodiments, a tablet containing the subject combination contains 1-cysteine hydrochloride monohydrate. In some embodiments, a tablet containing the subject combination contains carbomer homopolymer. In some embodiments, a tablet containing the subject combination contains microcrystalline cellulose. In some embodiments, a tablet containing the subject combination contains colloidal silicon dioxide. In some embodiments, a tablet containing the subject combination contains crospovidone. In some embodiments, a tablet containing the subject combination contains stearic acid. In some embodiments, a tablet containing the subject combination contains magnesium stearate.

In some embodiments, a tablet containing the subject combination contains the following inactive ingredients: 1-cysteine hydrochloride monohydrate, carbomer homopolymer, microcrystalline cellulose, colloidal silicon dioxide, crospovidone, stearic acid, and magnesium stearate.

In some embodiments, the starting dosage of the subject combination is 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride in one tablet that is administered once daily in the morning. In some embodiments, after 3 days, the dosage is increased to one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) twice daily, e.g., given at least 8 hours apart. In some embodiments, no more than two doses containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are administered in the same day.

The subject combination may be administered orally with or without food. In some embodiments, the tablets are swallowed whole, and not crushed, divided, or chewed.

Patients having renal impairment may require special dosing. In some embodiments, the recommended dosage of the subject combination for patients with moderate renal impairment (estimated glomerular filtration rate (eGFR) or glomerular filtration rate (GFR) of 30 to 59 mL/minute/1.73 m^2) is a daily dose of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride, or a molar equivalent amount of another form of dextromethorphan and/or bupropion, such as administration of one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning.

Patients who are concomitantly using the subject combination with strong CYP2D6 inhibitors may require special dosing. Concomitant use of the subject combination with a strong CYP2D6 inhibitor increases plasma concentrations of dextromethorphan. In some embodiments, the recommended dosage of the subject combination when coadministered with a strong CYP2D6 inhibitor is one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning. In some embodiments, the patients are monitored for adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

Patients who are known CYP2D6 poor metabolizers (PMs) may require special dosing. In some embodiments, the recommended dosage for patients known to be poor CYP2D6 metabolizers is one tablet (or one dosage form containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride) once daily, such as one tablet or other oral dosage form daily in the morning.

Special precautions may be required when switching a patient to or from a monoamine oxidase inhibitor (MAOI) antidepressant to the subject combination. In some embodiments, at least 14 days must elapse between discontinuation of an MAOI intended to treat depression and initiation of therapy with the subject combination. Conversely, in some embodiments, at least 14 days must be allowed after stopping the subject combination before starting an MAOI antidepressant.

In the subject combination, bupropion inhibits the metabolism of dextromethorphan via CYP2D6. Dextromethorphan, when co-administered with bupropion, displays nonlinear pharmacokinetics at steady state, with greater than dose-proportional changes in AUC and C_{max} for varying doses of dextromethorphan (30 to 60 mg) and less than dose-proportional changes for varying doses of bupropion (75 to 150 mg).

Steady state plasma concentrations of dextromethorphan and bupropion when given as the subject combination are achieved within 8 days. The accumulation ratios for dextromethorphan at steady state are about 20 and about 32, respectively based on C_{max} and AUC_{0-12}. The accumulation ratios for bupropion at steady state are 1.1 and 1.5, respectively based on C_{max} and AUC_{0-12}.

After administration of the subject combination, the median T_{max} of dextromethorphan is about 3 hours and the median T_{max} of bupropion is about 2 hours. The C_{max} of hydroxybupropion metabolite occurs approximately 3 hours post-dose and is approximately 14 times the peak level of bupropion. The AUC_{0-12} hydroxybupropion is about 19 times that of bupropion. The C_{max} of the erythrohydroxybupropion and threohydroxybupropion metabolites occurs approximately 4 hours post-dose and is approximately equal to and about 5 times that of bupropion, respectively. The AUC_{0-12} values of erythrohydroxybupropion and threohydroxybupropion are about 1.2 and about 7 times that of bupropion, respectively.

The subject combination can be taken with or without food. Dextromethorphan C_{max} and AUC_{0-12} were unchanged and decreased by 14%, respectively, and bupropion C_{max} and AUC_{0-12} were increased by 3% and 6%, respectively, when the subject combination was administered with food.

The plasma protein binding of dextromethorphan is approximately 60-70% and bupropion is 84%. The extent of protein binding of the hydroxybupropion metabolite is similar to that for bupropion; whereas the extent of protein binding of the threohydrobupropion metabolite is about half that seen with bupropion.

Following 8 days of administration of the subject combination in extensive metabolizers, the mean elimination half-life of dextromethorphan was increased approximately 3-fold to about 22 hours, as compared to dextromethorphan given without bupropion.

The mean elimination half-life of dextromethorphan and bupropion was 22 hours and 15 hours, respectively. The apparent elimination half-life of hydroxybupropion, erythrohydroxybuporpion and threohydroxybupropion metabolites were approximately 35, 44 and 33 hours, respectively.

Esketamine is a non-competitive NMDA receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults. Treatment of treatment-resistant depression carries a risk of dissociation. The label for esketamine states that because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting.

Dissociation includes: delusional perception; depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paranesthesia; paranesthesia oral; pharyngeal paranesthesia; photophobia; time perception altered; tinnitus; vision blurred; visual impairment.

The subject combination is a combination of dextromethorphan, an uncompetitive N-methyl D-aspartate (NDMA) receptor antagonist and sigma-1 receptor agonist, and bupropion, an aminoketone and CYP450 2D6 inhibitor, indicated for the treatment of major depressive disorder (MDD) in adults. Unlike esketamine, the subject combination can be administered as a without dissociation or dissociative events. In some embodiments, the patient is not monitored for dissociation after the subject combination is administered.

Unlike the combination of quinidine and dextromethorphan, at a dose of a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide given twice a day, the subject combination does not prolong the QT interval to any clinically relevant extent. Thus, for a human patient who is experiencing major depressive disorder and is at risk of QT prolongation and torsades de pointer, electrocardiographic evaluation of QT interval is not typically conducted on the human patient.

The subject combination may be used for adjunctive treatment of major depressive disorder or depression.

In addition to major depressive disorder, the subject combination may be used to treat other diseases in conditions in the patient populations or circumstances described herein. For example, the subject combination may be used to treat pain or a neurological disorder. Examples of neurological disorders that may be treated with the subject combination include, but are not limited to: affective disorders, psychiatric disorders, cerebral function disorders, movement disorders, dementias, motor neuron diseases, neurodegenerative diseases, seizure disorders, and headaches.

Affective disorders that may be treated by the subject combination include, but are not limited to, depression, major depression, treatment resistant depression, treatment resistant bipolar depression, bipolar disorders including cyclothymia, seasonal affective disorder, mood disorders, chronic depression (dysthymia), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, atypical depression, mania, anxiety disorders, attention deficit disorder (ADD), attention deficit disorder with hyperactivity (ADDH), and attention deficit/hyperactivity disorder (AD/HD), bipolar and manic conditions, obsessive-compulsive disorder, bulimia, obesity or weight-gain, narcolepsy, chronic fatigue syndrome, premenstrual syndrome, substance addiction or abuse, nicotine addiction, psycho-sexual dysfunction, pseudobulbar affect, and emotional lability.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts, or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restlessness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Psychiatric disorders that may be treated by the subject combination, include, but are not limited to, anxiety disorders, including but not limited to, phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD); mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, somatoform disorders, personality disorders, psychosis, schizophrenia, delusional disorder, schizoaffective disorder, schizotypy, aggression, aggression in Alzheimer's disease, agitation, and agitation in Alzheimer's disease. Alzheimer's disease may also be referred to as dementia of the Alzheimer's type. Other neurobehavioral symptoms of Alzheimer's disease that may be treated include disinhibition and apathy.

Agitation in Alzheimer's disease occurs as the disease progresses. Agitation may present itself as inappropriate verbal, emotional, and/or physical behaviors. Inappropriate behaviors may include, but are not limited to, incoherent babbling, inappropriate emotional response, demands for attention, threats, irritability, frustration, screaming, repetitive questions, mood swings, cursing, abusive language, physical outbursts, emotional distress, restlessness, shredding, sleeping disturbances, delusions, hallucinations, pacing, wandering, searching, rummaging, repetitive body motions, hoarding, shadowing, hitting, scratching, biting, combativeness, hyperactivity, and/or kicking.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Managing agitation is a priority in AD. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality. There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Neurobehavioral symptoms have been known to appear during dementia and may be treated by the combination. Caregivers or families may feel more overwhelmed by patients' behavioral/psychological symptoms than by their cognitive impairment. Common forms of the syndrome are Alzheimer's disease, vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The symptoms that dementia patients have are similar to those of psychiatric disorders, but some are

slightly different from each other. Neurobehavioral symptoms associated with dementia include depression, apathy, agitation, disinhibition, hallucinations, delusions, psychosis, impulsiveness, aggressiveness, compulsion, excessive sex drive, and personality disorders. Neurobehavioral symptoms such as disinhibition may also be found in other conditions such as traumatic brain injury.

Agitation in patients with Alzheimer's disease may be assessed using the Cohen Mansfield Agitation Inventory or CMAI. The CMAI assesses various behaviors including, Hitting (including self), Kicking, Grabbing onto people, Pushing, Throwing things, Biting, Scratching, Spitting, Hurting self or others, Tearing things or destroying property, Making physical sexual advances, Pacing, aimless wandering, Inappropriate dress or disrobing, Trying to get to a different place, Intentional falling, Eating/drinking inappropriate substances, Handling things inappropriately, Hiding things, Hoarding things, Performing repetitive mannerisms, General restlessness, Screaming, Making verbal sexual advances, Cursing or verbal aggression, Repetitive sentences or questions, Strange noises (weird laughter or crying), Complaining, Negativism, Constant unwarranted request for attention or help.

Schizophrenia may treated by the combination including positive symptoms and/or negative symptoms of schizophrenia, or residual symptoms of schizophrenia. Other conditions that may treated include intermittent explosive disorder.

Cerebral function disorders that may be treated by the subject combination include, but are not limited to, disorders involving intellectual deficits such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, voice spasms, Parkinson's disease, Lennox-Gastaut syndrome, autism, hyperkinetic syndrome, and schizophrenia. Cerebral function disorders also include disorders caused by cerebrovascular diseases including, but not limited to, stroke, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like where symptoms include disturbance of consciousness, senile dementia, coma, lowering of attention, and speech disorders.

Substance addiction abuse that may be treated by the subject combination includes, but is not limited to, drug dependence, addiction to cocaine, psychostimulants (e.g., crack, cocaine, speed, meth), nicotine, alcohol, opioids, anxiolytic and hypnotic drugs, *cannabis* (marijuana), amphetamines, hallucinogens, phencyclidine, volatile solvents, and volatile nitrites. Nicotine addiction includes nicotine addiction of all known forms, such as smoking cigarettes, cigars and/or pipes, e-cigarettes or vaping, and addiction to chewing tobacco.

Movement disorders that may be treated by the subject combination include, but are not limited to, akathisia, akinesia, associated movements, athetosis, ataxia, ballismus, hemiballismus, bradykinesia, cerebral palsy, chorea, Huntington's disease, Huntington's disease chorea, rheumatic chorea, Sydenham's chorea, dyskinesia, tardive dyskinesia, dystonia, blepharospasm, spasmodic torticollis, dopamine-responsive dystonia, Parkinson's disease, restless legs syndrome (RLS), tremor, essential tremor, and Tourette's syndrome, and Wilson's disease.

Dementias that may be treated by the subject combination include, but are not limited to, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, fronto-temporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, Wernicke-Korsakoff Syndrome, and Pick's disease.

Motor neuron diseases that may be treated by the subject combination include, but are not limited to, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, post-polio syndrome (PPS), spinal muscular atrophy (SMA), spinal motor atrophies, Tay-Sach's disease, Sandoff disease, and hereditary spastic paraplegia.

Neurodegenerative diseases that may be treated the subject combination include, but are not limited to, Alzheimer's disease, prion-related diseases, cerebellar ataxia, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), bulbar muscular atrophy, Friedrich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis (MS), multiple system atrophy, Shy-Drager syndrome, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, Menkes disease, adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), muscular dystrophies, Charcot-Marie-Tooth disease (CMT), familial spastic paraparesis, neurofibromatosis, olivopontine cerebellar atrophy or degeneration, striatonigral degeneration, Guillain-Barré syndrome, and spastic paraplesia.

Seizure disorders that may be treated by the subject combination include, but are not limited to, epileptic seizures, nonepileptic seizures, epilepsy, febrile seizures; partial seizures including, but not limited to, simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua; generalized seizures including, but not limited to, generalized tonic-clonic seizures, absence seizures, atonic seizures, myoclonic seizures, juvenile myoclonic seizures, and infantile spasms; and status epilepticus.

Types of headaches that may be treated by the subject combination include, but are not limited to, migraine, tension, and cluster headaches.

Other neurological disorders that may be treated by the subject combination include, Rett Syndrome, autism, tinnitus, disturbances of consciousness disorders, sexual dysfunction, intractable coughing, narcolepsy, cataplexy; voice disorders due to uncontrolled laryngeal muscle spasms, including, but not limited to, abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; diabetic neuropathy, chemotherapy-induced neurotoxicity, such as methotrexate neurotoxicity; incontinence including, but not limited, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

In some embodiments, the subject combination may be used to treat pain, joint pain, pain associated with sickle cell disease, pseudobulbar affect, depression (including treatment resistant depression), disorders related to memory and cognition, schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Rhett's syndrome, seizures, cough (including chronic cough), etc.

In some embodiments, the subject combination may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

In some embodiments, the subject combination may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

In some embodiments, the subject combination is used to treat chronic musculoskeletal pain.

In some embodiments, the subject composition may be administered to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component. Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor, and sensory changes.

In some embodiments, the subject composition may be administered orally to relieve neuropathic pain.

Examples of neuropathic pain include pain due to diabetic peripheral neuropathy or diabetic peripheral neuropathic pain, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, central pain, pain due to multiple sclerosis, etc. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio- or chemotherapy associated neuropathy, etc.

In some embodiments, the subject composition may be administered to relieve fibromyalgia.

The term "treating" or "treatment" includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

A subject combination may be used to treat any disease or condition identified as treatable by the combination of bupropion and dextromethorphan in any of the following U.S. Pat. Nos. 8,569,328, 9,168,234, 9,189,905 9,205,083, 9,238,032, 9,278,095, 9,314,462, 9,370,513, 9,375,429, 9,408,815, 9,421,176, 9,457,023, 9,457,025, 9,474,731, 9,486,450, 9,700,528, 9,700,553, 9,707,191, 9,763,932, 9,861,595, 9,867,819, 9,968,568, 10,058,518, 10,064,857, 10,092,560, 10,092,561, 10,105,327, 10,105,361, 10,251,879, 10,463,634, 10,512,643, 10,548,857, 10,596,167, 10,772,850, 10,780,064, 10,780,066, 10,786,469, 10,799,497, 10,806,710, 10,864,209, 10,874,663, 10,874,664, 10,874,665, 10,881,657, 10,894,046, 10,894,047, 10,898,453, all of which are incorporated by reference herein in their entireties for their disclosure of diseases that may be treated by a combination of bupropion and dextromethorphan, including specific embodiments and combinations described therein.

Example 1

In a study of the subject combination in 7 subjects with moderate (GFR 30-60 mL/min) renal impairment compared to 6 matched controls with normal renal function (matched in gender, age, and weight range to impaired subjects), both

dextromethorphan and bupropion exposures increased by approximately 2-fold and clearances were reduced by 50%.

Example 2

Approximately 7 to 10% of Caucasians and 3 to 8% of African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers. In 3 poor metabolizers the pharmacokinetics of the subject combination resulted in an approximate 3-fold and 3.4-fold increase in dextromethorphan C_{max} and $AUC_{0\text{-}42}$, respectively, compared to extensive metabolizers. An exploration of steady state pharmacokinetic data in 12 poor metabolizers treated with the subject combination in efficacy trials showed plasma concentrations of dextromethorphan that were generally higher than exposures for non-poor metabolizers.

Example 3

Co-administration of the SSRI paroxetine and the subject combination was studied in 29 healthy volunteers. Paroxetine increased the overall exposure of dextromethorphan by 2.5-fold and had no effect on bupropion. The overall exposure of paroxetine was increased by 1.2-fold when co-administered with the subject combination. Based on these results, when the subject combination is prescribed with drugs that inhibit CYP2D6, the subject combination should be dosed once daily. Use caution when administering the subject combination in conjunction with drugs which are extensively metabolized via CYP2D6.

Example 4

The properties of a tablet containing a combination of dextromethorphan hydrobromide, which is an uncompetitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, which is an aminoketone and CYP450 2D6 inhibitor, were studied.

The tablets are for oral administration and are round bilayer tablets. Each tablet contains mg dextromethorphan hydrobromide (equivalent to 32.98 mg of the dextromethorphan free base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg of the bupropion free base) in an extended-release formulation. Each tablet contains the following inactive ingredients: carbomer homopolymer, colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, 1-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and/or yellow iron oxide.

The effects of renal impairment, hepatic impairment, and CYP2D6 poor metabolizer status on the exposure to a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride are summarized in FIG. **1**.

Results depicted in FIG. **1** are based on plasma concentrations in human patients after 8 days of twice daily dosing of a tablet containing 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride. Data are GMRs and 90% CIs. Reference used are the matched healthy subjects for renal and hepatic impairment studies, and extensive or ultra-extensive CYP2D6 metabolizers. AUC represents the area under the plasma concentration-time curve from zero to 12 hours; BUP represents bupropion; CI is confidence interval; C_{max} is maximum plasma

concentration; DM represents dextromethorphan; GMRs represents geometric mean ratios; PK represents pharmacokinetics.

For patients having moderate renal impairment, a 2.21-fold increase in dextromethorphan AUC_{0-12}, a 2.10-fold increase in dextromethorphan C_{max}, a 1.80-fold increase in bupropion AUC_{0-12}, and a 1.87-fold increase in bupropion C_{max} were observed.

Based upon these results, dosage adjustment is recommended in patients known to have moderate renal impairment because these patients have higher dextromethorphan and bupropion concentrations than patients with healthy renal function. The recommended total daily dose for patients known to have moderate renal impairment is about 45 mg of dextromethorphan hydrobromide and about 105 mg of bupropion hydrochloride (e.g. one tablet containing about 45 mg of dextromethorphan hydrobromide and about 105 mg of bupropion hydrochloride for administration once daily, such as in the morning), or an equivalent dose of another form dextromethorphan and/or bupropion.

The invention claimed is:

1. A method of treating major depressive disorder, comprising: selecting a human patient for having: 1) moderate renal impairment and 2) major depressive disorder, wherein the human patient orally receives a maximum of one tablet once daily, wherein the tablet contains about 105 mg of bupropion hydrochloride and about 45 mg of dextromethorphan hydrobromide, wherein the human patient has an estimated glomerular filtration rate that is between 30 mL/min/1.73 m^2 and 59 mL/min/1.73 m^2, wherein the dextromethorphan hydrobromide is in an immediate-release formulation, wherein the bupropion hydrochloride is in an extended-release formulation, and wherein the tablet is a bilayer tablet.

2. The method of claim **1**, wherein the tablet is swallowed whole by the patient.

3. The method of claim **1**, wherein after the human patient has orally received one tablet daily for 8 days, steady state plasma concentrations of dextromethorphan and bupropion in the human patient are achieved, and wherein the accumulation ratio for dextromethorphan at steady state is about based on the C_{max}.

4. The method of claim **1**, wherein after the human patient has orally received one tablet daily for 8 days, steady state plasma concentrations of dextromethorphan and bupropion in the human patient are achieved, and wherein the accumulation ratio for dextromethorphan at steady state is about 32 based on the AUC_{0-12}.

5. The method of claim **1**, wherein the once-daily administration of the tablet avoids the human patient having an about 2.2-fold increase in AUC_{0-12} of dextromethorphan as compared to the AUC_{0-12} of dextromethorphan that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

6. The method of claim **1**, wherein the once-daily administration of the tablet avoids the human patient having an about 2.1-fold increase in C_{max} of dextromethorphan as compared to the C_{max} of dextromethorphan that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

7. The method of claim **1**, wherein the once-daily administration of the tablet avoids the human patient having an about 1.8-fold increase in AUC_{0-12} of bupropion as compared to the AUC_{0-12} of bupropion that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

8. The method of claim **1**, wherein the once-daily administration of the tablet avoids the human patient having an about 1.9-fold increase in C_{max} of bupropion as compared to the C_{max} of bupropion that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

9. The method of claim **1**, wherein the T_{max} of dextromethorphan is about 3 hours.

10. A method of treating major depressive disorder, comprising: selecting a human patient for having: 1) moderate renal impairment and 2) major depressive disorder, wherein the human patient orally receives a maintenance dose of one tablet once daily, wherein the tablet contains about 105 mg of bupropion hydrochloride and about 45 mg of dextromethorphan hydrobromide, wherein the dextromethorphan hydrobromide is in an immediate-release formulation, wherein the bupropion hydrochloride is in an extended-release formulation, and wherein the tablet is a bilayer tablet.

11. The method of claim **10**, wherein the tablet is swallowed whole by the patient.

12. The method of claim **10**, wherein after the human patient has orally received one tablet daily for 8 days, steady state plasma concentrations of dextromethorphan and bupropion are achieved in the human patient, and wherein the accumulation ratio for dextromethorphan at steady state is about 20 based on the C_{max}.

13. The method of claim **10**, wherein after the human patient has orally received one tablet daily for 8 days, steady state plasma concentrations of dextromethorphan and bupropion are achieved in the human patient, and wherein the accumulation ratio for dextromethorphan is about 32 based on the AUC_{0-12}.

14. The method of claim **10**, wherein the once-daily administration of the tablet avoids the human patient having an about 2.2-fold increase in AUC_{0-12} of dextromethorphan as compared to the AUC_{0-12} of dextromethorphan that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

15. The method of claim **10**, wherein the once-daily administration of the tablet avoids the human patient having an about 2.1-fold increase in C_{max} of dextromethorphan as compared to the C_{max} of dextromethorphan that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

16. The method of claim **10**, wherein the once-daily administration of the tablet avoids the human patient having an about 1.8-fold increase in AUC_{0-12} of bupropion as compared to the AUC 012 of bupropion that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

17. The method of claim **10**, wherein the once-daily administration of the tablet avoids the human patient having an about 1.9-fold increase in C_{max} of bupropion as compared to the C_{max} of bupropion that would result from twice daily administration of the tablet for 8 days to a human patient who has no renal impairment.

18. The method of claim **10**, wherein the human patient has an estimated glomerular filtration rate that is between 30 mL/min/1.73 m^2 and 59 mL/min/1.73 m^2.

19. The method of claim **10**, wherein the T_{max} of dextromethorphan is about 3 hours.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,883,373 B1
APPLICATION NO. : 18/333944
DATED : January 30, 2024
INVENTOR(S) : Herriot Tabuteau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

Right above "Related U.S. Application Data" in item (63), add --(65) Prior Publication Data US 2024/0009147 A1 January 11, 2024.--

In the Claims

Column 11, Claim 3, Line 6: add --20-- before "based on"

Column 12, Claim 16, Line 4: replace "AUC 012" with --AUC_{0-12}--

Signed and Sealed this
Nineteenth Day of March, 2024

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

EXHIBIT D

US011896563B2

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,896,563 B2**
(45) **Date of Patent: Feb. 13, 2024**

(54) **BUPROPION AND DEXTROMETHORPHAN FOR REDUCTION OF SUICIDE RISK IN DEPRESSION PATIENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(65) **Prior Publication Data**

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(60) Provisional application No. 63/120,160, filed on Dec. 1, 2020, provisional application No. 63/120,672, filed on Dec. 2, 2020, provisional application No. 63/122,902, filed on Dec. 8, 2020.

(51) **Int. Cl.**

A61K 31/137	(2006.01)
A61P 25/24	(2006.01)
A61K 31/485	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/137*** (2013.01); ***A61K 31/485*** (2013.01); ***A61P 25/24*** (2018.01)

(58) **Field of Classification Search**

CPC A61K 31/137; A61K 31/485; A61P 25/24

See application file for complete search history.

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(Continued)

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(57) **ABSTRACT**

This disclosure relates to a method of treating depression and/or reducing risk of suicide, comprising administering a combination of about 90 mg to about 120 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion, and about 40 mg to about 50 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan. The combination may be administered twice a day to a human being suffering from major depressive disorder and having a score of 3 or greater on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI).

17 Claims, No Drawings

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BUPROPION AND DEXTROMETHORPHAN FOR REDUCTION OF SUICIDE RISK IN DEPRESSION PATIENTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of International Patent Application No. PCT/US2021/061492, filed Dec. 1, 2021; which claims the benefit of U.S. Provisional Application No. 63/120,160, filed Dec. 1, 2020, U.S. Provisional Application No. 63/120,672, filed December 2, 2020, and U.S. Provisional Application No. 63/122,902, filed Dec. 8, 2020; all of which are incorporated by reference herein in their entireties.

SUMMARY

This disclosure relates to a method of treating depression and/or reducing risk of suicide, comprising administering combination of about 90 mg to about 120 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion, and about 40 mg to about 50 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan. The combination may be administered twice a day to a human being suffering from major depressive disorder and having a score of 3 or greater on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI).

DETAILED DESCRIPTION

The combination of dextromethorphan and bupropion may be used to treat depression, such as major depressive disorder and/or reduce the risk of suicide. Patients being treated by this combination may suffer from depression and may have a score of 2 or greater, or 3 or greater on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI).

Dextromethorphan is rapidly metabolized in the human liver. This rapid hepatic metabolism may limit systemic drug exposure in individuals who are extensive metabolizers. Human beings can be: 1) extensive metabolizers of dextromethorphan—those who rapidly metabolize dextromethorphan; 2) poor metabolizers of dextromethorphan—those who only poorly metabolize dextromethorphan; or 3) intermediate metabolizers of dextromethorphan—those whose metabolism of dextromethorphan is somewhere between that of an extensive metabolizer and a poor metabolizer. Extensive metabolizers can also be ultra-rapid metabolizers. Non-poor metabolizers of dextromethorphan include extensive metabolizers of dextromethorphan and intermediate metabolizers of dextromethorphan. Extensive metabolizers of dextromethorphan are a significant portion of the human population. Dextromethorphan can, for example, be metabolized to dextrorphan.

When given the same oral dose of dextromethorphan, plasma levels of dextromethorphan are significantly higher in poor metabolizers or intermediate metabolizers as compared to extensive metabolizers of dextromethorphan. The low plasma concentrations of dextromethorphan can limit its clinical utility as a single agent for extensive metabolizers, and possibly intermediate metabolizers, of dextromethorphan. Bupropion inhibits the metabolism of dextromethorphan, and raises the plasma concentration of dextromethorphan, and can thus improve its therapeutic efficacy.

Similarly, bupropion may allow dextromethorphan to be given less often or in a lower amount, such as once a day instead of twice a day, once a day instead of three times a day, once a day instead of four times a day, twice a day instead of three times a day, or twice a day instead of four times a day, without loss of therapeutic efficacy.

The MADRS is a clinician-rated scale. The MADRS is used to assess depressive symptomatology during the previous week. Subjects are rated on 10 items to assess symptoms: 1) apparent sadness, 2) reported sadness, 3) inner tension, 4) reduced sleep, 5) reduced appetite, 6) concentration difficulties, 7) lassitude, 8) inability to feel, 9) pessimistic thoughts, 10) suicidal thoughts. Each item yields a score of 0 to 6.

The overall score ranges from 0 to 60. A score of 0 indicates the absence of symptoms, and a score of 60 indicates symptoms of maximum severity. A total score ranging from 0 to 6 indicates that the patient is in the normal range (no depression), a score ranging from 7 to 19 indicates "mild depression," 20 to 34 indicates "moderate depression," a score of 35 and greater indicates"severe depression."

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a MADRS score that is at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, about 20-25, about 25-30, about 30-35, about 35-40, about 40-45, about 45-50, about 50-55, about 55-60, about 25-35, about 35-45, about 45-60, about 25-40, or about 40-60.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS score that is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, about 10-20%, about 20-30%, about 30-40%, about 40-50%, about 50-60%, about 60-80%, about 80-90%, or about 90-100% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo. In some embodiments, the reduction is compared to the baseline before treatment.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS score that is less than 34, about 20-34, about 7-19, about 0-6, about 30 or less, about 26 or less, about 25 or less, about 20 or less, about 19 or less, about 17 or less, about 14 or less, about 12 or less, about 10 or less, about 8 or less, about 6 or less, about 5 or less, about 4 or less, about 3 or less, about 2 or less, about 1 or less, about 0, about 7 or less, about 0-6, about 1-2, about 2-3, about 3-4, about 4-5, about 5-6, about 6-7, about 7-8, about 8-9, about 9-10, about 10-11, about 11-12, about 12-13, about 13-14, about 14-15, about 15-16, about 16-17, about 17-18, about 18-19, about 19-20, about 18-20, about 1-3, about 3-6, about 6-9, about 9-12, about 12-14, about 12-15, about 15-19, or about 15-20.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restless-

ness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Some patients, even after treatment with medications such as antidepressants, may have an inadequate or no response to the treatment. Treatment resistant depression (TRD), or treatment-refractory depression, is a condition generally associated with patients who have failed treatment with at least two antidepressants. Part of the diagnosis for TRD is for the patient to have had an inadequate response to treatment with the antidepressants after an adequate dose and adequate course, e.g. in the current depressive episode. TRD may be more difficult to treat due to the comorbidity of other medical or psychological illnesses, such as drug/alcohol abuse or eating disorders, or TRD being misdiagnosed. Some TRD patients have had an inadequate response to 1, 2, 3, or more adequate antidepressant treatment trials or have failed or had an inadequate response to 1, 2, 3, or more prior antidepressant treatments. In some embodiments, a patient being treated for treatment resistant depression has failed treatment with at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more antidepressant therapies. In addition to other depressed patients, the combination of bupropion and dextromethorphan may be effective in treating patients suffering from treatment resistant depression with suicidal ideation.

Patients who may benefit from the treatments described herein include pediatric patients, such as patients under about 18 years of age, about 0-5 years of age, about 5-10 years of age, about 10-12 years of age, or about 12-18 years of age; adult patients, such as patients having an age of about 18-70 years, about 18-65 years, about 18-30 years, about 18-20 years, about 20-30 years, about 30-40 years, about 40-50 years, about 50-60 years, about 60-70 years, about 70-80 years, about 80-90 years, about 30-50 years, about 50-65 years; elderly patients, such as patients over 65 years of age, about 65-75 years of age, about 75-90 years of age, or over 90 years of age; and about 41 years of age or older.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being, of Asian descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being, of Japanese descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being, of Korean descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being, of Chinese descent. The assignment of an individual as having Asian, Chinese, Japanese, or Korean descent may be based upon self-reporting by the individual. In these Asian individuals, the combination of dextromethorphan and bupropion may be effective for treating depression where bupropion alone is not effective for treating depression. This may be of particular importance because patients of Asian descent may suffer from more severe depression than those of other ethnic or cultural groups.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is suffering from, or is selected for suffering from, a major depressive episode that has lasted between about 8 weeks and about 24 months, about 1-6 months, about 6-12 months, about 1-2 years, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 6 weeks, at least 7 weeks, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 9 months, at least about 1 year, at least about 18 months, at least about 2 years, about 1-12 weeks, about 3-6 months, about 6-9 months, about 9-12 months, about 12-18 months, about 18-24 months, about 2-4 years, about 4-6 years, about 6-10 years, about 10-20 years or longer.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected having, about 1-100, or more, lifetime depressive episodes, such as a major depressive episodes, including at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 10, at least 15, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, 1-5, 5-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, or 4-7 lifetime depressive episodes.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, an inadequate response to one or more prior antidepressant therapies, e.g. 1, 2, 3, 4, 5 or more prior antidepressant therapies, including prior antidepressant therapies in the current depressive episode (e.g. the current major depressive episode).

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being male. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is, or is selected for being female.

The combination of bupropion and dextromethorphan is administered once a day or twice a day for at least one week, at least two weeks, at least three weeks, at least four weeks, at least six weeks, at least eight weeks, at least three months, at least four months, at least five months, or at least six months; and/or may be administered for up to four months, up to six months, up to one year, up to two years, or longer. In some embodiments, the combination of bupropion and dextromethorphan is administered twice a day for at least one week, at least two weeks, at least three weeks, at least four weeks, at least six weeks, at least eight weeks, at least three months, at least four months, at least five months, or at least six months; and/or may be administered for up to four months, up to six months, up to one year, up to two years, or longer. In some embodiments, the combination of bupropion and dextromethorphan is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, at least about 50 mg, at least about 70 mg, at least about 90 mg, at least about 100 mg, at least about 110 mg, or at least about 120 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the bupropion is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, up to about 70 mg, up to about 90 mg, up to about 100 mg, up to about 110 mg, up to about 120 mg up to about 130 mg, or up to about 150 mg, of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the bupropion is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, about 0.8×mg to about 1.2×mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion (such as another salt form or the free base form) is administered once or twice a day, wherein x is about 50 mg (e.g. 40-60 mg), about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 120 mg, or about 140 mg. In some embodiments, the bupropion is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, about 50-150 mg, about 90-120 mg, about 100-110 mg, or about 105 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the bupropion is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, at least about 30 mg, at least about 35 mg, at least about 40 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the dextromethorphan is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, up to about 50 mg, up to about 55 mg, up to about 60 mg, or up to about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the dextromethorphan is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, about 0.8×mg to about 1.2×mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan (such as another salt form or the free base form) is administered once a day or twice a day, wherein x is about 30 mg (e.g. 24-36 mg), about 40 mg, about 50 mg, or about 60 mg. In some embodiments, the dextromethorphan is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

In some embodiments, about 30-60 mg, about 40-50 mg, about 44-46 mg, or about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan (such as another salt form or the free base form) is administered once a day or twice a day. In some embodiments, the dextromethorphan is administered once a day for 1, 2, 3, 4, 5, 6, or 7 days, and then administered twice a day thereafter.

Administration of the combination of bupropion and dextromethorphan may improve depression symptoms, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) score. It may also reduce the Suicidality Item of the MADRS (MADRS-SI), such as by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 80%, or up to about 100%, e.g. after the combination is administered daily, such as twice a day, for one week, two weeks, four weeks, six weeks, eight weeks, or twelve weeks, etc.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{max} of dextromethorphan in the human being is increased about 15- to about 25-fold as compared to administration of 60 mg of dextromethorphan hydrobromide without bupropion or as compared to administration of a single dose of the combination of bupropion and dextromethorphan.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{min} of dextromethorphan in the human being is increased about 35- to about 45-fold as compared to administration of 60 mg of dextromethorphan hydrobromide without bupropion or as compared to administration of a single dose of the combination of bupropion and dextromethorphan.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the AUC_{0-12} of dextromethorphan in the human being is increased about 25- to about 45-fold as compared to administration of 60 mg of dextromethorphan hydrobromide without bupropion or as compared to administration of a single dose of the combination of bupropion and dextromethorphan.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{max} of dextromethorphan in the human being is about 75-80 ng/mL.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{min} of dextromethorphan is about 42-50 ng/mL.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the AUC_{0-12} of dextromethorphan in the human being is about 755 ng·hr/mL.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{max} of bupropion in the human being is about 85-90 ng/mL.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the C_{min} of bupropion is about 25-35 ng/mL.

In some embodiments, after eight days of receiving the combination of bupropion and dextromethorphan twice a day, the AUC_{0-12} of bupropion in the human being is about 660-670 ng·hr/mL.

EXAMPLE 1

An open label Phase III clinical trial was conducted using a tablet containing 45 mg dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride with modulated delivery. This tablet was administered twice a day to patients suffering from major depressive disorder. A total of 611 patients participated in the trial, and a total of 597 patients were treated for at least 6 months when the trial was concluded. The mean MADRS score of the total patient population was 32.7 prior to treatment. The results for the total patient population are summarized in Table 1.

TABLE 1

MADRS reduction for all patients after treatment

Timepoint	MADRS Reduction-all patients
Baseline	0
1 week	−10.4
2 weeks	−14.7
6 weeks	−20.6

A total of 37 of these patients suffered from major depressive disorder with suicidal ideation, defined as a score

of ≥3 on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI). For the patients with suicidal ideation, the mean MADRS score was 36.8 and the mean MADRS-SI score was 3.4 prior to treatment. The results for these patients are summarized in Table 2.

TABLE 2

MADRS reduction for suicidal ideation patients after treatment

Timepoint	MADRS Reduction-suicidal ideation patients
Baseline	0
1 week	−12.9
2 weeks	−17.8
6 weeks	−22.8

Additionally, in the patients who suffered from suicidal ideation, the MADRS-SI score was reduced by 67.1% at the end of 1 week of treatment, 73.5% at the end of 2 weeks of treatment, and 82.4% at the end of 4 weeks of treatment as compared with baseline. This is potentially lifesaving because it shows a quick reduction in the risk of suicide.

The invention claimed is:

1. A method of treating depression and reducing risk of suicide, comprising: selecting a human being suffering from major depressive disorder and having a score of 3 or greater on the Suicidality Item of the Montgomery-Åsberg Depression Rating Scale (MADRS-SI), and administering a combination of about 90 mg to about 120 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion, and about 40 mg to about 50 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan, to the human being; wherein the combination is administered twice a day to the human being.

2. The method of claim **1**, wherein the combination comprises about 105 mg of bupropion hydrochloride, or a molar equivalent amount of another form of bupropion, and about 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another form of dextromethorphan.

3. The method of claim **1**, wherein the combination is administered twice a day for at least one week.

4. The method of claim **3**, wherein the combination is administered twice a day for at least two weeks.

5. The method of claim **4**, wherein the combination is administered twice a day for at least six weeks.

6. The method of claim **1**, wherein the MADRS-SI of the human being is reduced by at least 30% after the combination is administered to the human being twice a day for one week.

7. The method of claim **1**, wherein the MADRS-SI of the human being is reduced by at least 50% after the combination is administered to the human being twice a day for two weeks.

8. The method of claim **1**, wherein the MADRS-SI of the human being is reduced by at least 60% after the combination is administered to the human being twice a day for four weeks.

9. The method of claim **1**, wherein after eight days of administration of the combination twice a day, the C_{max} of dextromethorphan in the human being is increased about 15-fold to about 25-fold as compared to a single administration of the combination.

10. The method of claim **1**, wherein after eight days of administering the combination twice a day, the C_{min} of dextromethorphan in the human being is increased about 35-fold to about 45-fold as compared to a single administration of the combination.

11. The method of claim **1**, wherein after eight days of administering the combination twice a day, the AUC_{0-12} of dextromethorphan in the human being is increased about 25-fold to about 45-fold as compared to a single administration of the combination.

12. The method of claim **2**, wherein after eight days of administering the combination twice a day, the C_{max} of dextromethorphan in the human being is about 75 ng/mL to about 80 ng/mL.

13. The method of claim **2**, wherein after eight days of administering the combination twice a day, the C_{min} of dextromethorphan is about 42 ng/mL to about 50 ng/mL.

14. The method of claim **2**, wherein after eight days of administering the combination twice a day, the AUC_{0-12} of dextromethorphan in the human being is about 755 ng·hr/mL.

15. The method of claim **2**, wherein after eight days of administering the combination twice a day, the C_{max} of bupropion in the human being is about 85 ng/mL to about 90 ng/mL.

16. The method of claim **2**, wherein after eight days of administering the combination twice a day, the C_{min} of bupropion is about 25 ng/mL to about 35 ng/mL.

17. The method of claim **2**, wherein after eight days of administering the combination twice a day, the AUC_{0-12} of bupropion in the human being is about 660 ng·hr/mL to about 670 ng·hr/mL.

* * * * *

EXHIBIT E

US011925636B2

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,925,636 B2**
(45) **Date of Patent: *Mar. 12, 2024**

(54) **BUPROPION DOSAGE FORMS WITH REDUCED FOOD AND ALCOHOL DOSING EFFECTS**

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See application file for complete search history.

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(57) **ABSTRACT**

This disclosure relates to dosage forms comprising bupropion hydrochloride, another salt form of bupropion, or the free base form of bupropion; dextromethorphan hydrobromide, another salt form of dextromethorphan, or the free base form of dextromethorphan, and a polymer. In some embodiments, the dosage form has no significant dose dumping of bupropion in the presence of ethanol in vitro. In some embodiments, the dosage form does not have a food effect for bupropion or dextromethorphan when taken with a high-fat meal in human subjects. Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, including treatment-resistant depression, agitation associated with Alzheimer's disease (or agitation associated with dementia of the Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) comprising, administering a dosage form described herein to a human being in need thereof.

22 Claims, No Drawings

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BUPROPION DOSAGE FORMS WITH REDUCED FOOD AND ALCOHOL DOSING EFFECTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 18/157,393, filed Jan. 20, 2023; which claims priority to U.S. Provisional Patent Application No. 63/357,521, filed Jun. 30, 2022, U.S. Provisional Patent Application No. 63/370,590, filed Aug. 5, 2022, and U.S. Provisional Patent Application No. 63/370,771, filed Aug. 8, 2022, all of which are incorporated by reference herein in their entireties.

FIELD

This disclosure relates to dosage forms containing bupropion, optionally in the presence of dextromethorphan, and use of these dosage forms for various therapeutic purposes.

SUMMARY

This disclosure relates to dosage forms comprising bupropion hydrochloride, another salt form of bupropion, or the free base form of bupropion; dextromethorphan hydrobromide, another salt form of dextromethorphan, or the free base form of bupropion, and a polymer. In some embodiments, the dosage form has no significant dose dumping of bupropion in the presence of ethanol in vitro. In some embodiments, the dosage form does not have a food effect for bupropion when taken with a high-fat meal in human subjects. In some embodiments, the dosage form does not have a food effect for dextromethorphan when taken with a high-fat meal in human subjects.

Some embodiments include a dosage form comprising: 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer, wherein the dosage form, in the presence of ethanol in vitro, shows no significant dose dumping of bupropion.

Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, including treatment-resistant depression, agitation associated with Alzheimer's disease (or agitation associated with dementia of the Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) comprising administering, once a day or twice a day, a dosage form to a human patient in need thereof, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer, wherein the dosage form, in the presence ethanol in vitro, shows no significant dose dumping of bupropion.

Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, agitation associated with Alzheimer's disease (or agitation associated with dementia of the

Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) comprising administering, once a day or twice a day, a dosage form to a human patient in need thereof, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer, and wherein the patient consumes alcohol on a day that the dosage form is administered.

Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, agitation associated with Alzheimer's disease (or agitation associated with dementia of the Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) in a human patient who is consuming alcohol, comprising administering, once a day or twice a day, a dosage form to a human patient in need thereof, and limiting but not discontinuing consumption of alcohol by the human patient, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer.

Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, agitation associated with Alzheimer's disease (or agitation associated with dementia of the Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) in a human patient who is consuming alcohol, comprising administering, once a day or twice a day, a dosage form to a human patient in need thereof, and reducing but not discontinuing consumption of alcohol by the human patient, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer.

Some embodiments include a method of treating a nervous system condition (such as depression, e.g., major depressive disorder, agitation associated with Alzheimer's disease (or agitation associated with dementia of the Alzheimer's type), agitation associated with dementia, anxiety (or generalized anxiety disorder), neuropathic pain, or peripheral diabetic neuropathic pain) in a human patient who is consuming alcohol, comprising administering, once a day or twice a day, a dosage form to a human patient in need thereof, and minimizing but not discontinuing consumption of alcohol by the human patient, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer.

Some embodiments include a method of treating major depressive disorder in an adult human patient who is consuming alcohol, comprising administering, once a day or twice a day, a dosage form to a human patient in need

thereof, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer; wherein if the human patient is a male, the human patient is consuming two servings or less of alcohol per day; and if the human patient is a female, the human patient is consuming one serving or less of alcohol per day.

Some embodiments include a method of treating major depressive disorder comprising, administering a dosage form described herein to a human being in need thereof. In some embodiments, the dosage form is taken with an alcoholic beverage. In some embodiments, the dosage form is taken with a high-fat meal.

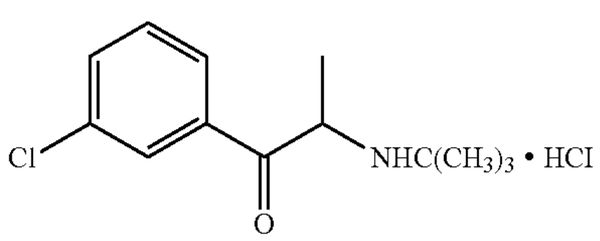
DETAILED DESCRIPTION

Dose dumping is a phenomenon in which relatively a large amount of drug in a controlled release formulation is quickly released and a potentially toxic quantity of the drug is introduced into systemic circulation.

A pharmaceutical composition or dosage form described herein may include, or be prepared from, any suitable form of bupropion, such as a salt form, e.g. bupropion hydrochloride, the free base form, hydrates, solvates, polymorphs, other solid forms, etc. In some embodiments, the pharmaceutical composition is free of any other active pharmaceutical agents.

The pharmaceutical dosage form may include any suitable amount of bupropion, such as about 90-100 mg, about 100-110 mg, about 110-120 mg, about 103-107 mg, or about 105 mg of the bupropion, such as bupropion hydrochloride, a molar equivalent amount of another salt form of bupropion, or the free base form of bupropion.

The chemical name of bupropion hydrochloride is: (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride. Bupropion hydrochloride has the empirical formula $C_{13}H_{18}$ ClNO·HCl and a molecular weight of 276.2 (239.74 bupropion base). The structural formula is:



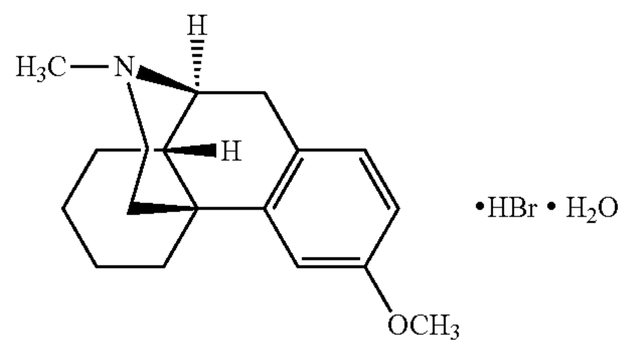
Bupropion hydrochloride powder is white and highly soluble in water.

A pharmaceutical composition or dosage form described herein may include, or be prepared from, any suitable form of dextromethorphan, such as a salt form, e.g. dextromethorphan hydrobromide, the free base form, hydrates, solvates, polymorphs, other solid forms, etc. In some embodiments, the pharmaceutical composition is free of any other active pharmaceutical agents.

The pharmaceutical dosage form may include any suitable amount of dextromethorphan, such as about 30-60 mg, about 30-50 mg, about 30-34 mg, about 34-38 mg, about 38-42 mg, about 42-46 mg, about 46-50 mg, about 40-45 mg, about 45-50 mg, about 44-46 mg, or about 45 mg of the dextromethorphan, such as bupropion hydrochloride, a molar

equivalent amount of another salt form of dextromethorphan, or the free base form of dextromethorphan.

The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula $C_{18}H_{25}NO{\cdot}HBr{\cdot}H_2O$ and a molecular weight of 370.33 (271.4 dextromethorphan base). The structural formula is:



Dextromethorphan hydrobromide powder is white or almost white, crystalline, and sparingly soluble in water.

In some embodiments, the dosage form may contain bupropion and dextromethorphan, and no other active pharmaceutical ingredients. In some embodiments, the bupropion and the dextromethorphan are in two different layers or phases of the dosage form, e.g. each layer contains only bupropion or dextromethorphan and none of the other.

The pharmaceutical composition or dosage form may include cysteine (e.g. L-cysteine), such as about 30-100 mg, or about 50-100 mg of the cysteine, such as L-cysteine hydrochloride, another salt form of L-cysteine, or the neutral or zwitterionic form of L-cysteine. Cysteine in these amounts may be helpful in stabilizing bupropion in the presence of other excipients.

The pharmaceutical composition or dosage form may further comprises a sustained release or controlled release polymer, such as a crosslinked or uncrosslinked acrylate polymer or copolymer (including a poly(acrylic acid) or a poly(alkacrylic acid), such as poly(methacrylic acid), e.g. a carbomer homopolymer Type A such as Carbopol 971P), a cellulose derivative, such as methylcellulose, etc. In some embodiments, the controlled release polymer (e.g. a carbomer copolymer Type A) is about 1-40%, about 1-5%, about 5-10%, about 10-15%, about 15-20%, about about 30-40%, about 11-13%, or about 12% of the weight of the pharmaceutical composition. In some embodiments, the controlled release polymer is about 0.1-20%, about 0.1-2%, about 2-4%, about 4-6%, about 6-8%, about 8-10%, about 10-15%, about 15-20%, or about 7% of the weight of the dosage form.

The pharmaceutical composition or dosage form may further comprise a filler such as microcrystalline cellulose. In some embodiments, the filler may be about 20-60%, about 20-30%, about 30-40%, about 40-50%, or about 50-60% of the weight of the pharmaceutical composition or the dosage form.

The pharmaceutical composition or dosage form may further comprise a lubricant such as magnesium stearate. In some embodiments, the lubricant is about 0.1-10%, about 0.1-2%, about 2-4%, about 4-6%, about 6-8%, or about 8-10% of the weight of the pharmaceutical composition or the dosage form.

The dosage form may be formulated for any suitable route of administration, such as oral administration.

Dosage forms, such as solid dosage forms, e.g. capsules, tablets, or pills, for oral administration may also contain one

or more of the following: a binder such as gum tragacanth, acacia, corn starch, or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a sweetening agent such as sucrose, lactose, or saccharin; or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as a coating, for example, tablets, pills, or capsules may be coated with shellac, sugar, or both. It may be desirable for material in a dosage form or pharmaceutical composition to be pharmaceutically pure and nontoxic in the amounts employed.

In some embodiments, the dosage form contains cysteine, Carbopol 971P, microcrystalline cellulose, silicon dioxide, and magnesium. In some embodiments, the dosage form contains a first layer comprising bupropion and cysteine, and a second layer comprising dextromethorphan, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

An example of a single layer dosage form is show below:

Layer 1

Ingredient	Amount (mg)
Bupropion	90-120
Cysteine	30-100
Carbopol 971P	20-60
Microcrystalline Cellulose	200-300
Colloidal Silicon Dioxide	1-10
Magnesium Stearate	1-10

A two layer dosage form may contain a first layer with the composition shown above (Layer 1), and a second layer detailed below (Layer 2).

Layer 2

Ingredient	Amount (mg)
Dextromethorphan	30-60
Microcrystalline Cellulose	100-150
Croscarmellose sodium	1-20
Magnesium Stearate	1-10

In some embodiments, the dosage form may be for oral administration and may be a round bilayer tablet. Each tablet may contain 45 mg dextromethorphan hydrobromide (equivalent to 32.98 mg dextromethorphan base) in an immediate-release formulation and 105 mg bupropion hydrochloride (equivalent to 91.14 mg bupropion base) in an extended-release formulation. Each tablet may further contain any, or all, of the following inactive ingredients: carbomer homopolymer, colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, I-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and/or yellow iron oxide. The pharmaceutical compositions or dosage forms described herein may be useful in treating neurological disorders or psychiatric conditions, such as depression, including major depressive disorder or treatment-resistant major depressive disorder, agitation, such as agitation associated with Alzheimer's disease, addiction, such as nicotine addiction, etc. For example, the pharmaceutical composition of dosage form may be administered once or twice a day to a human being suffering from a neurological disorder or psychiatric condition. Treatment may be continued as needed while the treatment is effective and safe, e.g. for at least 1 week, at least 4 weeks, at least one month, at least 2 months, at least 3 months, at least 6 months, at least 1 year, 1 week to 2 months, 1-3 months, 3-6 months, 6-12 months, 1-2 years, or possibly longer.

Due to US Food and Drug Administration (FDA) concern of dose dumping of bupropion hydrochloride when taken with ethanol, the FDA currently requests that dissolution testing on dosage forms containing bupropion be conducted using various concentrations of ethanol in the dissolution medium, as follows:

- Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) at 50 rpm, with or without ethanol;
- Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours;
- Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP (ethanol) and data collection every 15 minutes for a total of 2 hours;
- Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP (ethanol) and data collection every 15 minutes for a total of 2 hours; and
- Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP (ethanol) and data collection every 15 minutes for a total of 2 hours.

According to the FDA, both test and reference products must be tested accordingly and data must be provided on individual unit, means, range and % CV on both strengths. (FDA Draft Guidance on Bupropion Hydrochloride, p. 2.)

Literature Examples

According to FDA documents the bupropion product Forfivo XL was tested for ethanol dose dumping. (Center for Drug Evaluation and Research, Application No. 022497Orig1s000), CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S) ("Forfivo Resubmission"), p. 17.) The Forfivo Resubmission discloses that Forfivo contains bupropion hydrochloride, hydroxypropyl cellulose, hydrochloric acid, polyethylene oxide, stearic acid, colloidal silicon dioxide, magnesium stearate, methacrylic acid copolymer, talc, polyethylene glycol (PEG) 8000, titanium oxide (TiO_2), and carboxymethylcellulose sodium (NaCMC). (Forfivo Resubmission, p. The Forfivo Resubmission further reports that experiment described above was conducted for BUP 450 XL tablets. According to the Forfivo Resubmission, "[f]or 2 hours, no dissolved bupropion HCl from BUP 450 XL tablets was seen at 0% of alcohol. In the presence of 20% of alcohol, 7% of dissolved bupropion HCl from BUP 450 XL tablets was observed in two hours. In the presence of 40% of alcohol, 22% (range of 16-25%) of dissolved bupropion HCl from BUP 450 XL tablets was seen in two hours. The drug product is showing dose dumping with alcohol in vitro." (p. 17)

According to the CONTRAVE label, when a dosage form containing 8 mg of naltrexone HCl, 90 mg of bupropion HCl, microcrystalline cellulose, hydroxypropyl cellulose, lactose anhydrous, L-cysteine hydrochloride, crospovidone, magnesium stearate, hypromellose, edetate disodium, lactose monohydrate, colloidal silicon dioxide, Opadry II Blue, and FD&C Blue #2 aluminum lake was administered with a high-fat meal, the AUC and C_{max} for naltrexone increased 2.1-fold and 3.7-fold, respectively, and the AUC and C_{max} for bupropion increased 1.4-fold and 1.8-fold, respectively. At steady state, the food effect increased AUC and C_{max} for

naltrexone by 1.7-fold and 1.9-fold, respectively, and increased AUC and C_{max} for bupropion by 1.1-fold and 1.3-fold, respectively. Thus, the label indicates that CONTRAVE should not be taken with high-fat meals because of the resulting significant increases in bupropion and naltrexone systemic exposure.

The subject combination may be used for adjunctive treatment of major depressive disorder or depression.

In addition to major depressive disorder, the subject combination may be used to treat other diseases in conditions in the patient populations or circumstances described herein. For example, the subject combination may be used to treat pain or a neurological disorder. Examples of neurological disorders that may be treated with the subject combination include, but are not limited to: affective disorders, psychiatric disorders, cerebral function disorders, movement disorders, dementias, motor neuron diseases, neurodegenerative diseases, seizure disorders, and headaches.

Affective disorders that may be treated by the subject combination include, but are not limited to, depression, major depression, treatment resistant depression, treatment resistant bipolar depression, bipolar disorders including cyclothymia, seasonal affective disorder, mood disorders, chronic depression (dysthymia), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, atypical depression, mania, anxiety disorders, attention deficit disorder (ADD), attention deficit disorder with hyperactivity (ADDH), and attention deficit/hyperactivity disorder (AD/HD), bipolar and manic conditions, obsessive-compulsive disorder, bulimia, obesity or weight-gain, narcolepsy, chronic fatigue syndrome, premenstrual syndrome, substance addiction or abuse, nicotine addiction, psycho-sexual dysfunction, pseudobulbar affect, and emotional lability.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts, or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restlessness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Psychiatric disorders that may be treated by the subject combination, include, but are not limited to, anxiety disorders, including but not limited to, phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD); mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, somatoform disorders, personality disorders, psychosis, schizophrenia, delusional disorder, schizoaffective disorder, schizotypy, aggression, aggression in Alzheimer's disease, agitation, and agitation in Alzheimer's disease. Alzheimer's disease may also be referred to as dementia of the Alzheimer's type. Other neurobehavioral symptoms of Alzheimer's disease that may be treated include disinhibition and apathy.

Agitation in Alzheimer's disease occurs as the disease progresses. Agitation may present itself as inappropriate verbal, emotional, and/or physical behaviors. Inappropriate behaviors may include, but are not limited to, incoherent babbling, inappropriate emotional response, demands for attention, threats, irritability, frustration, screaming, repetitive questions, mood swings, cursing, abusive language, physical outbursts, emotional distress, restlessness, shredding, sleeping disturbances, delusions, hallucinations, pacing, wandering, searching, rummaging, repetitive body motions, hoarding, shadowing, hitting, scratching, biting, combativeness, hyperactivity, and/or kicking.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Managing agitation is a priority in AD. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality. There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Neurobehavioral symptoms have been known to appear during dementia and may be treated by the combination. Caregivers or families may feel more overwhelmed by patients' behavioral/psychological symptoms than by their cognitive impairment. Common forms of the syndrome are Alzheimer's disease, vascular dementia, dementia with Lewy bodies (abnormal aggregates of protein that develop inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). The symptoms that dementia patients have are similar to those of psychiatric disorders, but some are slightly different from each other. Neurobehavioral symptoms associated with dementia include depression, apathy, agitation, disinhibition, hallucinations, delusions, psychosis, impulsiveness, aggressiveness, compulsion, excessive sex drive, and personality disorders. Neurobehavioral symptoms such as disinhibition may also be found in other conditions such as traumatic brain injury.

Agitation in patients with Alzheimer's disease may be assessed using the Cohen Mansfield Agitation Inventory or CMAI. The CMAI assesses various behaviors including, Hitting (including self), Kicking, Grabbing onto people, Pushing, Throwing things, Biting, Scratching, Spitting, Hurting self or others, Tearing things or destroying property, Making physical sexual advances, Pacing, aimless wandering, Inappropriate dress or disrobing, Trying to get to a different place, Intentional falling, Eating/drinking inappropriate substances, Handling things inappropriately, Hiding things, Hoarding things, Performing repetitive mannerisms, General restlessness, Screaming, Making verbal sexual advances, Cursing or verbal aggression, Repetitive sentences or questions, Strange noises (weird laughter or crying), Complaining, Negativism, Constant unwarranted request for attention or help.

Schizophrenia may treated by the combination including positive symptoms and/or negative symptoms of schizophrenia, or residual symptoms of schizophrenia. Other conditions that may treated include intermittent explosive disorder.

Cerebral function disorders that may be treated by the subject combination include, but are not limited to, disorders involving intellectual deficits such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, voice spasms, Parkinson's disease, Lennox-Gastaut syndrome, autism, hyperkinetic syndrome, and schizophrenia. Cerebral function dis-

orders also include disorders caused by cerebrovascular diseases including, but not limited to, stroke, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like where symptoms include disturbance of consciousness, senile dementia, coma, lowering of attention, and speech disorders.

Substance addiction abuse that may be treated by the subject combination includes, but is not limited to, drug dependence, addiction to cocaine, psychostimulants (e.g., crack, cocaine, speed, meth), nicotine, alcohol, opioids, anxiolytic and hypnotic drugs, *cannabis* (marijuana), amphetamines, hallucinogens, phencyclidine, volatile solvents, and volatile nitrites. Nicotine addiction includes nicotine addiction of all known forms, such as smoking cigarettes, cigars and/or pipes, e-cigarettes or vaping, and addiction to chewing tobacco.

Movement disorders that may be treated by the subject combination include, but are not limited to, akathisia, akinesia, associated movements, athetosis, ataxia, ballismus, hemiballismus, bradykinesia, cerebral palsy, chorea, Huntington's disease, Huntington's disease chorea, rheumatic chorea, Sydenham's chorea, dyskinesia, tardive dyskinesia, dystonia, blepharospasm, spasmodic torticollis, dopamine-responsive dystonia, Parkinson's disease, restless legs syndrome (RLS), tremor, essential tremor, and Tourette's syndrome, and Wilson's disease.

Dementias that may be treated by the subject combination include, but are not limited to, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, fronto-temporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, Wernicke-Korsakoff Syndrome, and Pick's disease.

Motor neuron diseases that may be treated by the subject combination include, but are not limited to, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, post-polio syndrome (PPS), spinal muscular atrophy (SMA), spinal motor atrophies, Tay-Sachs disease, Sandhoff disease, and hereditary spastic paraplegia.

Neurodegenerative diseases that may be treated the subject combination include, but are not limited to, Alzheimer's disease, prion-related diseases, cerebellar ataxia, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), bulbar muscular atrophy, Friedrich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis (MS), multiple system atrophy, Shy-Drager syndrome, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, Menkes disease, adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), muscular dystrophies, Charcot-Marie-Tooth disease (CMT), familial spastic paraparesis, neurofibromatosis, olivopontine cerebellar atrophy or degeneration, striatonigral degeneration, Guillain-Barré syndrome, and spastic paraplegia.

Seizure disorders that may be treated by the subject combination include, but are not limited to, epileptic seizures, nonepileptic seizures, epilepsy, febrile seizures; partial seizures including, but not limited to, simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua; generalized seizures including, but not limited to, generalized tonic-clonic seizures, absence seizures, atonic seizures, myoclonic seizures, juvenile myoclonic seizures, and infantile spasms; and status epilepticus.

Types of headaches that may be treated by the subject combination include, but are not limited to, migraine, tension, and cluster headaches.

Other neurological disorders that may be treated by the subject combination include, Rett Syndrome, autism, tinnitus, disturbances of consciousness disorders, sexual dysfunction, intractable coughing, narcolepsy, cataplexy; voice disorders due to uncontrolled laryngeal muscle spasms, including, but not limited to, abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; diabetic neuropathy, chemotherapy-induced neurotoxicity, such as methotrexate neurotoxicity; incontinence including, but not limited, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

In some embodiments, the subject combination may be used to treat pain, joint pain, pain associated with sickle cell disease, pseudobulbar affect, depression (including treatment resistant depression), disorders related to memory and cognition, schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Rhett's syndrome, seizures, cough (including chronic cough), etc.

In some embodiments, the subject combination may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

In some embodiments, the subject combination may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

In some embodiments, the subject combination is used to treat chronic musculoskeletal pain.

In some embodiments, the subject composition may be administered to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component. Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor, and sensory changes.

In some embodiments, the subject composition may be administered orally to relieve neuropathic pain.

Examples of neuropathic pain include pain due to diabetic peripheral neuropathy or diabetic peripheral neuropathic pain, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, central pain, pain due to multiple sclerosis, etc. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio- or chemotherapy associated neuropathy, etc.

In some embodiments, the subject composition may be administered to relieve fibromyalgia.

The term "treating" or "treatment" includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

A subject combination may be used to treat any disease or condition identified as treatable by the combination of bupropion and dextromethorphan in any of the following U.S. Pat. Nos. 8,569,328, 9,168,234, 9,189,905 9,205,083, 9,238,032, 9,278,095, 9,314,462, 9,370,513, 9,375,429, 9,408,815, 9,421,176, 9,457,023, 9,457,025, 9,474,731, 9,486,450, 9,700,528, 9,700,553, 9,707,191, 9,763,932, 9,861,595, 9,867,819, 9,968,568, 10,058,518, 10,064,857, 10,092,560, 10,092,561, 10,105,327, 10,105,361, 10,251,879, 10,463,634, 10,548,857, 10,596,167, 10,772,850, 10,780,064, 10,780,066, 10,786,469, 10,799,497, 10,806,710, 10,864,209, 10,874,663, 10,874,664, 10,874,665, 10,881,657, 10,894,046, 10,894,047, 10,898,453, all of which are incorporated by reference herein in their entireties for their disclosure of diseases that may be treated by a combination of bupropion and dextromethorphan, including specific embodiments and combinations described therein.

As illustrated in the examples below, the subject combination has no dose dumping of bupropion in the presence of ethanol in vitro. As a result, patients may use alcohol as long as the use is minimized or limited. For example, an adult female may consume one serving of alcohol or less per day (such as one serving per day, 4 servings per week or less, 3 servings per week or less, 1 serving per week or less, 1 serving per month or less, 1 serving per year or less, etc.) or an adult male may consume two servings of alcohol or less per day (such as two servings per day, one serving per day, 4 servings per week or less, 3 servings per week or less, 1 serving per week or less, 1 serving per month or less, 1 serving per year or less, etc.).

Example 1

A two-layer dosage form having Layer 1 and Layer 2 as described above, was tested for ethanol dose dumping as described above. No dose dumping of bupropion in the presence of ethanol in vitro was observed.

Example 2

A two-layer dosage form having Layer 1 and Layer 2 as described above, was tested for a food effect by administering the dosage form with a high-fat meal to human subjects, and comparing the AUC and C_{max} to that obtained when administered to fasted human subjects. No significant difference between the two groups was observed in either the AUC or the C_{max} of bupropion or dextromethorphan.

U.S. Provisional Patent Application No. 63/370,771, filed Aug. 8, 2022, is incorporated by reference herein in its entirety.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as amounts, percentage, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

Use of the term "comprising" or "comprises" herein also contemplates that use of "consisting essentially of," "consists essentially of," "consisting of," or "consists of" in its place.

Affirmative recitation of an element anywhere herein should be understood to contemplate both including and excluding that element.

The terms "a," "an," "the" and similar referents used in the context of describing the embodiments (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claims.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from a group, for reasons of convenience and/or to expedite prosecution. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups if used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the claimed embodiments. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the claimed embodiments to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

The invention claimed is:

1. A method of treating major depressive disorder in a human patient who is consuming alcohol, comprising administering, twice a day, a dosage form to a human patient in need thereof, and reducing but not discontinuing consumption of alcohol by the human patient, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of

dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer.

2. The method of claim **1**, wherein the human patient is an adult male, and the human patient consumes two servings or less of alcohol per day.

3. The method of claim **1**, wherein the human patient is an adult female, and the human patient consumes one serving or less of alcohol per day.

4. The method of claim **1**, wherein the dosage form further comprises: colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, L-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, or yellow iron oxide, or a combination thereof.

5. The method of claim **1**, wherein the polymer is a carbomer homopolymer.

6. A method of treating major depressive disorder in a human patient who is consuming alcohol, comprising administering, twice a day, a dosage form to a human patient in need thereof, and minimizing but not discontinuing consumption of alcohol by the human patient, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer.

7. The method of claim **6**, wherein the dosage form further comprises: colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, L-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, or yellow iron oxide, or a combination thereof.

8. The method of claim **6**, wherein the human patient is an adult male, and the human patient consumes two servings or less of alcohol per day.

9. The method of claim **6**, wherein the human patient is an adult female, and the human patient consumes one serving or less of alcohol per day.

10. The method of claim **6**, wherein the polymer is a carbomer homopolymer.

11. A method of treating major depressive disorder in an adult human patient who is consuming alcohol, comprising administering, twice a day, a dosage form to a human patient in need thereof, wherein the dosage form comprises 105 mg of bupropion hydrochloride, or a molar equivalent amount of another salt form of bupropion or the free base form of bupropion, mg of dextromethorphan hydrobromide, or a molar equivalent amount of another salt form of dextromethorphan or the free base form of dextromethorphan, and a polymer,

wherein if the human patient is a male, the human patient is consuming two servings or less of alcohol per day; and

if the human patient is a female, the human patient is consuming one serving or less of alcohol per day.

12. The method of claim **11**, wherein the dosage form further comprises colloidal silicon dioxide.

13. The method of claim **11**, wherein the dosage form further comprises crospovidone.

14. The method of claim **11**, wherein the dosage form further comprises glyceryl monocaprylocaprate.

15. The method of claim **11**, wherein the dosage form further comprises L-cysteine hydrochloride monohydrate.

16. The method of claim **11**, wherein the dosage form further comprises magnesium stearate.

17. The method of claim **11**, wherein the dosage form further comprises microcrystalline cellulose.

18. The method of claim **11**, wherein the dosage form further comprises polyvinyl alcohol.

19. The method of claim **11**, wherein the dosage form further comprises sodium lauryl sulfate.

20. The method of claim **11**, wherein the dosage form further comprises stearic acid.

21. The method of claim **11**, wherein the dosage form further comprises titanium dioxide.

22. The method of claim **11**, wherein the polymer is a carbomer homopolymer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 11,925,636 B2
APPLICATION NO. : 18/353323
DATED : March 12, 2024
INVENTOR(S) : Herriot Tabuteau

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 14, Line 9: Claim 11, after “bupropion,” add --45--

Signed and Sealed this
Ninth Day of April, 2024

Katherine Kelly Vidal

Katherine Kelly Vidal
Director of the United States Patent and Trademark Office

EXHIBIT F

US011969421B2

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,969,421 B2**
(45) **Date of Patent: *Apr. 30, 2024**

(54) **BUPROPION AS A MODULATOR OF DRUG ACTIVITY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **17/841,274**

(22) Filed: **Jun. 15, 2022**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 17/468,149, filed on Sep. 7, 2021, now Pat. No. 11,364,233, which is a continuation-in-part of application No. 17/194,739, filed on Mar. 8, 2021, now Pat. No. 11,478,808, which is a continuation-in-part of application No. 17/068,309, filed on Oct. 12, 2020, now Pat. No. 10,980,800, which is a continuation-in-part of application No. 16/822,697, filed on Mar. 18, 2020, now Pat. No. 11,090,300, and a continuation-in-part of application No. 16/817,119, filed on Mar. 12, 2020, now Pat. No. 10,813,924, said application No. 16/822,697 is a continuation-in-part of application No. 16/359,958, filed on Mar. 20, 2019, now Pat. No. 10,881,657, said application No. 16/817,119 is a continuation-in-part of application No. 16/359,996, filed on Mar. 20, 2019, now Pat. No. 10,688,066, said application No. 16/559,958 is a continuation-in-part of application No. 15/821,563, filed on Nov. 22, 2017, now Pat. No. 10,512,643, which is a continuation-in-part of application No. 15/645,939, filed on Jul. 10, 2017, now Pat. No. 9,867,819, which is a continuation-in-part of application No. 15/263,138, filed on Sep. 12, 2016, now Pat. No. 9,700,553, which is a continuation of application No. 15/164,746, filed on May 25, 2016, now Pat. No. 9,457,023, which is a continuation-in-part of application No. 14/879,002, filed on Oct. 8, 2015, now Pat. No. 9,375,429, which is a continuation of application No. 14/554,988, filed on Nov. 26, 2014, now Pat. No. 9,205,083, which is a continuation of application No. 14/550,618, filed on Nov. 21, 2014, now Pat. No. 9,198,905, which is a continuation-in-part of application No. PCT/US2014/064184, filed on Nov. 5, 2014.

(60) Provisional application No. 63/224,323, filed on Jul. 21, 2021, provisional application No. 62/645,751, filed on Mar. 20, 2018, provisional application No. 62/576,538, filed on Oct. 24, 2017, provisional application No. 61/900,354, filed on Nov. 5, 2013.

(51) **Int. Cl.**

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A61K 31/137	(2006.01)
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A61K 31/165	(2006.01)
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A61K 31/381	(2006.01)
A61K 31/485	(2006.01)

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CPC ***A61K 31/485*** (2013.01); ***A61K 9/0053*** (2013.01); ***A61K 31/135*** (2013.01); ***A61K 31/137*** (2013.01); ***A61K 31/15*** (2013.01); ***A61K 31/343*** (2013.01); ***A61K 31/381*** (2013.01)

(58) **Field of Classification Search**

CPC A61K 31/439; A61K 31/165
USPC 514/281, 617
See application file for complete search history.

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(Continued)

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(57) **ABSTRACT**

Disclosed herein are methods of treating neurological or psychiatric diseases or disorders using a combination of bupropion and dextromethorphan. Related compositions and dosage forms are also described.

29 Claims, 16 Drawing Sheets

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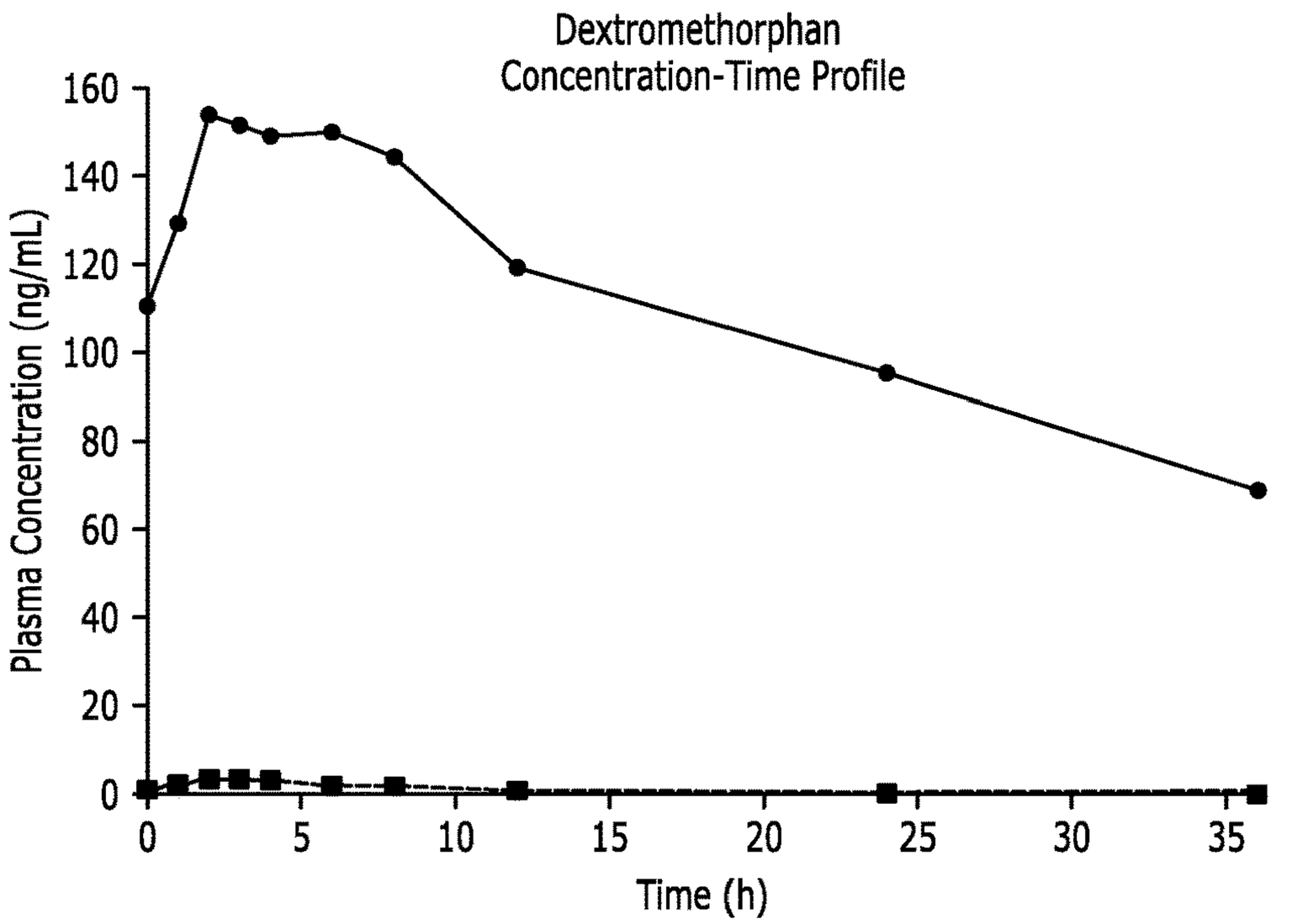

Dextromethorphan
Concentration-Time Profile
Plasma Concentration (ng/mL)
160
140
120
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Time (h)
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 1

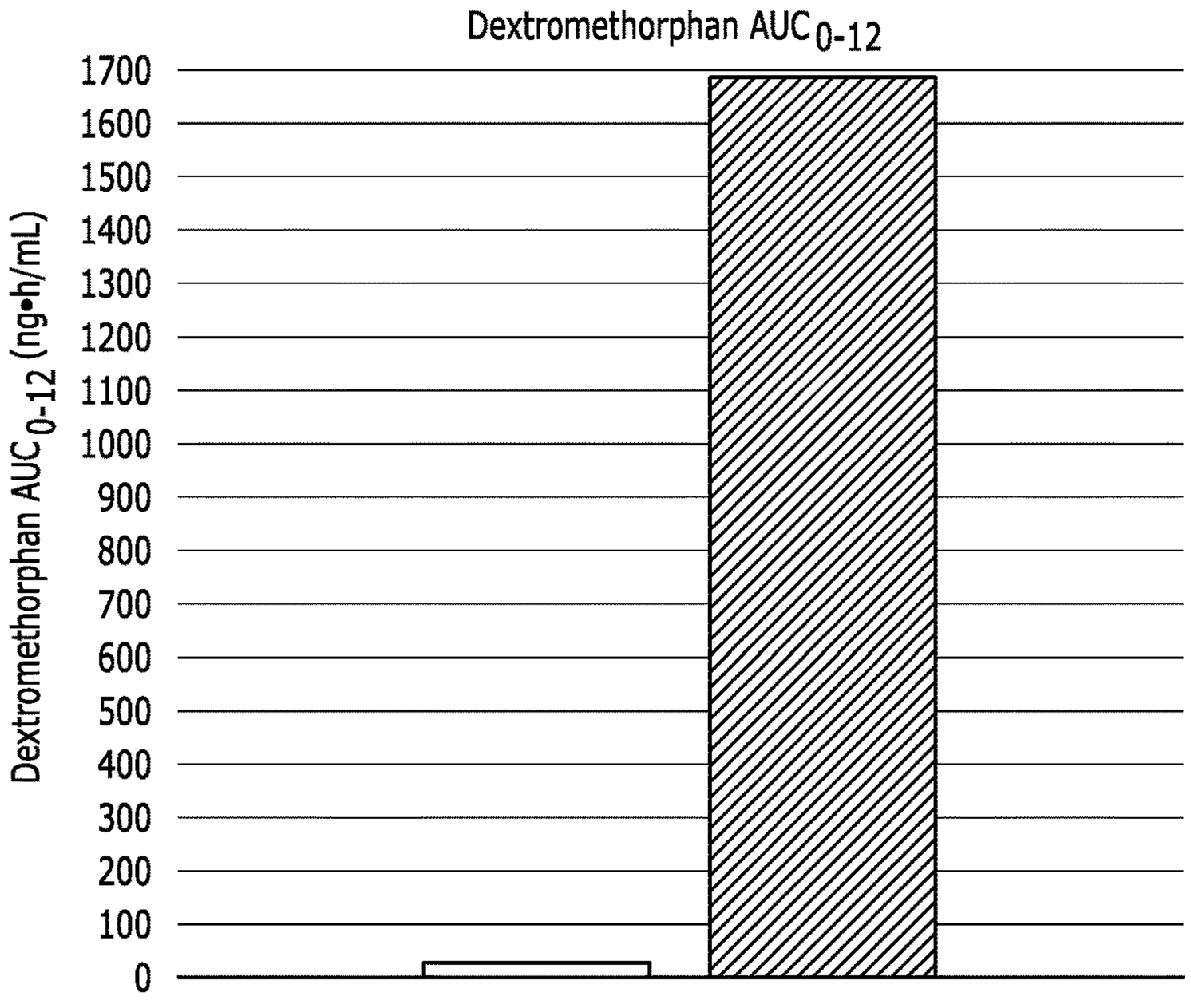

Dextromethorphan AUC0-12
Dextromethorphan AUC0-12 (ng•h/mL)
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 2

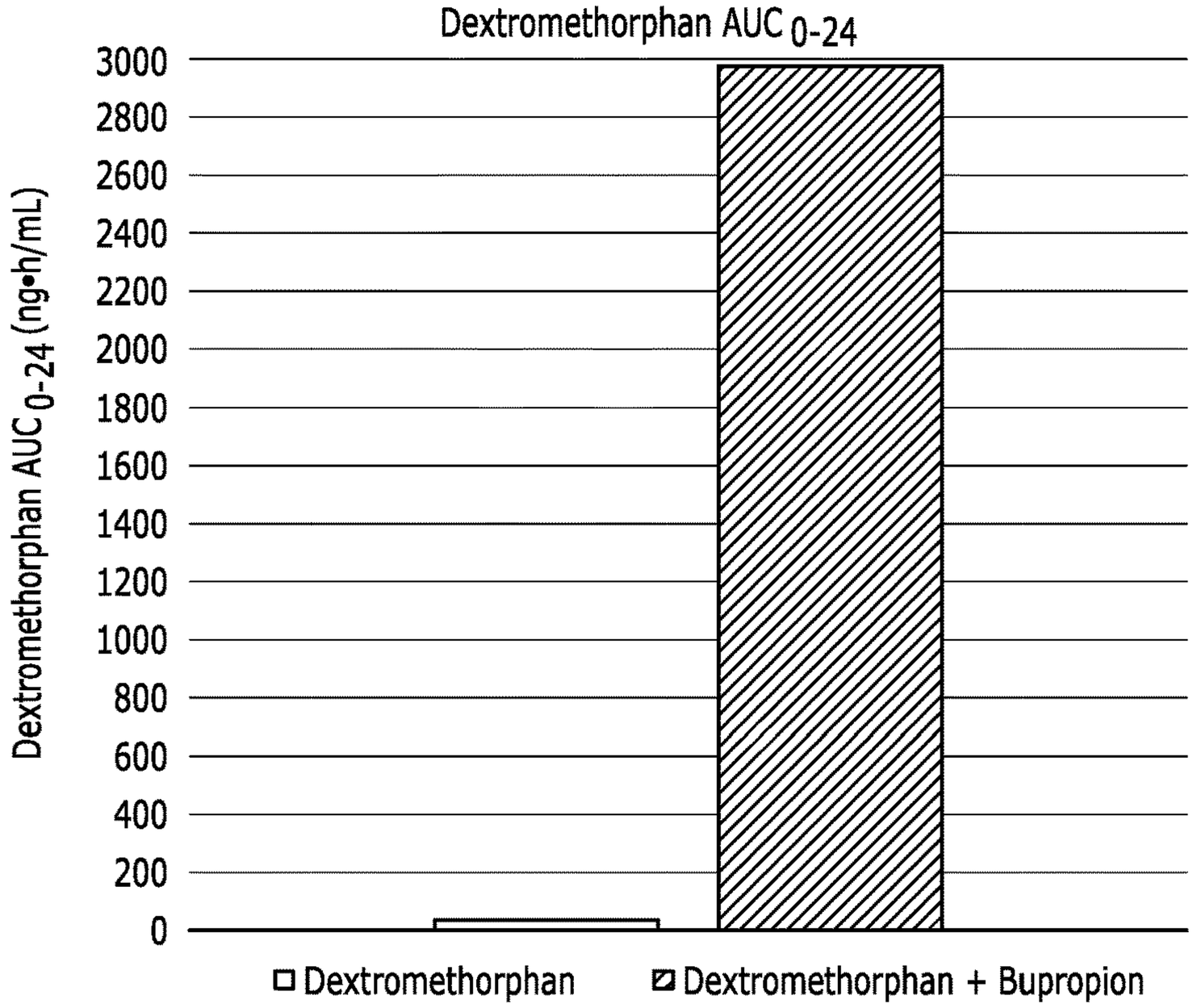

Dextromethorphan AUC 0-24
Dextromethorphan AUC 0-24 (ng•h/mL)
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 3

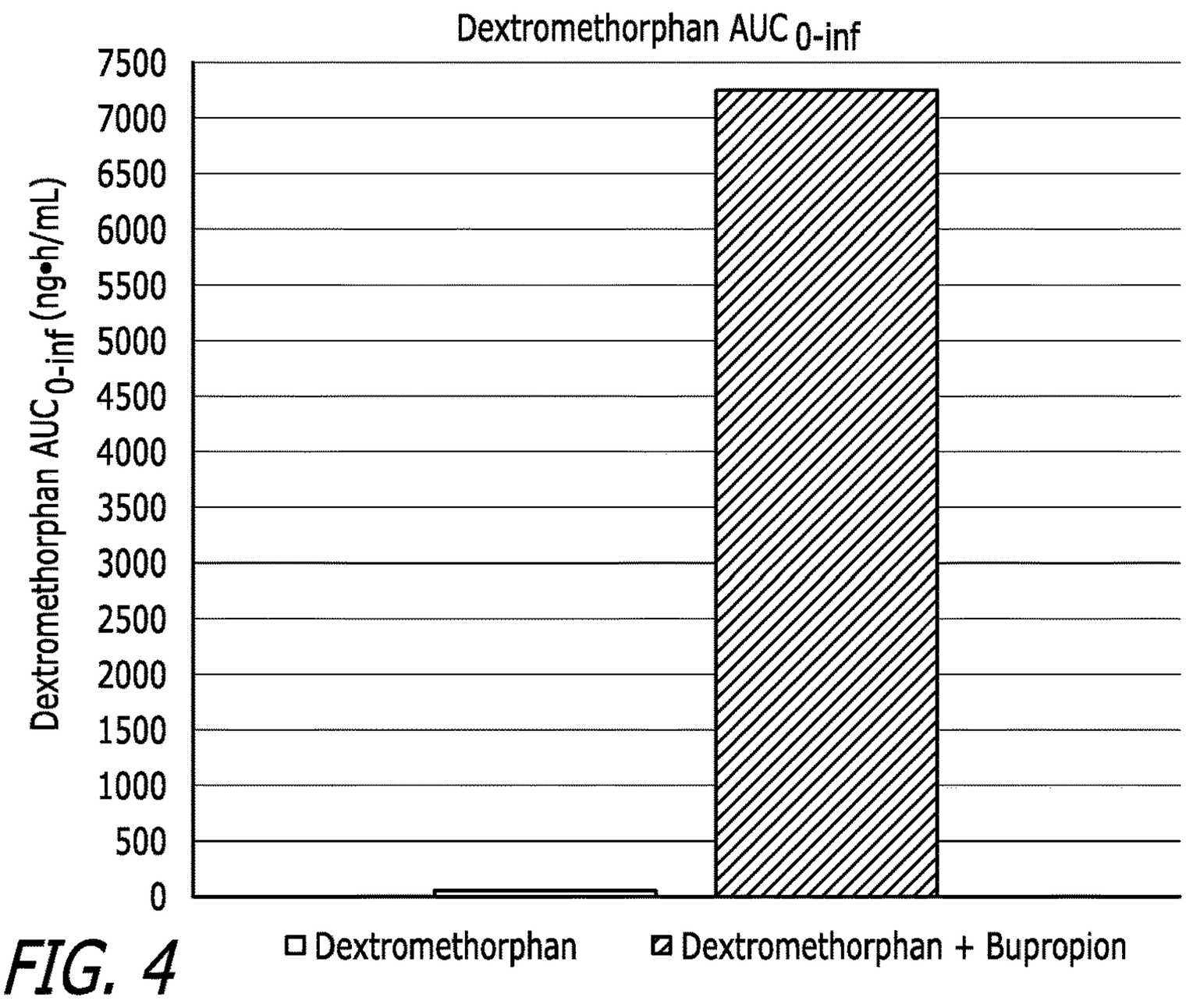

Dextromethorphan AUC 0-inf
Dextromethorphan AUC0-inf (ng•h/mL)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 4

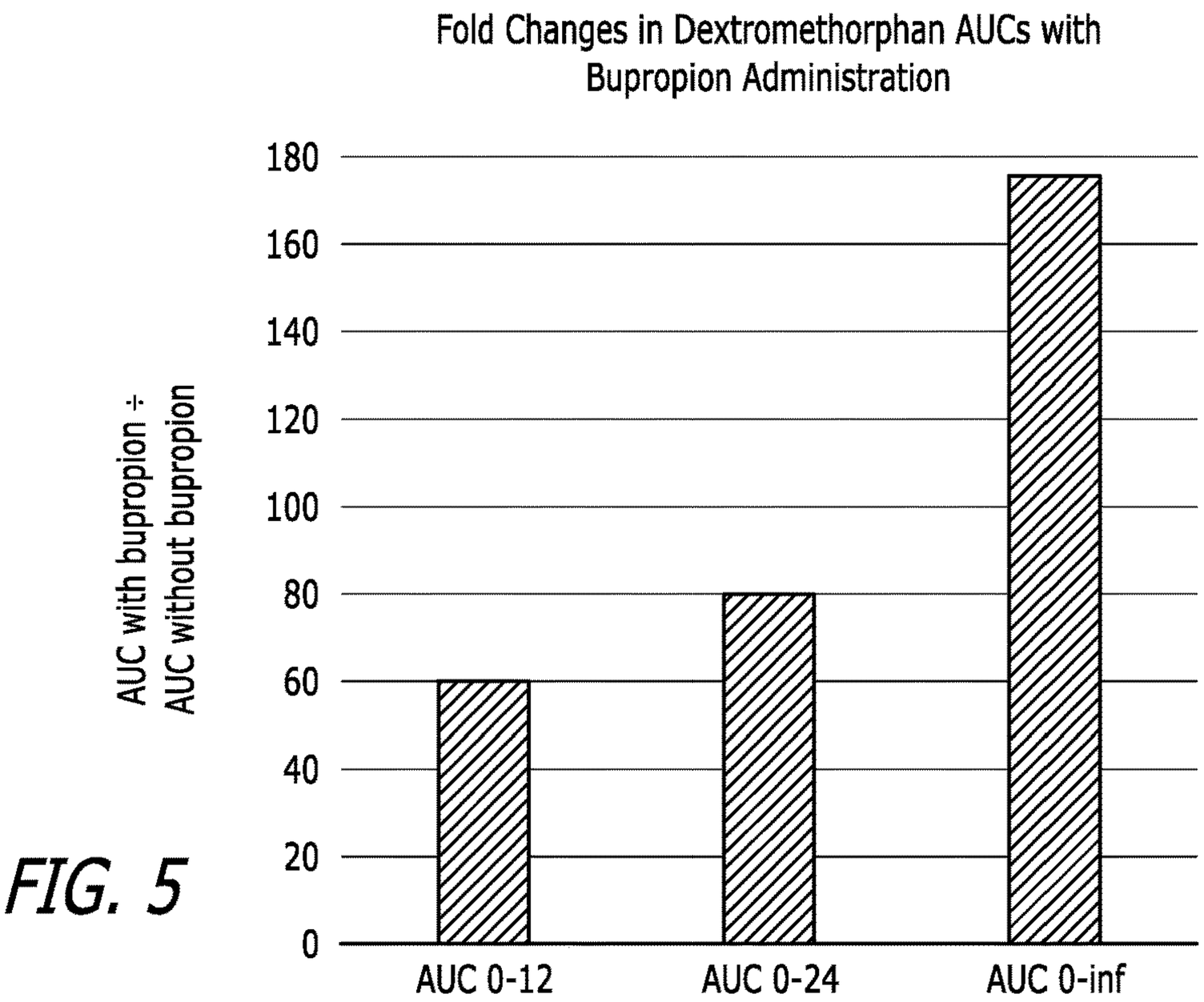

Fold Changes in Dextromethorphan AUCs with Bupropion Administration
AUC with bupropion ÷ AUC without bupropion
180
160
140
120
100
80
60
40
20
0
AUC 0-12
AUC 0-24
AUC 0-inf

FIG. 5

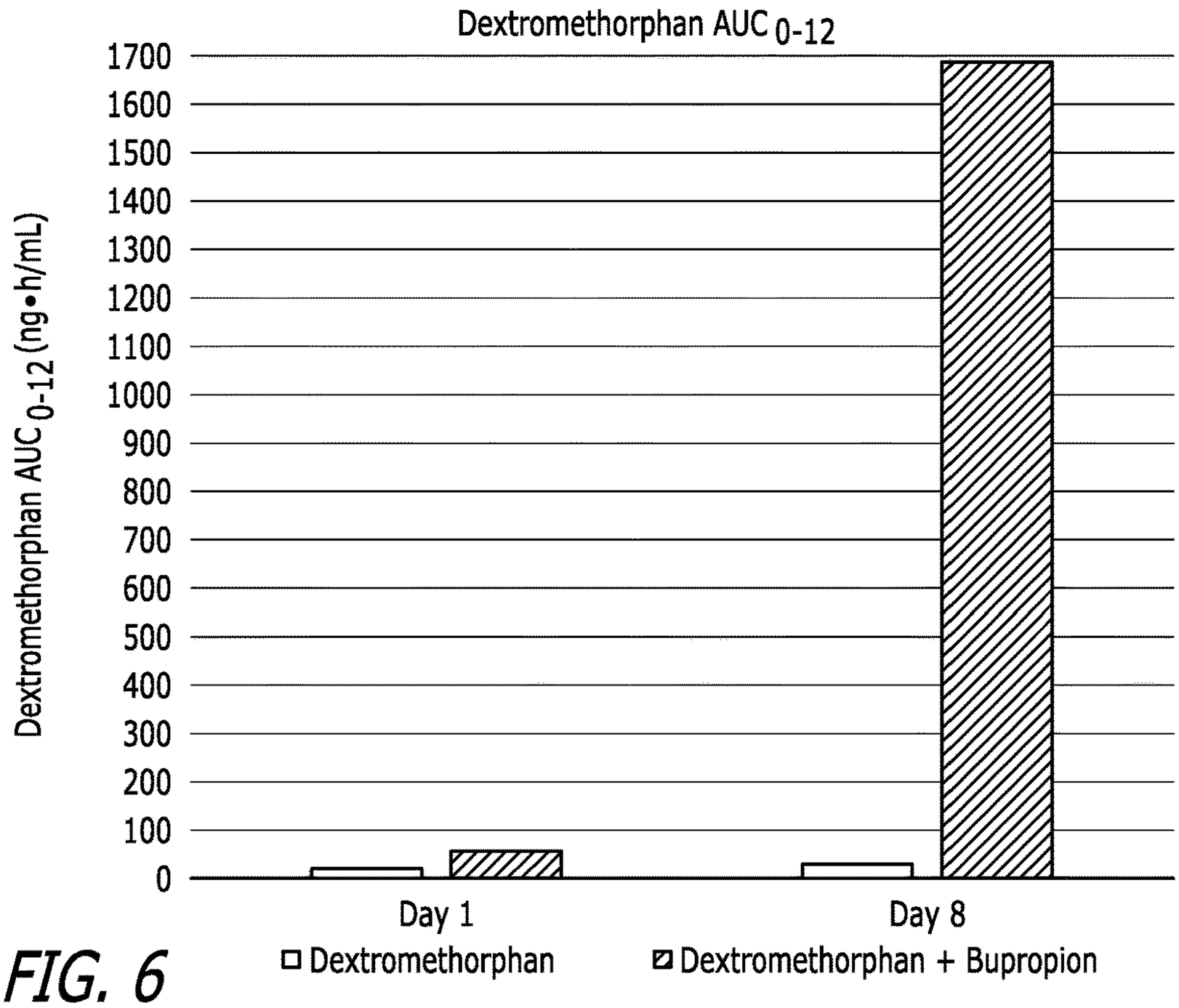

Dextromethorphan AUC 0-12
Dextromethorphan AUC 0-12 (ng•h/mL)
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
Day 1
Day 8
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 6

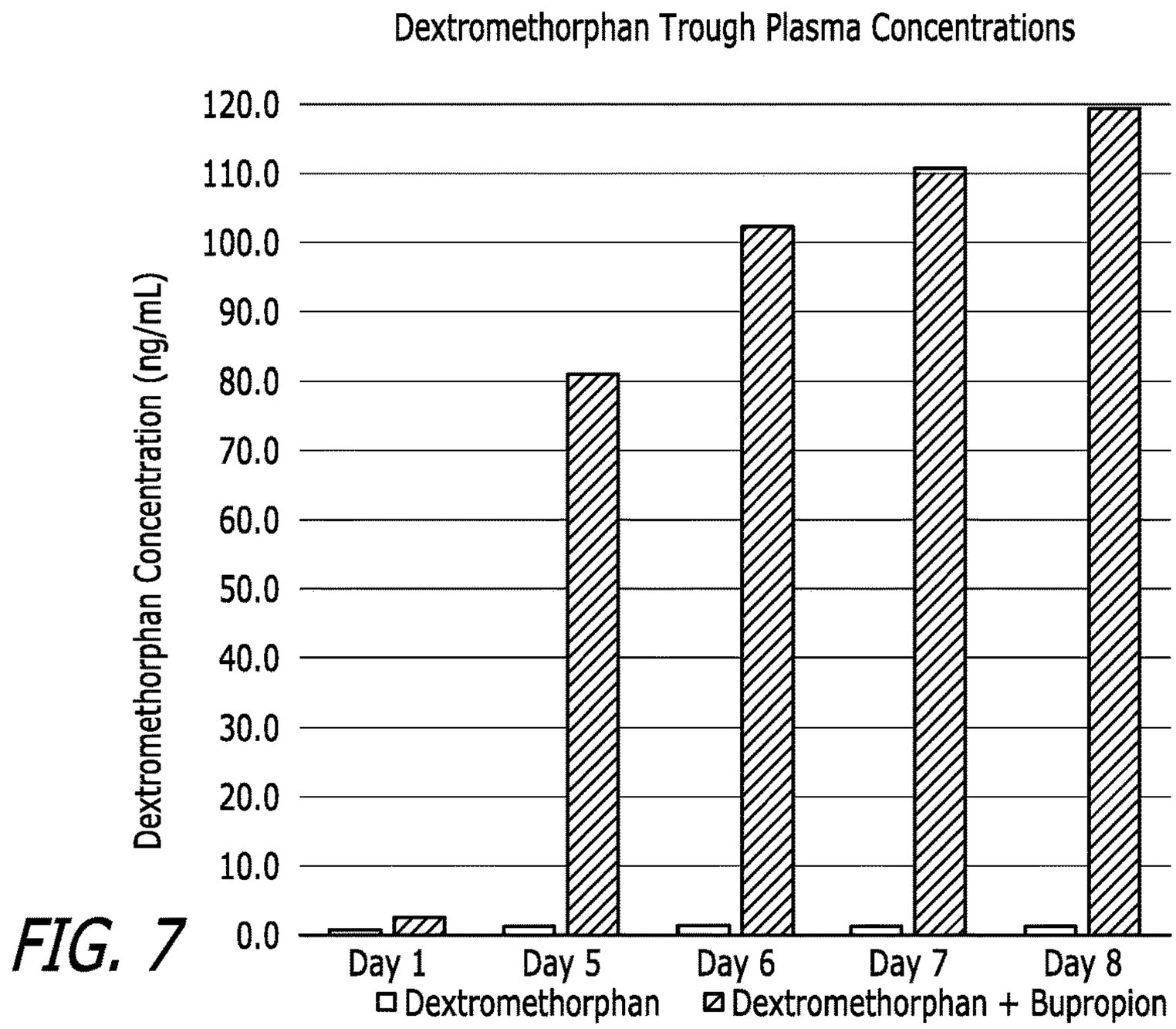

Dextromethorphan Trough Plasma Concentrations
Dextromethorphan Concentration (ng/mL)
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
Day 1
Day 5
Day 6
Day 7
Day 8
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 7

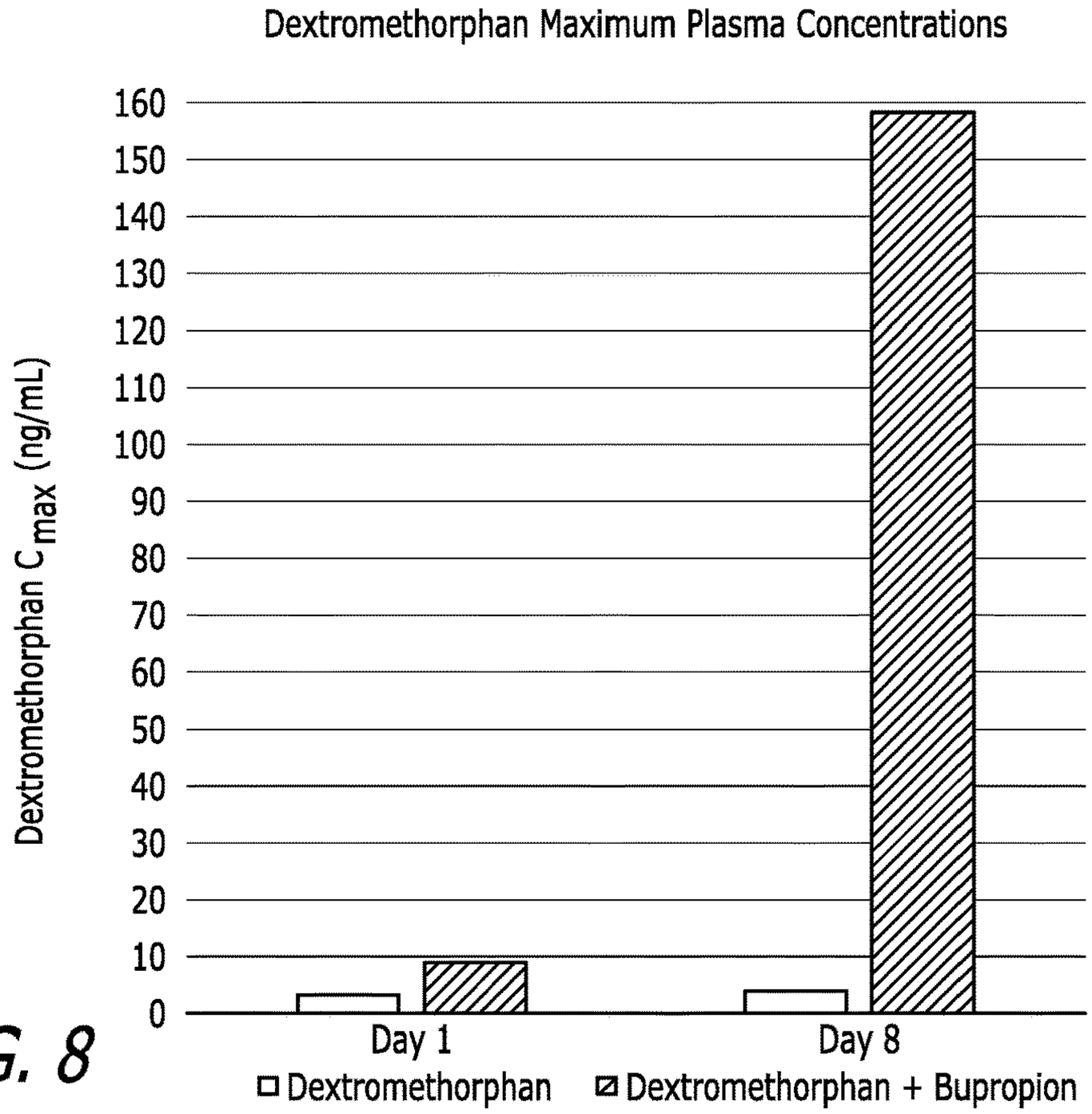

Dextromethorphan Maximum Plasma Concentrations
Dextromethorphan C_{max} (ng/mL)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Day 1
Day 8
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 8

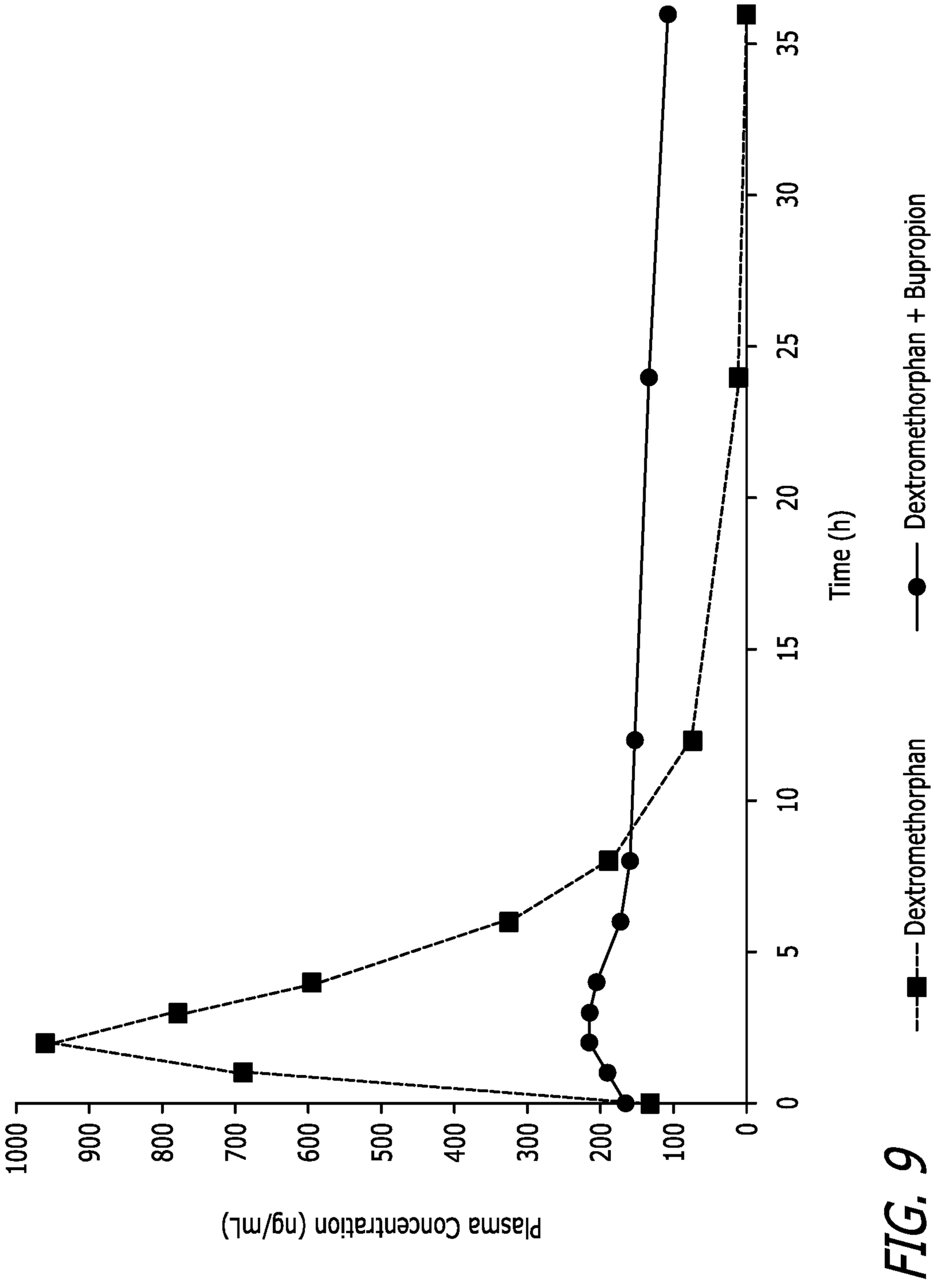

Dextrorphan Concentration-Time Profile
Plasma Concentration (ng/mL)
Time (h)
Dextromethorphan
Dextromethorphan + Bupropion
0
100
200
300
400
500
600
700
800
900
1000
0
5
10
15
20
25
30
35

FIG. 9

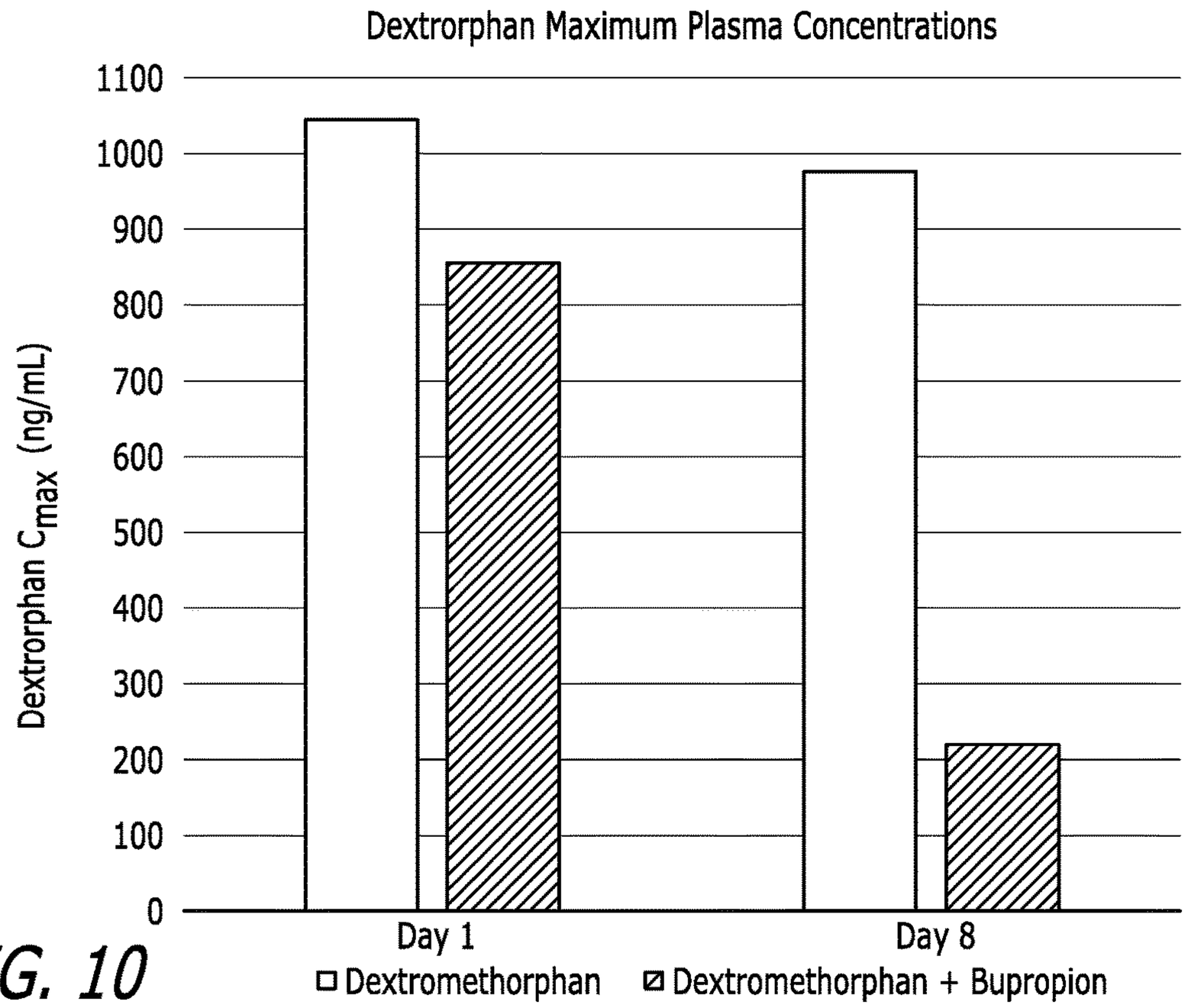

Dextrorphan Maximum Plasma Concentrations
Dextrorphan C_{max} (ng/mL)
1100
1000
900
800
700
600
500
400
300
200
100
0
Day 1
Day 8
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 10

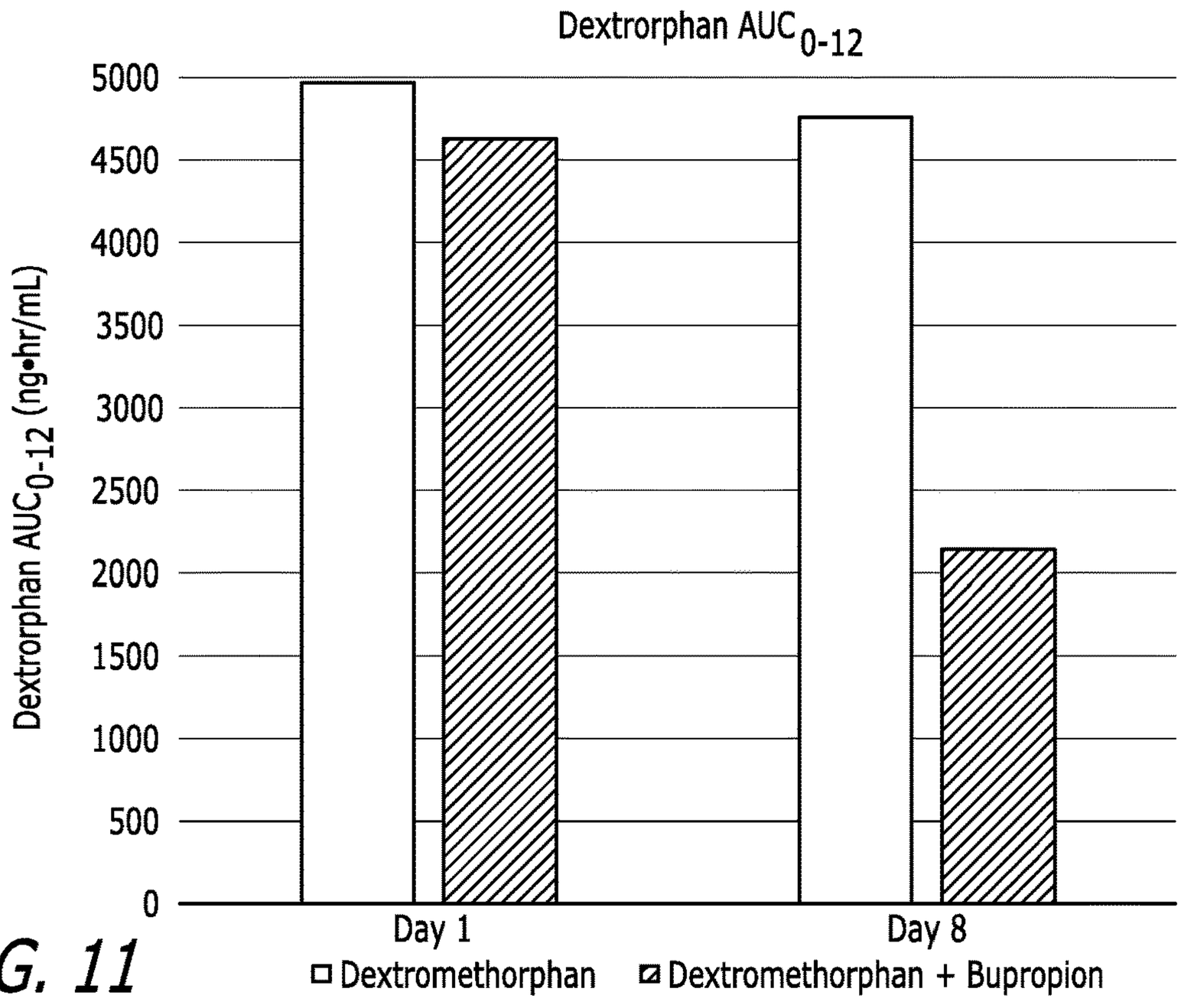
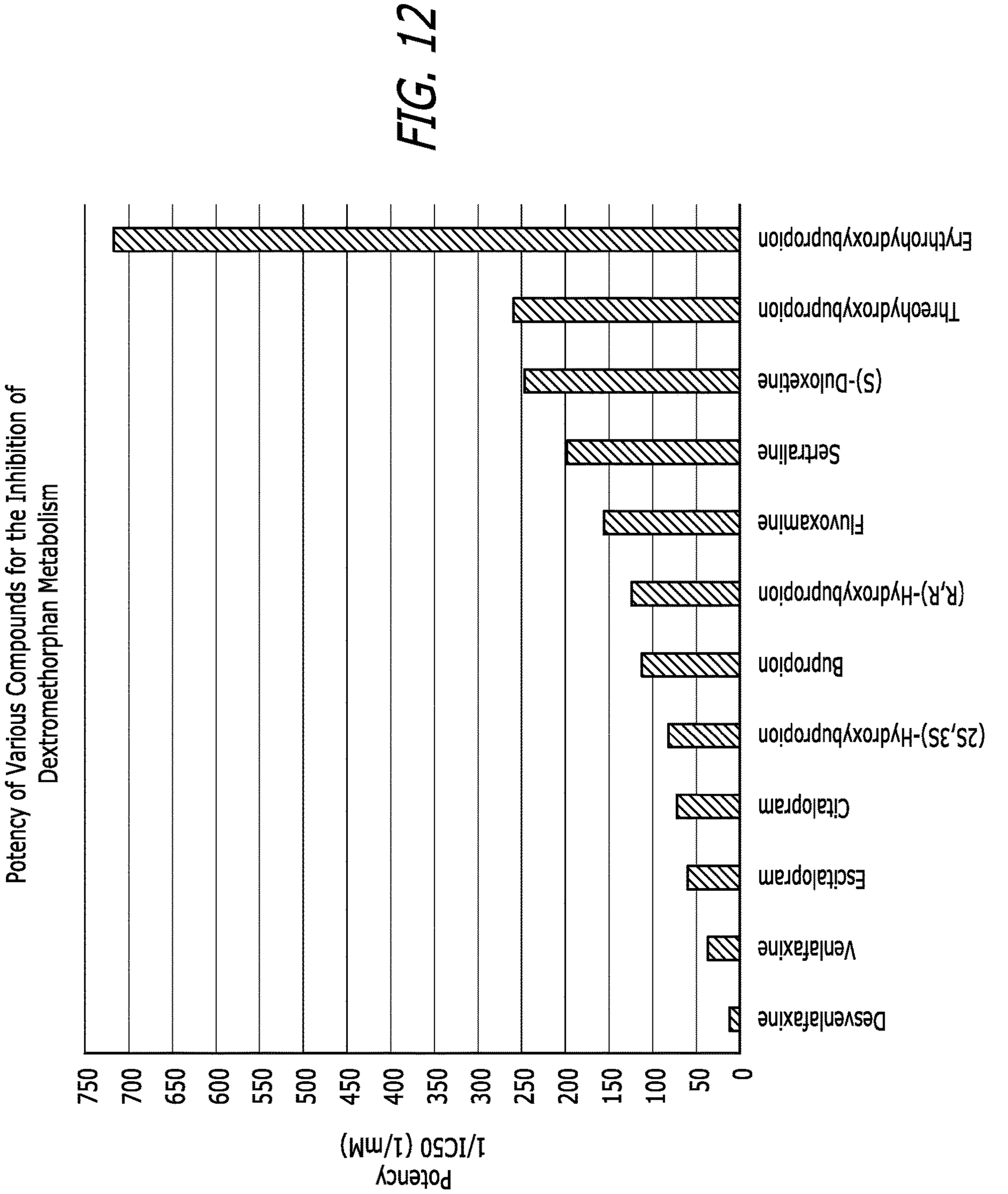

Dextrorphan AUC_{0-12}
Dextrorphan AUC_{0-12} (ng•hr/mL)
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Day 1
Day 8
Dextromethorphan
Dextromethorphan + Bupropion

FIG. 11

FIG. 12


Potency of Various Compounds for the Inhibition of Dextromethorphan Metabolism
Erythrohydroxybupropion
Threohydroxybupropion
(S)-Duloxetine
Sertraline
Fluvoxamine
(R,R)-Hydroxybupropion
Bupropion
(2S,3S)-Hydroxybupropion
Citalopram
Escitalopram
Venlafaxine
Desvenlafaxine
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700
750
Potency
1/IC50 (1/mM)

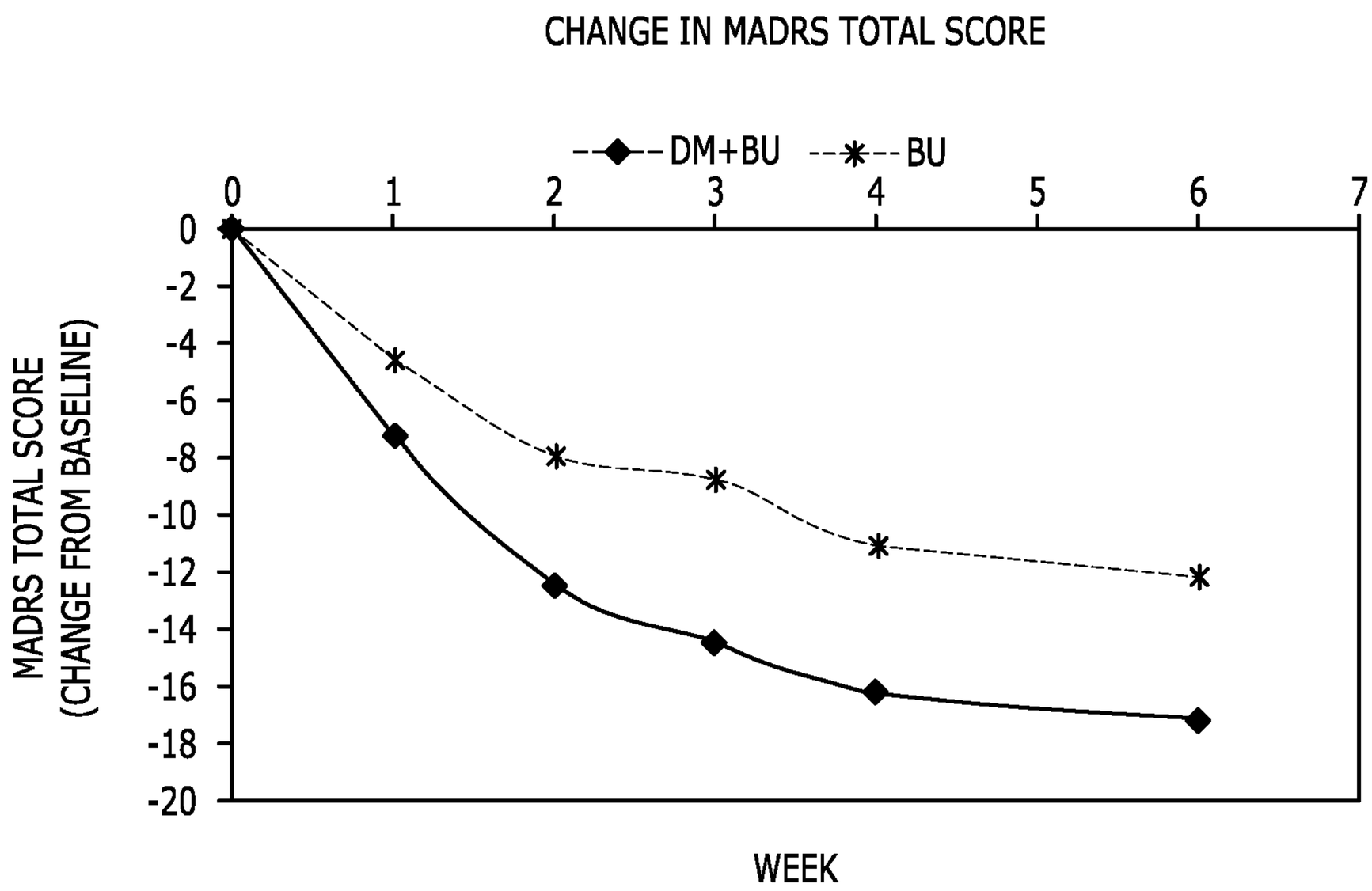

CHANGE IN MADRS TOTAL SCORE
DM+BU
BU
0
1
2
3
4
5
6
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
-20
MADRS TOTAL SCORE
(CHANGE FROM BASELINE)
WEEK

FIG. 13

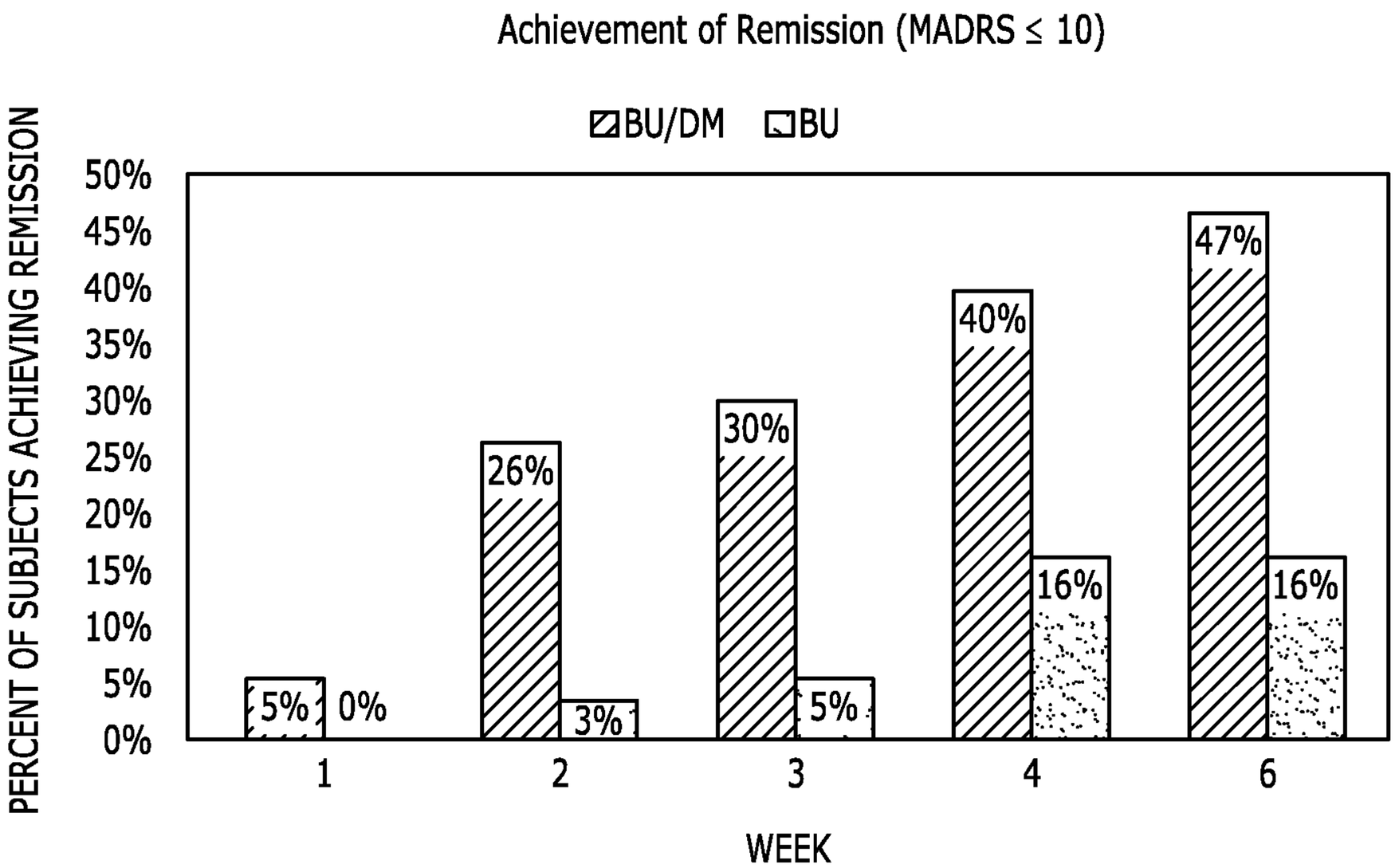
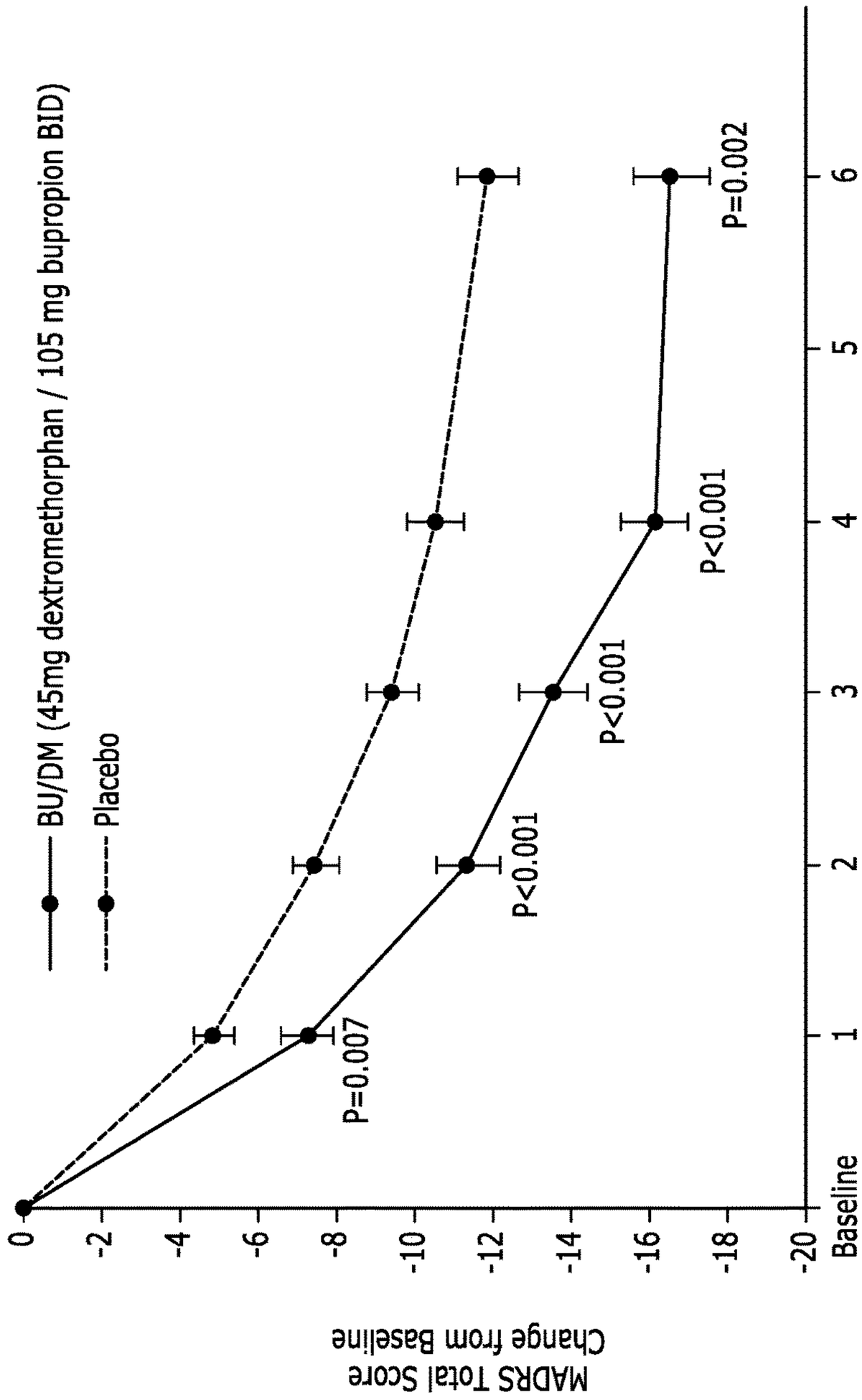

Achievement of Remission (MADRS ≤ 10)
BU/DM
BU
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
PERCENT OF SUBJECTS ACHIEVING REMISSION
5%
0%
26%
3%
30%
5%
40%
16%
47%
16%
1
2
3
4
6
WEEK

FIG. 14



	BU/DM (n=156)	Placebo (n=162)	Difference	P-Value
Primary Endpoint Change in MADRS Total Score at Week 6	-16.6	-11.9	-4.7	0.002
Key Secondary Endpoint Change in MADRS Total Score at Week 1	-7.3	-4.9	-2.4	0.007

FIG. 15

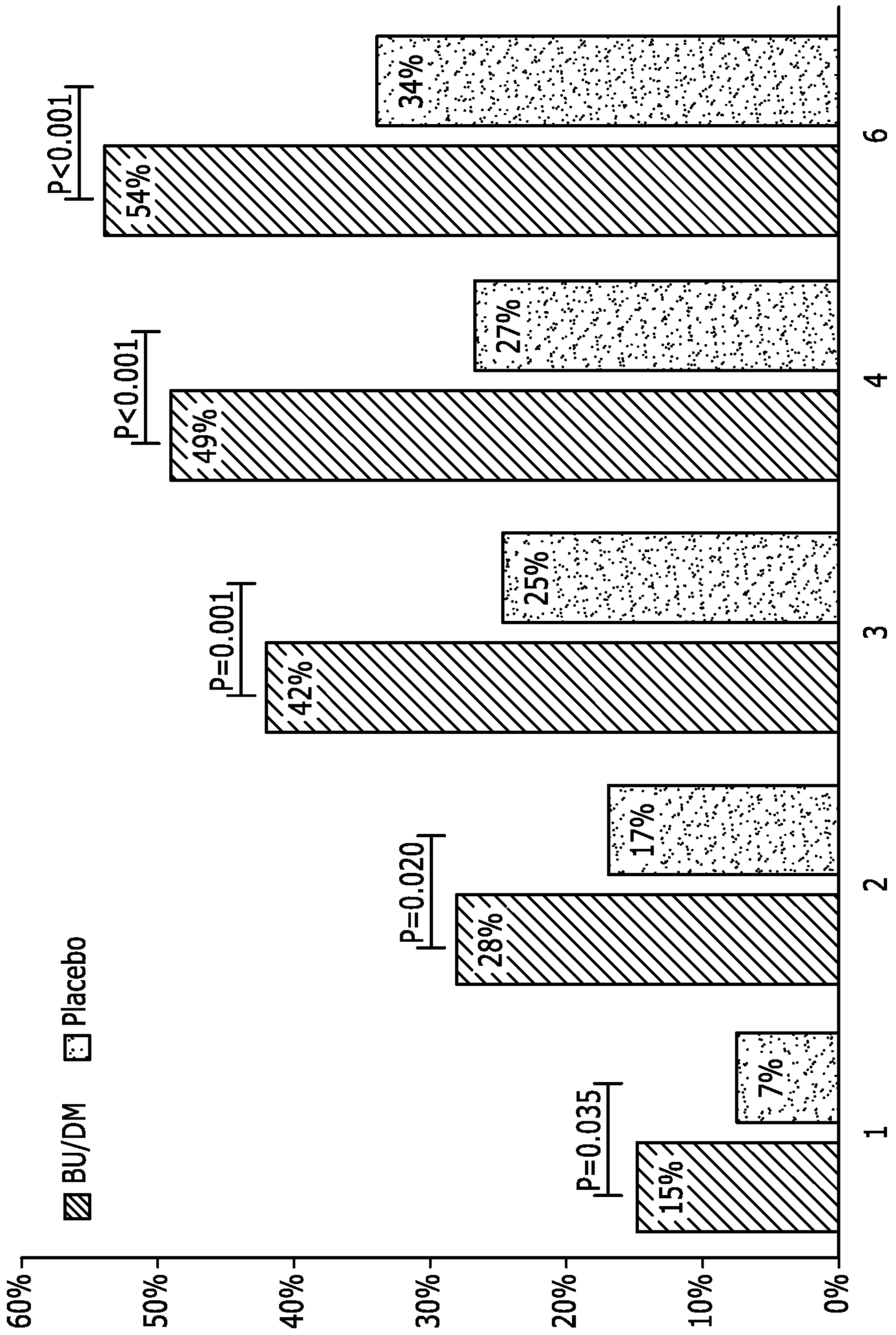

BU/DM
Placebo
Percentage of Responders
(≥ 50% MADRS improvement)
60%
50%
40%
30%
20%
10%
0%
P=0.035
15%
7%
P=0.020
28%
17%
P=0.001
42%
25%
P<0.001
49%
27%
P<0.001
54%
34%
1
2
3
4
6
Week

FIG. 16

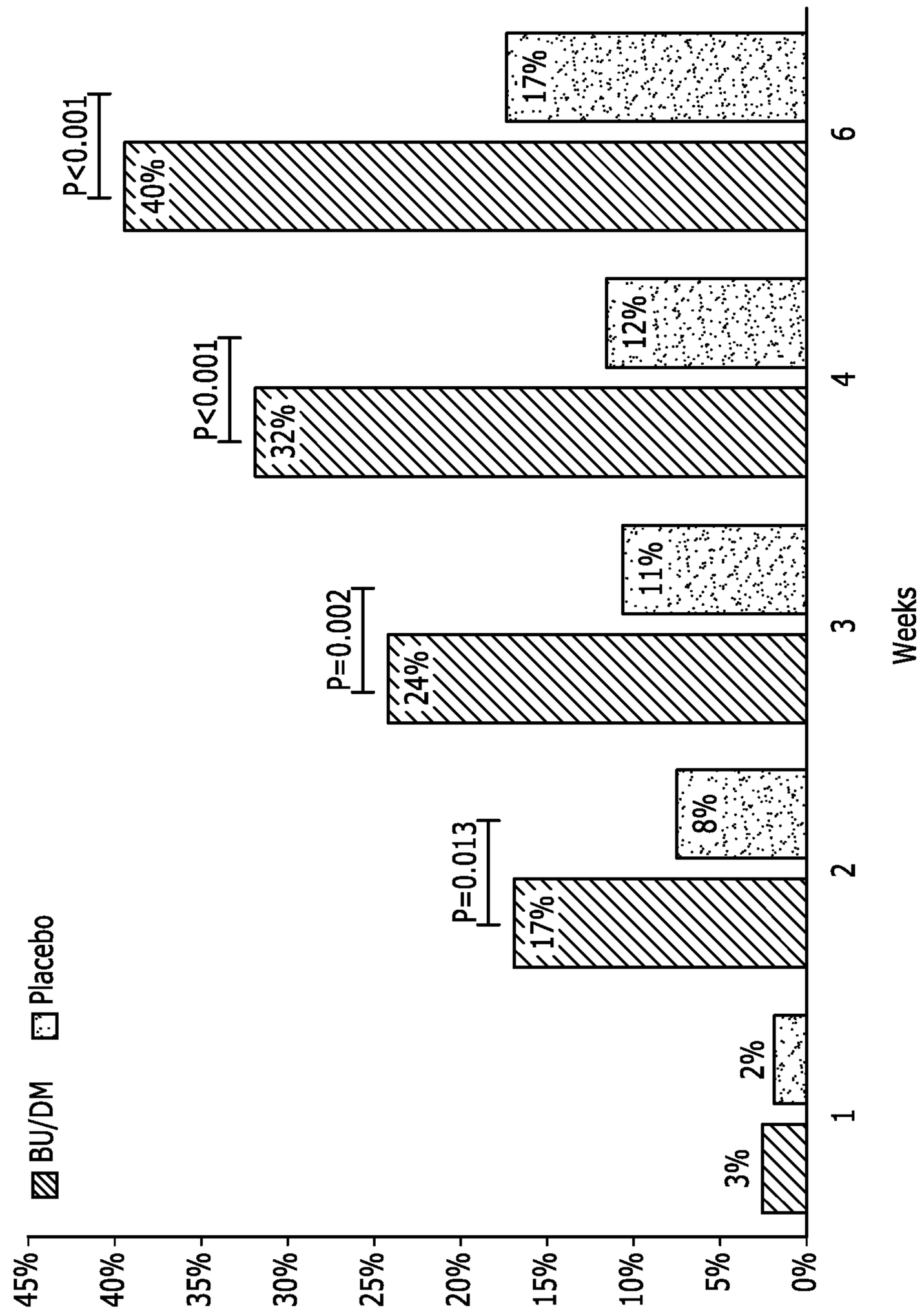

Percentage of Subjects
Achieving Remission (MADRS ≤ 10)
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
BU/DM
Placebo
3%
2%
17%
8%
24%
11%
32%
12%
P=0.013
P=0.002
P<0.001
P<0.001
1
2
3
4
Weeks

FIG. 17

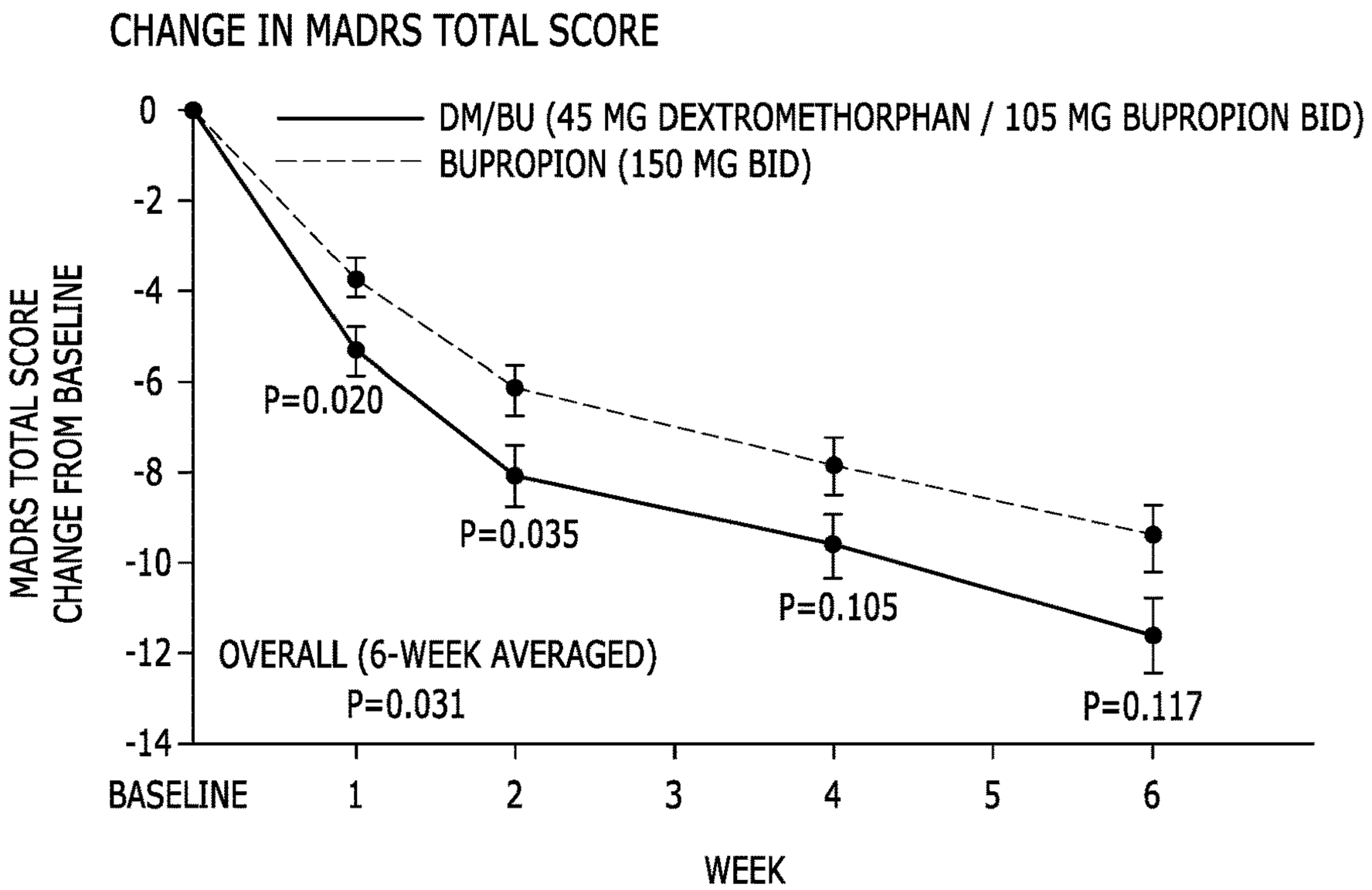

CHANGE IN MADRS TOTAL SCORE
DM/BU (45 MG DEXTROMETHORPHAN / 105 MG BUPROPION BID)
BUPROPION (150 MG BID)
MADRS TOTAL SCORE CHANGE FROM BASELINE
0
-2
-4
-6
-8
-10
-12
-14
P=0.020
P=0.035
P=0.105
P=0.117
OVERALL (6-WEEK AVERAGED)
P=0.031
BASELINE
1
2
3
4
5
6
WEEK

FIG. 18

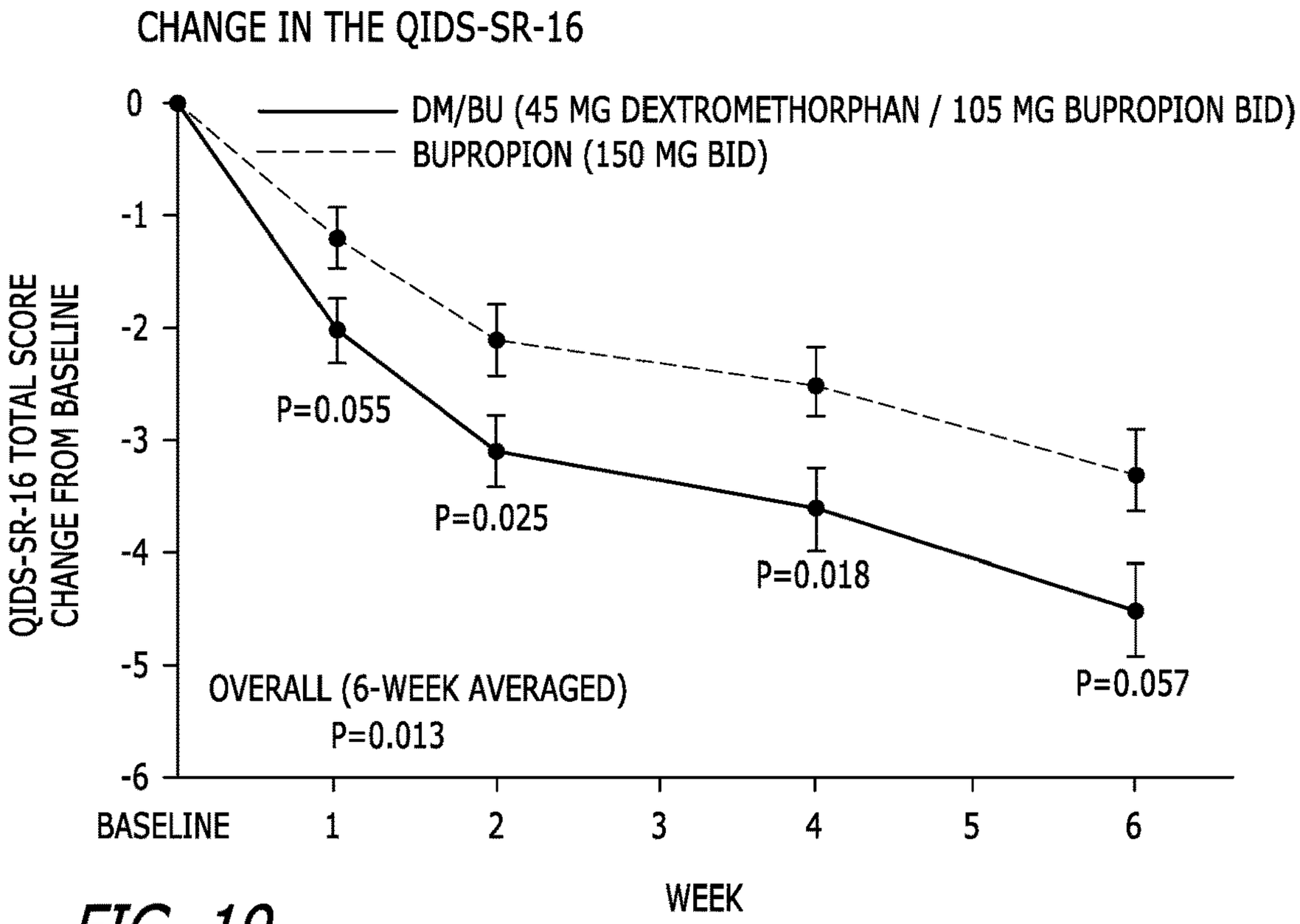

CHANGE IN THE QIDS-SR-16
DM/BU (45 MG DEXTROMETHORPHAN / 105 MG BUPROPION BID)
BUPROPION (150 MG BID)
QIDS-SR-16 TOTAL SCORE CHANGE FROM BASELINE
0
-1
-2
-3
-4
-5
-6
P=0.055
P=0.025
P=0.018
P=0.057
OVERALL (6-WEEK AVERAGED)
P=0.013
BASELINE
1
2
3
4
5
6
WEEK

FIG. 19

FIG. 20

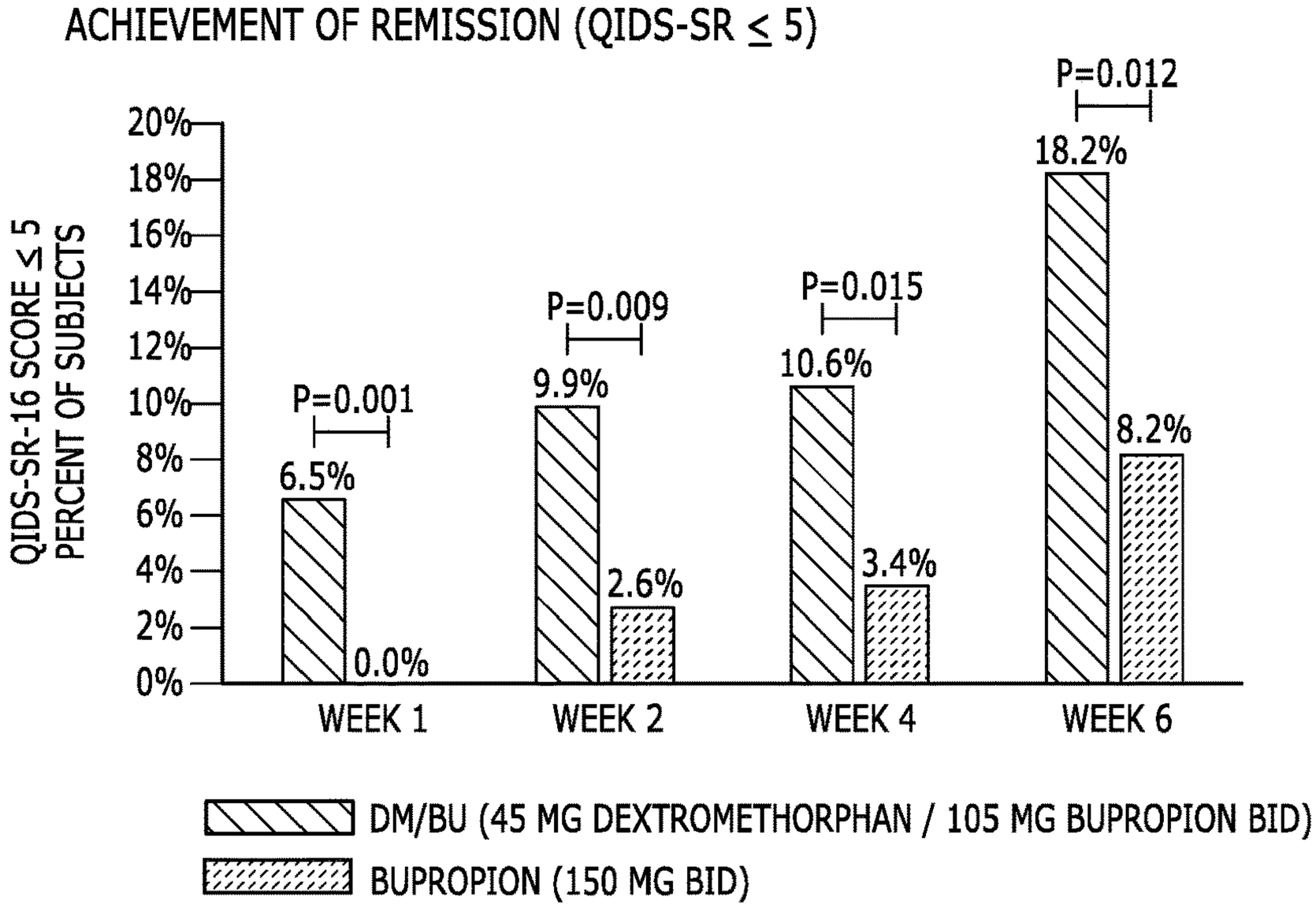

ACHIEVEMENT OF REMISSION (QIDS-SR ≤ 5)
QIDS-SR-16 SCORE ≤ 5
PERCENT OF SUBJECTS
20%
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
P=0.001
6.5%
0.0%
P=0.009
9.9%
2.6%
P=0.015
10.6%
3.4%
P=0.012
18.2%
8.2%
WEEK 1
WEEK 2
WEEK 4
WEEK 6
DM/BU (45 MG DEXTROMETHORPHAN / 105 MG BUPROPION BID)
BUPROPION (150 MG BID)

FIG. 21

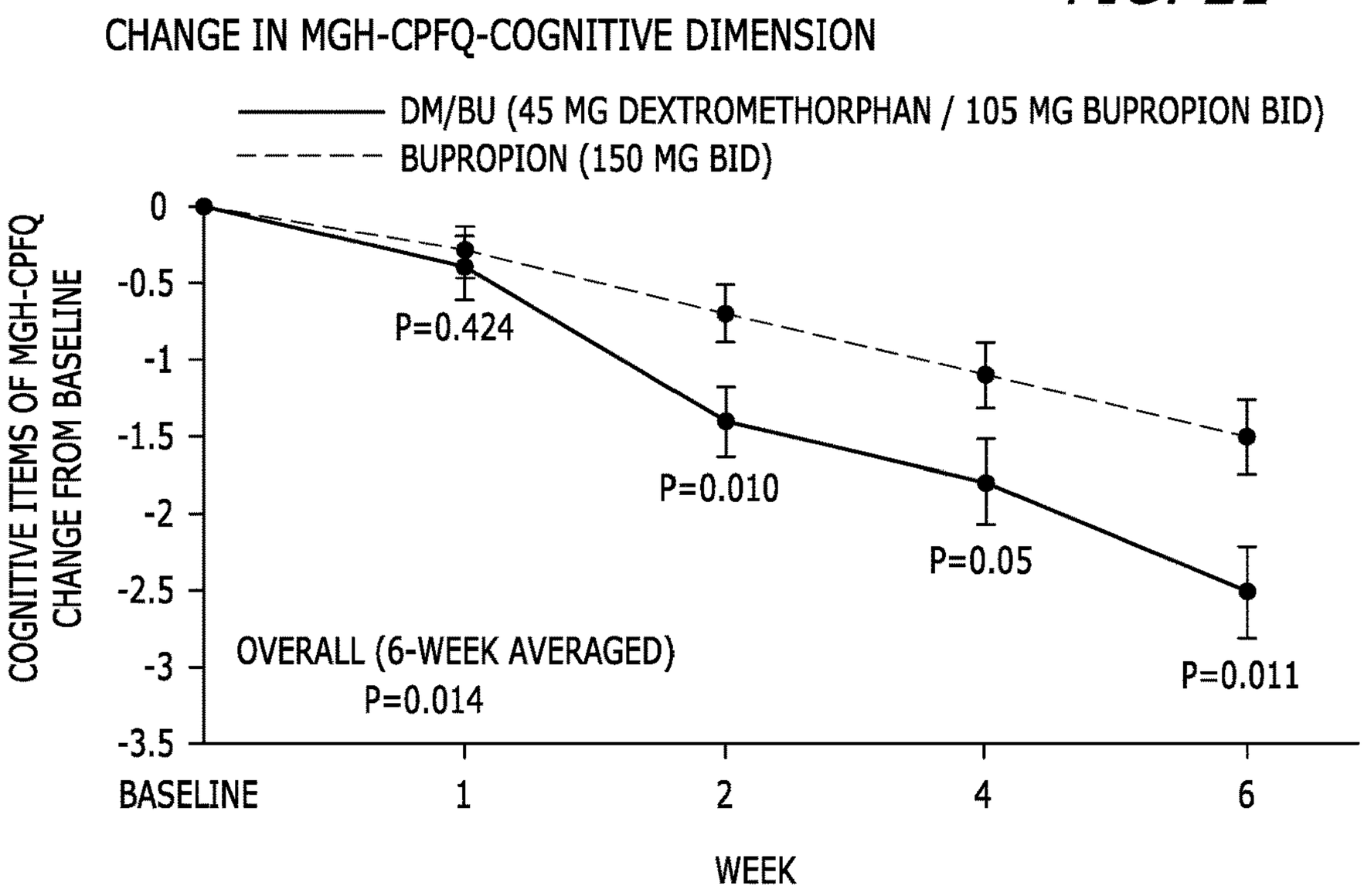
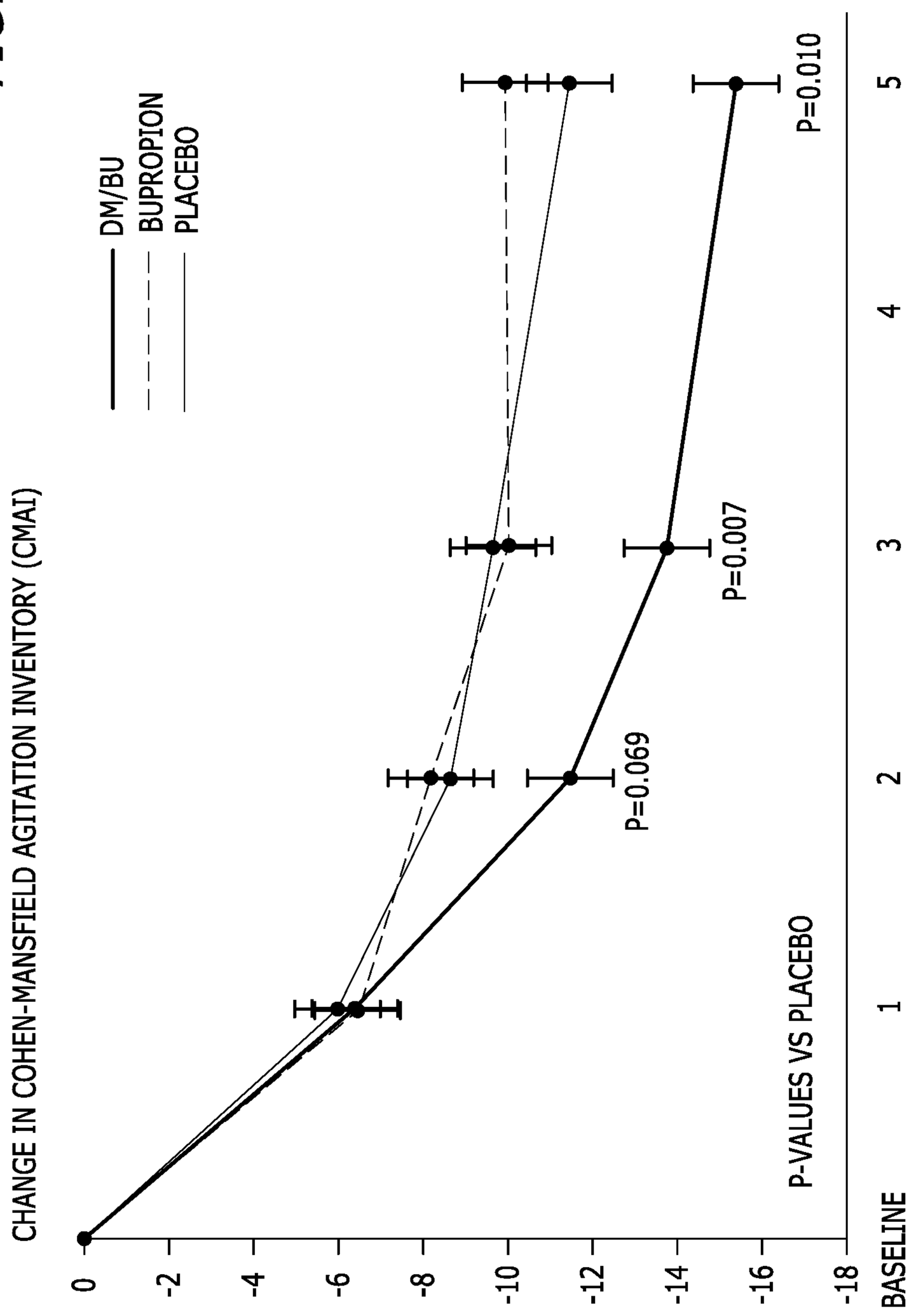

CHANGE IN MGH-CPFQ-COGNITIVE DIMENSION
DM/BU (45 MG DEXTROMETHORPHAN / 105 MG BUPROPION BID)
BUPROPION (150 MG BID)
COGNITIVE ITEMS OF MGH-CPFQ
CHANGE FROM BASELINE
0
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
P=0.424
P=0.010
P=0.05
P=0.011
OVERALL (6-WEEK AVERAGED)
P=0.014
BASELINE
1
2
4
6
WEEK

FIG. 22


DM/BU
BUPROPION
PLACEBO
CHANGE IN COHEN-MANSFIELD AGITATION INVENTORY (CMAI)
CMAI TOTAL SCORE
CHANGE FROM BASELINE
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
BASELINE
1
2
3
4
5
WEEK
P=0.069
P=0.007
P=0.010
P-VALUES VS PLACEBO

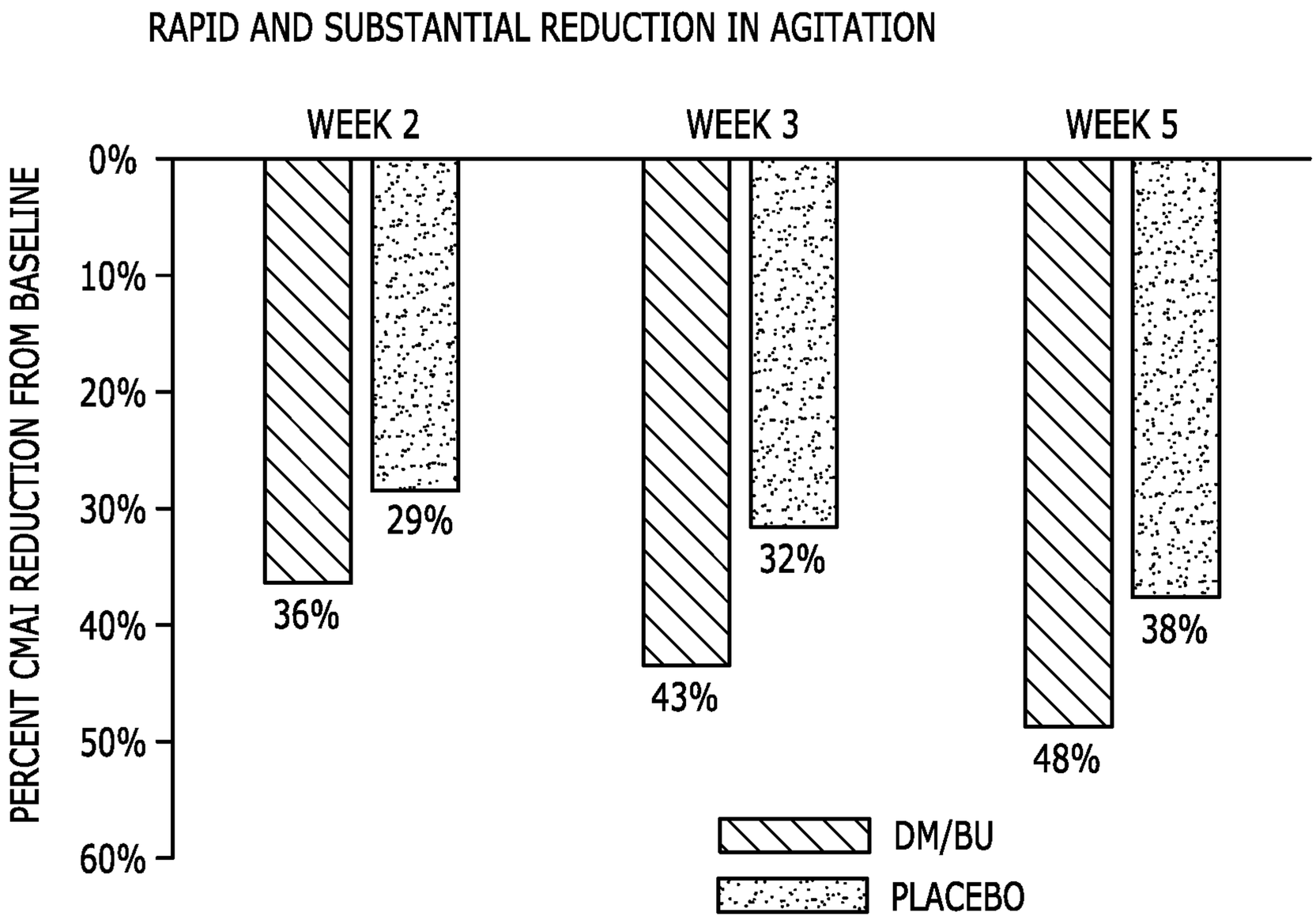

RAPID AND SUBSTANTIAL REDUCTION IN AGITATION
WEEK 2
WEEK 3
WEEK 5
PERCENT CMAI REDUCTION FROM BASELINE
0%
10%
20%
30%
40%
50%
60%
36%
29%
43%
32%
48%
38%
DM/BU
PLACEBO

FIG. 23

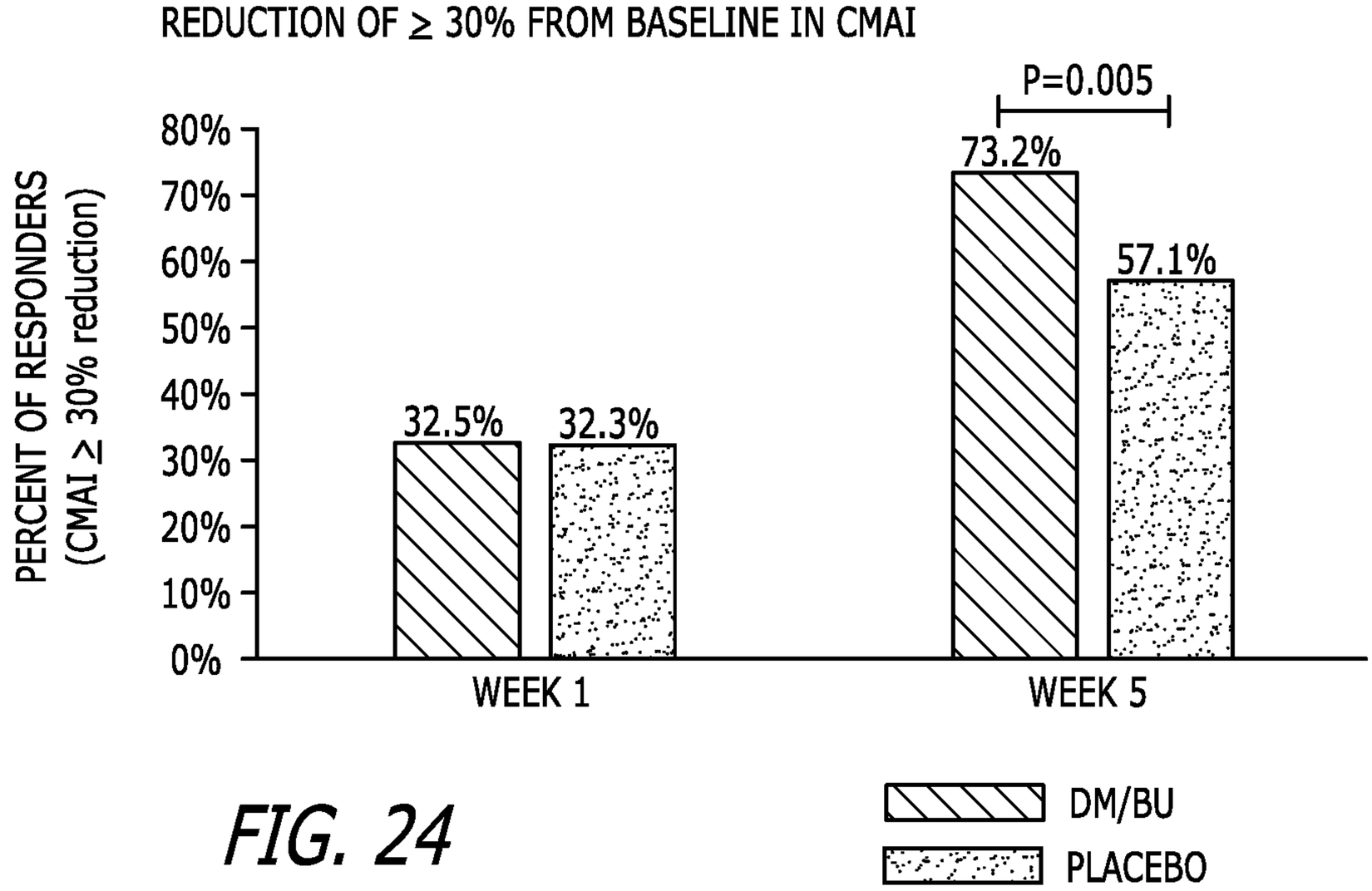

REDUCTION OF ≥ 30% FROM BASELINE IN CMAI
PERCENT OF RESPONDERS
(CMAI ≥ 30% reduction)
80%
70%
60%
50%
40%
30%
20%
10%
0%
32.5%
32.3%
P=0.005
73.2%
57.1%
WEEK 1
WEEK 5
DM/BU
PLACEBO

FIG. 24

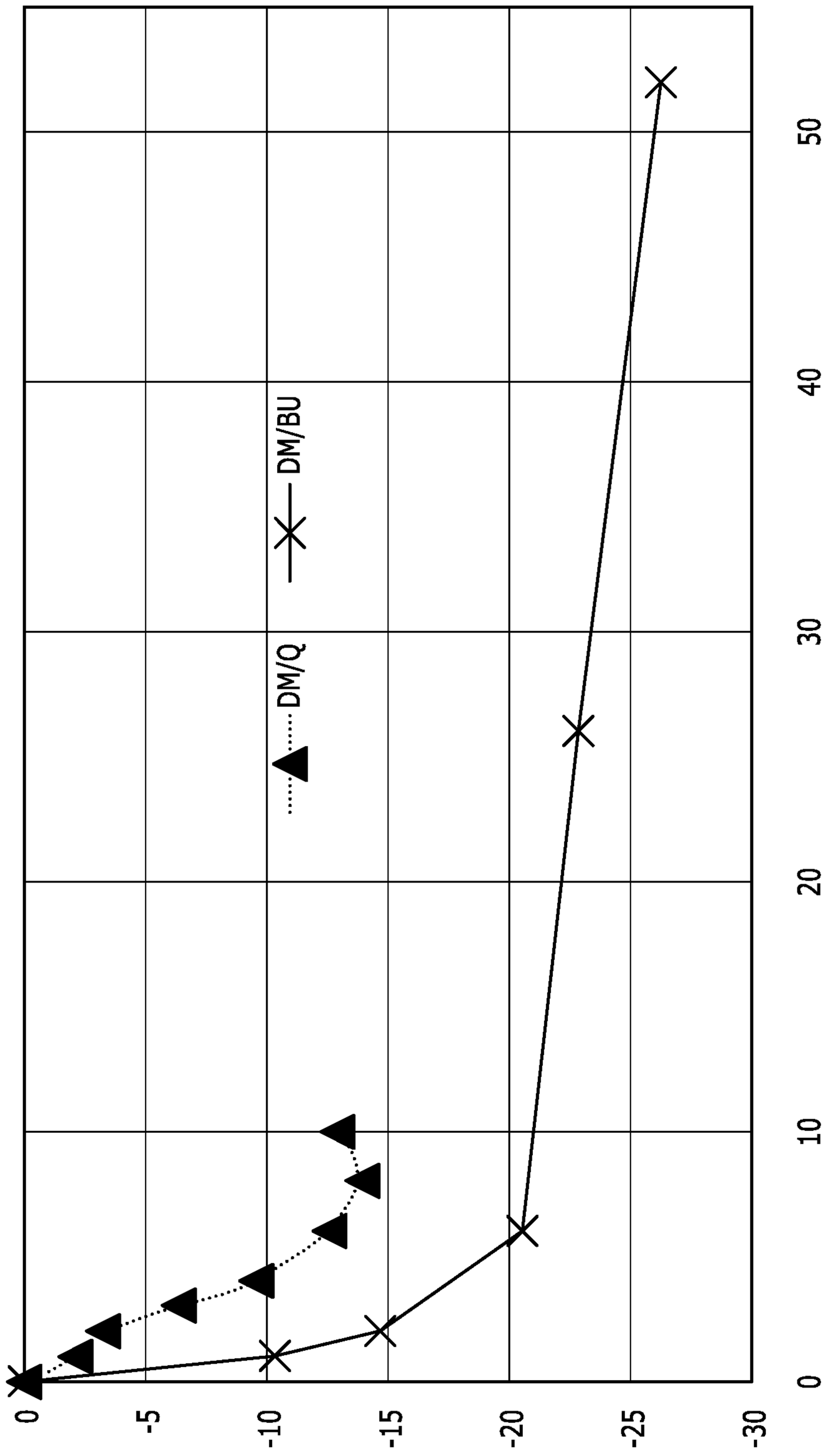

Reduction in MADRS Score From Baseline
0
-5
-10
-15
-20
-25
-30
0
10
20
30
40
50
Time (Weeks)
DM/BU
DM/Q
Reduction in MADRS Score

FIG. 25

BUPROPION AS A MODULATOR OF DRUG ACTIVITY

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 17/468,149, filed Sep. 7, 2021; which is a continuation-in-part of U.S. patent application Ser. No. 17/194,739, filed Mar. 8, 2021, now U.S. Pat. No. 11,147,808; which is a continuation-in-part of U.S. Pat. App. No. of Ser. No. 17/068,309, filed Oct. 12, 2020, now U.S. Pat. No. 10,980,800; which is a continuation-in-part of U.S. patent application Ser. No. 16/817,119, filed Mar. 12, 2020, now U.S. Pat. No. 10,813,924; which is a continuation-in-part of U.S. patent application Ser. No. 16/359,996, filed Mar. 20, 2019, now U.S. Pat. No. 10,688,066; which claims the benefit of U.S. Prov. Pat. App. No. 62/645,751, filed Mar. 20, 2018; this application also claims the benefit of U.S. Prov. Pat. App. No. 63/224,323, filed Jul. 21, 2021; U.S. patent application Ser. No. 17/068,309 is also a continuation-in-part of U.S. patent application Ser. No. 16/822,697, filed Mar. 18, 2020, now U.S. Pat. No. 11,090,300; which is a continuation-in-part of U.S. patent application Ser. No. 16/359,958, filed Mar. 20, 2019, now U.S. Pat. No. 10,881,657; which is a continuation-in-part of U.S. patent application Ser. No. 15/821,563, filed Nov. 22, 2017, now U.S. Pat. No. 10,512,643; which is a continuation-in-part of U.S. patent application Ser. No. 15/645,939, filed Jul. 10, 2017, now U.S. Pat. No. 9,867,819; which is a continuation-in-part of U.S. patent application Ser. No. 15/263,138, filed on Sep. 12, 2016, now U.S. Pat. No. 9,700,553; which is a continuation of U.S. patent application Ser. No. 15/164,746, filed on May 25, 2016, now U.S. Pat. No. 9,457,023; which is a continuation-in-part of U.S. patent application Ser. No. 14/879,002, filed Oct. 8, 2015, now U.S. Pat. No. 9,375,429; which is a continuation of U.S. patent application Ser. No. 14/554,988, filed Nov. 26, 2014, now U.S. Pat. No. 9,205,083; which is a continuation of U.S. patent application Ser. No. 14/550,618, filed Nov. 21, 2014, now U.S. Pat. No. 9,198,905; which is a continuation-in-part of International Pat. App. No. PCT/US2014/064184, filed Nov. 5, 2014; which claims the benefit of U.S. Prov. Pat. App. No. 61/900,354, filed Nov. 5, 2013; U.S. patent application Ser. No. 15/821,563 also claims the benefit of U.S. Prov. Pat. App. No. 62/576,538, filed Oct. 24, 2017; all of the above applications, U.S. patents issued from, or U.S. publications of any of the above applications are incorporated by reference in their entirety; U.S. patent application Ser. No. 17/468,149 is now U.S. Pat. No. 11,364,233.

SUMMARY

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being, comprising co-administering bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds with dextromethorphan.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being, comprising co-administering erythrohydroxybupropion or a prodrug thereof, with dextromethorphan to the human being, wherein the erythrohydroxybupropion or a prodrug thereof is administered in an amount that results in an AUC_{0-12} of dextromethorphan that is at least about 40 ng·hr/mL.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being, comprising co-administering erythrohydroxybupropion or a prodrug thereof, with dextromethorphan to the human being, wherein the erythrohydroxybupropion or a prodrug thereof is administered in an amount that results in a C_{max} of dextromethorphan that is at least about 6 ng/mL.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being, comprising co-administering erythrohydroxybupropion or a prodrug thereof, with dextromethorphan to the human being, wherein the erythrohydroxybupropion or a prodrug thereof is administered in an amount that results in a C_{avg} of dextromethorphan, over the period between two separate and consecutive administrations of dextromethorphan, that is at least about 5 ng/mL.

Some embodiments include a method of increasing the metabolic lifetime of dextromethorphan, comprising administering threohydroxybupropion, or a prodrug thereof, to a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as threohydroxybupropion.

Some embodiments include a method of reducing an adverse event associated with treatment by dextromethorphan, comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human patient in need of dextromethorphan treatment, wherein the human patient is at risk of experiencing the adverse event as a result of being treated with dextromethorphan.

Some embodiments include an oral sustained release delivery system for dextromethorphan, comprising bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, dextromethorphan, and a water soluble vehicle.

Some embodiments include a method of decreasing the number of doses of dextromethorphan that can be administered without loss of efficacy, comprising orally administering an effective amount of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, to a human being in need of treatment with dextromethorphan.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the threohydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of treatment with dextromethorphan, wherein a decrease in the dextrorphan plasma level occurs on the first day that threohydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without threohydroxybupropion or a prodrug thereof.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the hydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of treatment with dextromethorphan, wherein a decrease in the dextrorphan plasma level occurs on the first day that hydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without hydroxybupropion or a prodrug thereof.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupro-

pion and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the bupropion is administered on the first day of at least two days of treatment with dextromethorphan, wherein a decrease in the dextrorphan plasma level occurs on the first day that bupropion and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without bupropion.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the erythrohydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of treatment with dextromethorphan, wherein a decrease in the dextrorphan plasma level occurs on the first day that erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without erythrohydroxybupropion or a prodrug thereof.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least eight consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the eighth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for eight consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least eight consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the eighth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for eight consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least eight consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the eighth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for eight consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least eight consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the eighth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for eight consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the

dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least nine consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for nine consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least ten consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the tenth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for ten consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least ten consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the tenth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for ten consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least ten consecutive days, to a human being in need of treatment with dextromethorphan, wherein,

on the tenth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for ten consecutive days.

Some embodiments include a method of decreasing dextrorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least ten consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the tenth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for ten consecutive days.

Antidepressant compounds, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, can be used to improve the therapeutic properties, such as in the treatment of neurological disorders, of dextromethorphan. Bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, regardless of stereochemistry, can be effective in inhibiting or reducing the metabolism of dextromethorphan in some human beings. This may be accomplished by co-administering bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan.

Some embodiments include a method of treating a neurological disorder comprising administering: 1) dextromethorphan, or 2) a combination of an antidepressant compound and dextromethorphan to a human being in need thereof, wherein the human being is an extensive metabolizer of dextromethorphan.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, comprising co-administering bupropion with dextromethorphan to the human being.

Some embodiments include a method of inhibiting the metabolism of dextromethorphan, comprising administering bupropion to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as bupropion.

Some embodiments include a method of increasing the metabolic lifetime of dextromethorphan, comprising administering bupropion to a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as bupropion.

Some embodiments include a method of correcting extensive metabolism of dextromethorphan, comprising administering bupropion to a human being in need thereof.

Some embodiments include a method of improving the antitussive properties of dextromethorphan comprising administering bupropion in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Some embodiments include a method of treating cough comprising administering a combination of bupropion or another active compound and dextromethorphan to a human being in need thereof.

Some embodiments include a method of treating a neurological disorder comprising administering 1) dextromethorphan, or 2) bupropion and dextromethorphan to a human being in need thereof, wherein the 1) dextromethorphan, or 2) bupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Some embodiments include a method of treating a neurological disorder comprising administering about 150 mg/day to about 300 mg/day of bupropion and about 15 mg/day to about 60 mg/day of dextromethorphan to a human being in need thereof.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, comprising co-administering hydroxybupropion, or a prodrug thereof, with dextromethorphan to the human being.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, comprising co-administering erythrohydroxybupropion, or a prodrug thereof, with dextromethorphan to the human being.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, comprising co-administering threohydroxybupropion, or a prodrug thereof, with dextromethorphan to the human being.

Some embodiments include a method of inhibiting metabolism of dextromethorphan, comprising administering bupropion to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as bupropion.

Some embodiments include a method of inhibiting metabolism of dextromethorphan, comprising administering hydroxybupropion, or a prodrug thereof, to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as hydroxybupropion.

Some embodiments include a method of inhibiting metabolism of dextromethorphan, comprising administering erythrohydroxybupropion, or a prodrug thereof, to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as erythrohydroxybupropion.

Some embodiments include a method of inhibiting metabolism of dextromethorphan, comprising administering threohydroxybupropion, or a prodrug thereof, to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as threohydroxybupropion.

Some embodiments include a method of increasing the metabolic lifetime of dextromethorphan, comprising administering hydroxybupropion, or a prodrug thereof, to a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as hydroxybupropion.

Some embodiments include a method of increasing the metabolic lifetime of dextromethorphan, comprising administering erythrohydroxybupropion, or a prodrug thereof, to a human being in need of treatment with dextromethorphan, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as erythrohydroxybupropion.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering bupropion and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the bupropion is administered on the first day of at least two days of co-administration of bupropion with dextromethorphan, wherein an increase in the dextromethorphan plasma level occurs on the first day that bupropion and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without bupropion.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the hydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of co-administration of hydroxybupropion, or a prodrug thereof, with dextromethorphan, wherein an increase in the dextromethorphan plasma level occurs on the first day that hydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without hydroxybupropion or a prodrug thereof.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the erythrohydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of co-administration of erythrohydroxybupropion, or a prodrug thereof, with dextromethorphan, wherein an increase in the dextromethorphan plasma level occurs on the first day that erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without erythrohydroxybupropion or a prodrug thereof.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need of treatment with dextromethorphan, wherein the threohydroxybupropion, or a prodrug thereof, is administered on the first day of at least two days of co-administration of threohydroxybupropion, or a prodrug thereof, with dextromethorphan, wherein an increase in the dextromethorphan plasma level occurs on the first day that threohydroxybupropion, or a prodrug thereof, and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without threohydroxybupropion or a prodrug thereof.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least five consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the fifth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for five consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering

hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least five consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the fifth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for five consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least five consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the fifth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for five consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least five consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the fifth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for five consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering bupropion and dextromethorphan, for at least six consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the sixth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion for six consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least six consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the sixth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without hydroxybupropion, or a prodrug thereof, for six consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least six consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the sixth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without erythrohydroxybupropion, or a prodrug thereof, for six consecutive days.

Some embodiments include a method of increasing dextromethorphan plasma levels comprising co-administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan, for at least six consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the sixth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without threohydroxybupropion, or a prodrug thereof, for six consecutive days.

Some embodiments include a method of reducing a trough effect of dextromethorphan comprising, co-administering bupropion with dextromethorphan to a human patient in need of treatment with dextromethorphan, wherein dextromethorphan has a plasma level 12 hours after co-administering bupropion with dextromethorphan that is at least twice the plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion.

Some embodiments include a method of reducing a trough effect of dextromethorphan comprising, co-administering hydroxybupropion, or a prodrug thereof, with dextromethorphan to a human patient in need of treatment with dextromethorphan, wherein dextromethorphan has a plasma level 12 hours after co-administering hydroxybupropion, or a prodrug thereof, with dextromethorphan that is at least twice the plasma level that would be achieved by administering the same amount of dextromethorphan without hydroxybupropion or a prodrug thereof.

Some embodiments include a method of reducing a trough effect of dextromethorphan comprising, co-administering erythrohydroxybupropion, or a prodrug thereof, with dextromethorphan to a human patient in need of treatment with dextromethorphan, wherein dextromethorphan has a plasma level 12 hours after co-administering erythrohydroxybupropion, or a prodrug thereof, with dextromethorphan that is at least twice the plasma level that would be achieved by administering the same amount of dextromethorphan without erythrohydroxybupropion or a prodrug thereof.

Some embodiments include a method of reducing a trough effect of dextromethorphan comprising, co-administering threohydroxybupropion, or a prodrug thereof, with dextromethorphan to a human patient in need of treatment with dextromethorphan, wherein dextromethorphan has a plasma level 12 hours after co-administering threohydroxybupropion, or a prodrug thereof, with dextromethorphan that is at least twice the plasma level that would be achieved by administering the same amount of dextromethorphan without threohydroxybupropion or a prodrug thereof.

Some embodiments include a method of reducing an adverse event associated with treatment by dextromethorphan, comprising co-administering bupropion and dextromethorphan to a human patient in need of dextromethorphan treatment, wherein the human patient is at risk of experiencing the adverse event as a result of being treated with dextromethorphan.

Some embodiments include a method of reducing an adverse event associated with treatment by dextromethorphan, comprising co-administering hydroxybupropion, or a prodrug thereof, and dextromethorphan to a human patient in need of dextromethorphan treatment, wherein the human patient is at risk of experiencing the adverse event as a result of being treated with dextromethorphan.

Some embodiments include a method of reducing an adverse event associated with treatment by dextromethorphan, comprising co-administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human patient in need of dextromethorphan treatment, wherein the human patient is at risk of experiencing the adverse event as a result of being treated with dextromethorphan.

Some embodiments include a method of reducing an adverse event associated with treatment by bupropion, comprising co-administering dextromethorphan and bupropion to a human patient in need of bupropion treatment, wherein

the human patient is at risk of experiencing the adverse event as a result of being treated with bupropion.

Some embodiments include a method of correcting extensive metabolism of dextromethorphan, comprising administering hydroxybupropion, or a prodrug thereof, to a human being in need thereof.

Some embodiments include a method of correcting extensive metabolism of dextromethorphan, comprising administering erythrohydroxybupropion, or a prodrug thereof, to a human being in need thereof.

Some embodiments include a method of correcting extensive metabolism of dextromethorphan, comprising administering threohydroxybupropion, or a prodrug thereof, to a human being in need thereof.

Some embodiments include a method of improving antitussive properties of dextromethorphan comprising administering bupropion in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Some embodiments include a method of improving antitussive properties of dextromethorphan comprising administering hydroxybupropion, or a prodrug thereof, in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Some embodiments include a method of improving antitussive properties of dextromethorphan comprising administering erythrohydroxybupropion, or a prodrug thereof, in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Some embodiments include a method of improving antitussive properties of dextromethorphan comprising administering threohydroxybupropion, or a prodrug thereof, in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Some embodiments include a method of treating cough comprising administering a combination of hydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof.

Some embodiments include a method of treating cough comprising administering a combination of erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof.

Some embodiments include a method of treating cough comprising administering a combination of threohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof.

Some embodiments include a method of treating a neurological disorder comprising administering bupropion and dextromethorphan to a human being in need thereof, wherein the bupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Some embodiments include a method of treating a neurological disorder comprising administering hydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof, wherein the bupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Some embodiments include a method of treating a neurological disorder comprising administering erythrohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof, wherein the erythrohydroxybupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Some embodiments include a method of treating a neurological disorder comprising administering threohydroxybupropion, or a prodrug thereof, and dextromethorphan to a human being in need thereof, wherein the threohydroxybupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Some embodiments include a pharmaceutical composition, dosage form, or medicament comprising a therapeutically effective amount of dextromethorphan, a therapeutically effective amount of an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, and a pharmaceutically acceptable excipient.

Some embodiments include a method of reducing a risk of seizure associated with use of bupropion to treat depression, comprising orally administering a dextromethorphan-bupropion combination twice a day, wherein the method is: 1) at least as effective in treating depression, and 2) reduces the risk of seizure to the human being, as compared to orally administering 150 mg of the bupropion alone twice a day to the human being for the same number of days.

Some embodiments include a method of improving the therapeutic effect of bupropion in treating depression, comprising orally co-administering a dextromethorphan with a bupropion, twice a day, to a human being suffering from depression, wherein the method is more effective than treating the depression of that human being by orally administering 150 mg of the bupropion alone twice a day to the human being for five weeks.

In some embodiments, the combination of the dextromethorphan and the bupropion is more effective than independently orally administering the same amount of the dextromethorphan or the bupropion alone.

Some embodiments include a method of improving the efficacy of bupropion in treating depression, comprising orally administering about 90 mg to about 125 mg of a bupropion in combination with about 0.3 mg/kg to about 1 mg/kg of a dextromethorphan, once or twice a day for at least 23 days, to a human being suffering from depression, wherein orally administering the bupropion in combination with the dextromethorphan is more effective in treating depression than orally administering the same dosage regimen of bupropion without dextromethorphan.

Some embodiments include a method of treating treatment-resistant depression comprising: selecting a human being suffering from depression who has previously been unsuccessfully treated with at least one antidepressant; and orally administering a dextromethorphan-bupropion combination treatment once or twice a day to the human being for at least about five weeks; wherein the dextromethorphan-bupropion combination treatment comprises about 40 mg to about 70 mg of a dextromethorphan and about 100 mg to about 140 mg of a bupropion.

Some embodiments include a method of rapidly relieving the symptoms of depression, comprising administering a combination of bupropion and dextromethorphan once daily or twice daily to a human being in need thereof, wherein the human being experiences a therapeutic effect within 2 weeks of the first day that the combination of bupropion and dextromethorphan is administered.

Some embodiments include a method of treating depression, comprising administering a combination of bupropion and dextromethorphan once daily or twice daily to a human being in need thereof, wherein the human being is of Asian descent.

Some embodiments include a method of treating nicotine addiction associated with smoking tobacco comprising

administering a combination of a bupropion and a dextromethorphan daily for at least 21 consecutive days to a person suffering from nicotine addiction, wherein the person is an ad-lib tobacco smoker, wherein a total amount of 200 mg to 250 mg of bupropion and 80 mg to 140 mg of dextromethorphan are administered to the person daily, and wherein the method is more effective than administering the same amount of bupropion alone.

In some embodiments involving treating nicotine addiction, administration of the combination of the bupropion and the dextromethorphan results in at least 20% greater reduction in an intensity of the nicotine self-administration as compared to bupropion alone as measured by the reduction in the average number of cigarettes smoked per day.

In some embodiments involving treating nicotine addiction, administration of the combination of the bupropion and the dextromethorphan results in at least 10% greater reduction in expired carbon monoxide levels as compared to bupropion alone.

In some embodiments involving treating nicotine addiction, administering the combination of the bupropion and the dextromethorphan twice a day in 2 equal divided doses results in a greater reduction in intensity of nicotine self-administration at a particular timepoint, such as 1 week, 2 weeks, 3 weeks, 4 weeks, or another timepoint recited herein, than would have resulted from administering one of the 2 divided doses for the same amount of time, or than would have resulted from not administering the combination.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a plot of the mean plasma concentrations of dextromethorphan over time after dosing on Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **2** depicts mean AUC_{0-12} of dextromethorphan on Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **3** depicts mean AUC_{0-24} of dextromethorphan on Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **4** depicts mean AUC_{0-inf} of dextromethorphan on Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **5** depicts the fold changes in AUCs of dextromethorphan on Day 8 for subjects administered dextromethorphan alone as compared to dextromethorphan and bupropion.

FIG. **6** depicts mean AUC_{0-12} of dextromethorphan on Day 1 and Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **7** depicts mean dextromethorphan trough plasma concentrations for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **8** depicts mean dextromethorphan maximum plasma concentrations on Day 1 and Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **9** is a plot of the mean plasma concentrations of dextrorphan over time after dosing on Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **10** depicts mean dextrorphan maximum plasma concentrations on Day 1 and Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **11** depicts mean AUC_{0-12} of dextrorphan on Day 1 and Day 8 for subjects administered dextromethorphan alone or dextromethorphan and bupropion.

FIG. **12** depicts the potency of various antidepressant compounds for inhibition of the metabolism of dextromethorphan in human liver microsomes.

FIG. **13** is a plot of the average MADRS total score change from baseline over time during the 6-week dosing period for subjects administered bupropion alone or the combination of dextromethorphan and bupropion.

FIG. **14** depicts the percent of subjects achieving remission (MADRS≤10) over time during the 6-week dosing period for subjects administered bupropion alone or the combination of dextromethorphan and bupropion.

FIG. **15** is a plot of the reduction in MADRS total score over time for the subjects described in Example 6.

FIG. **16** is a plot of the percentage of responders over time for the subjects described in Example 6.

FIG. **17** is a plot of the percentage of subjects in remission over time for the subjects described in Example 6.

FIG. **18** is a plot of the MADRS total score change from baseline over time for the subjects described in Example 7.

FIG. **19** is a plot of the QIDS-SR-16 total score change from baseline over time for the subjects described in Example 7.

FIG. **20** is a plot of the percentage of subjects in remission (QIDS-SR-16 Score≤5) over time for the subjects described in Example 7.

FIG. **21** is a plot of the Cognitive Items of MGH-CPFQ change from baseline over time for the subjects described in Example 7.

FIG. **22** is a plot of the CMAI total score change from baseline over time for the subjects described in Example 8.

FIG. **23** is a plot of the percent CMAI reduction from baseline over time for the subjects described in Example 8.

FIG. **24** is a plot of is a plot of the percentage of responders with CMAI reduction ≥30% from baseline over time for the subjects described in Example 8.

FIG. **25** depicts the reduction in MADRS Score from baseline from the clinical trial of DM/BU in Example 10 as compared to the combination of dextromethorphan and quinidine (DM/Q) as reported in Murrough (Journal of Affective Disorders 218 (2017) 277-283, FIG. 3A).

DETAILED DESCRIPTION

Some embodiments include a method of treating neurological disorders comprising administering a therapeutically effective amount of dextromethorphan and a therapeutically effective amount of an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, to a person in need thereof.

Some embodiments include a method of enhancing the therapeutic properties of dextromethorphan in treating neurological disorders, comprising co-administering dextromethorphan and an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

Some embodiments include a method of increasing dextromethorphan plasma levels in a human being that is an extensive metabolizer of dextromethorphan, comprising co-administering an antidepressant compound, such as bupropion, and dextromethorphan to the human being.

Some embodiments include a method of inhibiting the metabolism of dextromethorphan, comprising administering

an antidepressant compound, such as bupropion, to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as the antidepressant.

Some embodiments include a method of increasing the metabolic lifetime of dextromethorphan, including increasing the elimination half-life ($T_{1/2}$) of dextromethorphan. These embodiments may comprise administering an antidepressant compound, such as bupropion, to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as the antidepressant compound.

Some embodiments include a method of correcting extensive metabolism of dextromethorphan, comprising administering an antidepressant compound, such as bupropion, to a human being in need thereof, such as a human being in need of treatment for pain.

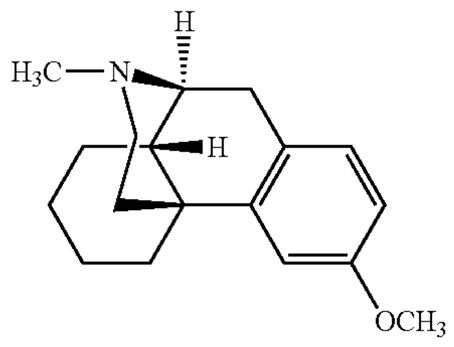
Some embodiments include a method of improving the therapeutic properties of dextromethorphan in treating neurological disorders comprising administering an antidepressant compound, such as bupropion, in conjunction with administration of dextromethorphan to a human being in need of treatment for a neurological disorder.

Some embodiments include a method of treating neurological disorders comprising administering a combination of an antidepressant compound, such as bupropion, and dextromethorphan to a human being in need thereof.

Co-administration of an antidepressant compound, such as bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a prodrug of the antidepressant compound, with dextromethorphan may occur one or more times for a single day, or for 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, or more consecutive days. In some embodiments, co-administration is at least daily for at least two consecutive days.

In some embodiments, co-administration of an antidepressant compound, such as bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a prodrug of the antidepressant compound, with dextromethorphan may occur once a day for 1, 2, 3, 4, 5, 6, or 7 days, prior to co-administration twice a day.

Dextromethorphan has the structure shown below.



Dextromethorphan is used as a cough suppressant. According to the FDA's dextromethorphan product labeling requirement under the OTC Monograph [21CFR341.74], dextromethorphan should be dosed 6 times a day (every 4 hours), 4 times a day (every 6 hours), or 3 times a day (every 8 hours). The OTC Monograph [21CFR341.74] also states that "the dosage is equivalent to dextromethorphan hydrobromide . . . [o]ral dosage is 10 to 20 milligrams every 4 hours or 30 milligrams every 6 to 8 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor."

Dextromethorphan is rapidly metabolized in the human liver. This rapid hepatic metabolism may limit systemic drug exposure in individuals who are extensive metabolizers. Human beings can be: 1) extensive metabolizers of dextromethorphan—those who rapidly metabolize dextromethorphan; 2) poor metabolizers of dextromethorphan—those who only poorly metabolize dextromethorphan; or 3) intermediate metabolizers of dextromethorphan—those whose metabolism of dextromethorphan is somewhere between that of an extensive metabolizer and a poor metabolizer. Extensive metabolizers can also be ultra-rapid metabolizers. Extensive metabolizers of dextromethorphan are a significant portion of the human population. Dextromethorphan can, for example, be metabolized to dextrorphan.

When given the same oral dose of dextromethorphan, plasma levels of dextromethorphan are significantly higher in poor metabolizers or intermediate metabolizers as compared to extensive metabolizers of dextromethorphan. The low plasma concentrations of dextromethorphan can limit its clinical utility as a single agent for extensive metabolizers, and possibly intermediate metabolizers, of dextromethorphan. Some therapeutically active compounds, including antidepressants such as bupropion, inhibit the metabolism of dextromethorphan, and raise the plasma concentration of dextromethorphan, and can thus improve its therapeutic efficacy. Similarly, antidepressants may allow dextromethorphan to be given less often, such as once a day instead of twice a day, once a day instead of three times a day, once a day instead of four times a day, twice a day instead of three times a day, or twice a day instead of four times a day, without loss of therapeutic efficacy.

Co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan may enhance the mechanisms of action, or pharmacological properties of dextromethorphan and dextrorphan. Mechanisms of action of dextromethorphan and dextrorphan can include sigma-1 agonist and NMDA antagonist properties, calcium channel blockade, muscarinic binding, serotonin transporter (5HTT) inhibition, and mu receptor potentiation.

Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to agonize, antagonize, or modulate a sigma-1 receptor, or an NMDA receptor; to block a calcium channel; to bind to a muscarinic receptor; to inhibit a serotonin transporter (5HTT); or to potentiate a mu receptor.

Pharmacological properties of dextromethorphan and dextrorphan can include NMDA high-affinity site, NMDR-2A, and functional NMDR-2B receptor antagonism, sigma-1 stimulation, putative mTOR activation (by sigma-1 stimulation, mu potentiation, beta adrenoreceptor stimulation, and 5HTT inhibition), putative AMPA receptor trafficking (by mTOR activation, PCP antagonism, sigma-1 stimulation, beta stimulation, mu potentiation, and 5HTT inhibition), and dendritogenesis, spinogenesis, synaptogenesis, and neuronal survival by NMDA antagonism and sigma-1 and mTOR signaling. Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to bind to, agonize, antagonize, stimulate, activate, inhibit, influence the trafficking of, or modulate an NMDA high-affinity site,

NMDR-2A, a functional NMDR-2B receptor, sigma-1 receptor, a putative mTOR receptor (such as by stimulating sigma-1, potentiating a mu receptor, stimulating a beta adrenoreceptor, or inhibiting a 5HTT), or a putative AMPA receptor (such as by activating mTOR, antagonizing PCP activity, stimulating a sigma-1 receptor, stimulating a beta adrenergic receptor, potentiating a mu receptor, or inhibiting 5HTT). Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to cause, increase, decrease, or otherwise modulate dendritogenesis, spinogenesis, or synaptogenesis. Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to cause, increase, decrease, or otherwise modulate neuronal survival by NMDA antagonism and/or sigma-1 and/or mTOR signaling.

Pharmacological properties of dextromethorphan and dextrorphan can include 5HTT and norepinephrine transporter inhibition, sigma-1 stimulation, NMDA and PCP antagonism, and possible serotonin 5HT1b/d receptor stimulation. Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to bind to, agonize, antagonize, stimulate, activate, inhibit, influence the trafficking of, or modulate the 5HTT and/or norepinephrine transporter, the sigma-1 receptor, NMDA and/or PCP receptor, and/or to stimulate the serotonin 5HT1b/d receptor.

Additional properties for dextromethorphan and dextrorphan can include possible presynaptic alpha-2 adrenoreceptor antagonism or postsynaptic alpha-2 stimulation, beta stimulation and possible muscarinic and mu antagonism. Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to bind to, agonize, antagonize, stimulate, activate, inhibit, influence the trafficking of, or modulate a presynaptic alpha-2 adrenoreceptor, postsynaptic alpha-2 receptor, beta adrenoreceptor, muscarinic receptor, or mu receptor. Dextromethorphan and dextrorphan may be glial cell modulators. Some embodiments include co-administration of an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan or dextrorphan to modulate glial cells.

Pain or other neurological disorders may be treated by enhancing dextromethorphan plasma levels or increasing dextromethorphan bioavailability, for example by a method comprising administering a therapeutically effective amount of dextromethorphan and a therapeutically effective amount of an antidepressant compound, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, to a person in need thereof.

Examples of neurological disorders that may be treated, or that may be treated with increased efficacy, by enhanced dextromethorphan levels, such as those achievable by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, include, but are not limited to: affective disorders, psychiatric disorders, cerebral function disorders, movement disorders, dementias, motor neuron diseases, neurodegenerative diseases, seizure disorders, and headaches.

Affective disorders that may be treated by enhanced dextromethorphan levels or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, include, but are not limited to, depression, major depression, treatment resistant depression and treatment resistant bipolar depression, bipolar disorders including cyclothymia, seasonal affective disorder, mood disorders, chronic depression (dysthymia), psychotic depression, postpartum depression, premenstrual dysphoric disorder (PMDD), situational depression, atypical depression, mania, anxiety disorders, attention deficit disorder (ADD), attention deficit disorder with hyperactivity (ADDH), and attention deficit/hyperactivity disorder (AD/HD), bipolar and manic conditions, obsessive-compulsive disorder, bulimia, obesity or weight-gain, narcolepsy, chronic fatigue syndrome, premenstrual syndrome, substance addiction or abuse, nicotine addiction, psycho-sexual dysfunction, pseudobulbar affect, and emotional lability.

Depression may be manifested by depressive symptoms. These symptoms may include psychological changes such as changes in mood, feelings of intense sadness, despair, mental slowing, loss of concentration, pessimistic worry, agitation, anxiety, irritability, guilt, anger, feelings of worthlessness, reckless behavior, suicidal thoughts, or attempts, and/or self-deprecation. Physical symptoms of depression may include insomnia, anorexia, appetite loss, weight loss, weight gain, decreased energy and libido, fatigue, restlessness, aches, pains, headaches, cramps, digestive issues, and/or abnormal hormonal circadian rhythms.

Some patients, even after treatment with medications such as antidepressants, may have an inadequate or no response to the treatment. Treatment resistant depression (TRD), or treatment-refractory depression, is a condition generally associated with patients who have failed treatment with at least two antidepressants. Part of the diagnosis for TRD is for the patient to have had an inadequate response to treatment with the antidepressants after an adequate dose and adequate course, e.g., in the current depressive episode. TRD may be more difficult to treat due to the comorbidity of other medical or psychological illnesses, such as drug/alcohol abuse or eating disorders, or TRD being misdiagnosed. Some TRD patients have had an inadequate response to 1, 2, 3, or more adequate antidepressant treatment trials or have failed or had an inadequate response to 1, 2, 3, or more prior antidepressant treatments. In some embodiments, a patient being treated for treatment resistant depression has failed treatment with at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more antidepressant therapies.

Measures of treatment effect that may be improved by treatment with enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, include, but are not limited to: Montgomery-Åsberg Depression Rating Scale (MADRS), Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, Range of Impaired Functioning Tool, Sheehan Disability Scale, Patient Rated Inventory of Side Effects (PRISE), Columbia—Suicide Severity Rating Scale (C-SSRS), Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR),

Clinical Global Impression (CGI) scale, Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), 17-item Hamilton Rating Scale for Depression (HAM-D17), Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ), 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16), Sheehan Disability Scale (SDS), Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global Impression of Change (CGI-C), EuroQOL 5 Dimension 5 Level (EQ-5D-5L), Patient Global Impression of Change (PGIC), 7-item Generalized Anxiety Disorder (GAD-7), Clinical Global Impressions—Improvement (CGI-I). Sheehan Disability Scale (SDS). 16-item Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR16), Hamilton Anxiety Scale (HAM-A), Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), CPFQ-Cognitive subscales (Items 4 to 7), Brief Psychiatric Rating Scale (BPRS), etc.; Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Task (RAVLT), Trail Making Test (TMT), Stroop Colour Naming Test (STROOP), Simple Reaction Time (SRT), Choice Reaction Time (CRT). etc. In some embodiments, treating a person with a combination of dextromethorphan and bupropion may improve (e.g. reduce) the person's score in one of the above assessments by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, about 10-20%, about 20-30%, about 30-40%, about 40-50%, about 5-15%, about 15-25%, about 25-35%, about 35-45%, about 45-55%, about 50-60%, about 60-70%, about 70-80%, about 80-90%, about 90-100% as compared to baseline or placebo. In some embodiments, the improvement is compared to baseline. In some embodiments, the improvement is compared to placebo.

Administering a combination of bupropion and dextromethorphan may result in a rapid treatment effect, e.g., within about 1 week, within about 2 weeks, within about 3 weeks, or within about 4 weeks of beginning the treatment. For example, an improvement in any of the assessments described herein, including, but not limited to MADRS, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, Range of Impaired Functioning Tool, PRISE, C-SSRS, QIDS-SR), CGI, CPFQ, HAM-D17, MGH ATRQ, CGI-S, CGI-C, EQ-5D-5L, PGIC, GAD-7, CGI-I, SDS, QIDS-SR16, HAM-A, CPFQ, CPFQ-Cognitive subscales (Items 4 to 7), BPRS, DSST, RAVLT, TMT, STROOP, SRT, CRT, etc., may be observed within those time periods.

In some embodiments, an enhanced bioavailability of dextromethorphan, or a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, may have an onset of action within 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 6-8 hours, 8-12 hours, 12 hours, a day, 1-7 days, 1 week, two weeks, three weeks, four weeks, six weeks, or eight weeks.

Patients who may benefit from the treatments described herein include pediatric patients, such as patients under about 18 years of age, about 0-5 years of age, about 5-10 years of age, about 10-12 years of age, or about 12-18 years of age; adult patients, such as patients having an age of about 18-70 years, about 18-65 years, about 18-30 years, about 10-20 years, about 20-30 years, about 30-40 years, about 40-50 years, about 50-60 years, about 60-70 years, about 70-80 years, about 80-90 years, about 30-50 years, about 50-65 years; elderly patients, such as patients over 65 years of age, about 65-75 years of age, about 75-90 years of age, or over 90 years of age; and about 41 years of age or older.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being, of Asian descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being, of Japanese descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being, of Korean descent. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being, of Chinese descent. The assignment of an individual as having Asian, Chinese, Japanese, or Korean descent may be based upon self-reporting by the individual. In these Asian individuals, the combination of dextromethorphan and bupropion may be effective for treating depression where bupropion alone is not. This may be of particular importance because patients of Asian descent may suffer from more severe depression than those of other ethnic or cultural groups.

In some embodiments, the human being does not have, or is selected for not having, a depressive episode with psychotic or catatonic features.

In some embodiments, the human being does not have, or is selected for not having, a manic, hypomanic, or mixed episode, including bipolar disorder (Type 1 or Type 2) and substance-induced (e.g., antidepressant-induced) manic, or a hypomanic/mixed episode.

In some embodiments, the human being does not have, or is selected for not having schizophrenia, schizoaffective, or another psychotic disorder.

In some embodiments, the human being does not have, or is selected for not having, a panic disorder, with or without agoraphobia.

In some embodiments, the human being does not have, or is selected for not having obsessive-compulsive disorder.

In some embodiments, the human being does not have, or is selected for not having bulimia or anorexia nervosa.

In some embodiments, the human being does not have, or is selected for not having, a persistent neurocognitive disorder.

In some embodiments, the human being does not have, or is selected for not having, any anxiety disorder for the six months prior to treatment.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a diagnosis with major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Clinical Trials Version SCID-5-CT. In some embodiments, the human being currently meets the DSM-5 criteria for MDD without psychotic features, based on the SCID-5-CT

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, is suffering from, or is selected for suffering from, a major depressive episode that has lasted between about 8 weeks and about 24 months, about 1-6 months, about 6-12 months, about 1-2 years, at least about 1 week, at least about 2 weeks, at least about 3 weeks, at least about 4 weeks, at least about 6 weeks, at least about 2 months, at least about 3 months, at least about 4 months, at

least about 6 months, at least about 9 months, at least about 1 year, at least about 18 months, at least about 2 years, about 1-12 weeks, about 3-6 months, about 6-9 months, about 9-12 months, about 12-18 months, about 18-24 months, about 2-4 years, about 4-6 years, about 6-10 years, about 10-20 years or longer.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected having, about 1-100, or more, lifetime depressive episodes, such as a major depressive episodes, including at least 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 10, at least about 15, at least about 20, at least about 30, at least about 40, at least about 50, at least about 60, at least about 70, at least about 80, at least about 90, at least about 100, about 1-5, about 5-10, about 10-20, about 20-30, about 30-40, about 40-50, about 50-60, about 60-70, about 70-80, about 80-90, about 90-100, or about 4-7 lifetime depressive episodes.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, an inadequate response to one or more prior antidepressant therapies, e.g., 1, 2, 3, 4, 5 or more prior antidepressant therapies, including prior antidepressant therapies in the current depressive episode (e.g., the current major depressive episode).

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has had, or is selected for having had a background antidepressant therapy with, such as a selective serotonin reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), or bupropion, taken at an adequate dose for at least 8 weeks, and at a stable dose for at least 4 weeks prior to entering the double-blind treatment period. In some embodiments, the antidepressant therapy is continued in conjunction with treatment with the combination of bupropion and dextromethorphan.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being male. In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, is, or is selected for being female.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a body mass index of about 18-40 kg/m^2, about 18.5 kg/m^2, less than 18.5 kg/m^2, about 19 kg/m^2, about 19-24.9 kg/m^2, about 25 kg/m^2, about 25-29 kg/m^2, about 29 kg/m^2, more than 29 kg/m^2, about 18-22 kg/m^2, about 22-24 kg/m^2, about 24-26 kg/m^2, about 26-28 kg/m^2, about 28-30 kg/m^2, about 30-32 kg/m^2, about 32-34 kg/m^2, about 34-36 kg/m^2, about 36-38 kg/m^2, about 38-40 kg/m^2, about 18-26 kg/m^2, about 26-34 kg/m^2, or about 34-40 kg/m^2.

The MADRS is a clinician-rated scale. The MADRS is used to assess depressive symptomatology during the previous week. Subjects are rated on 10 items to assess feelings of guilt, sadness, lassitude, pessimism, inner tension, suicidality, reduced sleep or appetite, agitation, anxiety, weight loss, somatic symptoms, difficulty concentrating and lack of interest. Each item is scored on a 7-point scale. A score of 0 indicates the absence of symptoms, and a score of 6 indicates symptoms of maximum severity.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a MADRS score that is at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, about 20-25, about 25-30, about 30-35, about 35-40, about 40-45, about 45-50, about 50-55, about 55-60, about 25-35, about 35-45, about 45-60, about 25-40, or about 40-60.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS score that is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, about 10-20%, about 20-30%, about 30-40%, about 40-50%, about 50-60%, about 60-80%, about 80-90%, or about 90-100% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS score that is less than 34, about 20-34, about 7-19, about 0-6, about 30 or less, about 26 or less, about 25 or less, about 20 or less, about 17 or less, about 14 or less, about 12 or less, about 10 or less, about 8 or less, about 6 or less, about 5 or less, about 4 or less, about 3 or less, about 2 or less, about 1 or less, about 0, about 0.1-6, about 0.1-1, about 1-2, about 2-3, about 3-4, about 4-5, about 5-6, about 6-7, about 7-8, about 8-9, about 9-10, about 10-11, about 11-12, about 12-13, about 13-14, about 14-15, about 15-16, about 16-17, about 17-18, about 18-19, about 19-20, about 18-20, about 0.1-3, about 3-6, about 6-9, about 9-12, about 12-14, about 12-15, or about 15-20.

The subscale MADRS-6 is the sum of responses to six of the 10 MADRS items that are thought to represent the core symptoms of depression: reported sadness, apparent sadness, inner tension, lassitude, inability to feel, and pessimistic thoughts. MADRS items not included in the MADRS-6 score are reduced sleep, reduced appetite, concentration difficulties, and suicidal thoughts. Higher MADRS score indicates more severe depression, and each item yields a score of 0 to 6. The overall score ranges from 0 to 60. The questionnaire includes questions on the following symptoms 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts. Usual cutoff points are: a) 0 to 6—normal/symptom absent; b) 7 to 19—mild depression; c) 20 to 34—moderate depression; and d) >34—severe depression.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a MADRS-6 score that is at least about 15, at least about 18, at least about 20, at least about 21, at least about 24, at least about 27, at least about 30, at least about 33, about 15-18, about 18-21, about 21-24, about 24-27, about 27-30, about 30-33, about 30-34, about 33-36, at least about 34, about 7-19, about 15-19, about 15-24, about 24-30, about 20-34, or about 30-36, prior to starting the treatment.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS-6 score reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50%, about 10-20%, about 20-30%, about 30-40%, about 40-50%, about 50-60%, about 60-80%, about 80-90%, or about 90-100% as compared to baseline or

placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a MADRS-6 score that is about 17 or less, about 15 or less, about 10 or less, about 8 or less, about 6 or less, about 5 or less, about 4 or less, about 3 or less, about 2 or less, about 1 or less, about 0.1-6, about 0.1-1, about 1-2, about 2-3, about 3-4, about 4-5, about 5-6, about 6-7, about 7-8, about 8-9, about 9-12, about 12-15, about 0.1-3, about 3-6, about 6-8, about 6-9, or about 9-15.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a score for item 1 (Apparent sadness) on the MADRS that is 2, 4, or 6, prior to starting the treatment.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a reduction of the score for item 1 on the MADRS that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a score on item 1 of the MADRS that is about 2 or less.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time. In some embodiments, the treatment effect is assessed weekly using the MADRS.

The CGI-S scale is a clinician-rated scale used to rate the severity of the subject's current state of mental illness compared with a subject population with MDD. The subject is rated on a scale from 1 to 7, with 1 indicating a "normal state" and 7 indicating "among the most extremely ill subjects." The CGI-S may be administered by a person with extensive professional training and experience in assessing mental illness. Possible ratings are: 1) Normal, not at all ill; 2) Borderline mentally ill; 3) Mildly ill; 4) Moderately ill; 5) Markedly ill; 6) Severely ill; and 7) Among the most extremely ill patients.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a Clinical Global Impression—Severity (CGI-S) score that is at least about 3, at least about 4, at least about 5, at least about 6, about 7, about 3-7, about 4-7, about 3-4, about 4-5, about 5-6, or about 6-7.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the CGI-S score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the CGI-S score that is at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, about 0.1-6, about 0.1-1, about 1-2, about 2-3, about 3-4, about 4-5, about 5-6, about 0.1-3, or about 3-6. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-6, weeks 2-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The 16-item QIDS-SR-16, a patient-rated scale, is an abbreviated version of the 30-item Inventory of Depressive Symptomatology (IDS) and is designed to assess the severity of depressive symptoms. The QIDS-SR-16 assesses criterion symptom domains to diagnose a major depressive episode.

The QIDS-SR may be used to assess the subject's depressive symptomatology over the prior 7 days. Subjects report severity of symptoms on 10 items: sleep, feelings of sadness, appetite, weight change, concentration, self-regard, suicidality, general interest level, energy level, psychomotor retardation, and restlessness. Each item may be scored on a 4-point scale with a score of 0 reflecting no symptoms and a score of 3 reflecting symptoms of maximum severity.

Total QIDS scores range from 0 to 27, with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 reflecting severe depression, and total scores greater than 21 indicating very severe depression.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a QIDS-SR-16 score that is at least about 16, at least about 18, at least about 21, at least about 24, at least about 27, at least about 30, at least about 33, about 16-18, about 16-19, about 16-20, about 18-21, about 21-24, about 24-27, about 15-21, or about 21-27, prior to starting the treatment.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the QIDS-SR-16 score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a QIDS-SR-16 score that is about 6 or less, about 5 or less, about 4 or less, about 3 or less, about 2 or less, about 1 or less, about 0.1-6, about 0.1-5, about 0.1-1, about 1-2,

about 2-3, about 3-4, about 4-5, about 5-6, about 0.1-3, or about 3-6. Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The CGI-I scale is a clinician-rated scale that is used to rate total improvement or worsening of mental illness regardless of whether the Investigator considers it to be a result of drug treatment or not. The subject is rated on a scale from 1 to 7, with 1 indicating that the subject is very much improved and 7 indicating that the subject is very much worse. The CGI-I may be administered by a person with extensive professional training and experience in assessing mental illness.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a CGI-I score that is about 3 or less, about 2 or less, about 1, about 1-2, or about 2-3.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The VAMS is a patient-rated mood scale consisting of a 100-mm line with graphical, schematic, or pictorial representations of extremes of mood, e.g., happiness and sadness, at the two ends of the line, such as a sad face at one end and a happy face at the other end. Each end of the line may be further anchored by a word statement which describe the extremes of mood. Subjects are asked to rate their mood as a mark on the line. The distance on the line is measured and calculated as a numerical score from 0 to 100. Subjects may be asked to complete the VAMS daily.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a VAMS score that is at least about 40 mm, at least about 50 mm, at least about 60 mm, at least about 70 mm, at least about 80 mm, at least about 90 mm, about 40-50 mm, about 50-60 mm, about 60-70 mm, about 70-80 mm, about 80-90 mm, about 90-100 mm, about 40-60 mm, about 60-80 mm, or about 80-100 mm.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the VAMS score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, treatment with the combination of dextromethorphan and bupropion results in the human being having a VAMS score that is less than about 50 mm, less than about 40 mm, less than about 30 mm, less than about 20 mm, less than about 10 mm, about 0-10 mm, about 10-20 mm, about 20-30 mm, about 30-40 mm, about 40-50 mm, about 0-25 mm, or about 25-50 mm.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The Columbia Suicide Severity Rating Scale (C-SSRS) is a clinician-rated instrument that reports the severity of both suicidal ideation and behavior. Suicidal ideation is classified on a 5-item scale: 1 (wish to be dead), 2 (nonspecific active suicidal thoughts), 3 (active suicidal ideation with any methods [not plan] without intent to act), 4 (active suicidal ideation with some intent to act, without specific plan), and 5 (active suicidal ideation with specific plan and intent). The C-SSRS also captures information about the intensity of ideation, specifically the frequency, duration, controllability, deterrents, and reasons for the most severe types of ideation. Suicidal behavior is classified on a 5-item scale: 0 (no suicidal behavior), 1 (preparatory acts or behavior), 2 (aborted attempt), 3 (interrupted attempt), and 4 (actual attempt). More than 1 classification can be selected provided they represent separate episodes. For actual attempts only, the actual or potential lethality is classified for the initial, most lethal, and most recent attempts.

The C-SSRS may be administered each time a person being treated sees a health professional. The C-SSRS may be completed for the subject's lifetime history of suicidal ideation and behavior, along with a recent recall period.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the Columbia—Suicide Severity Rating Scale (C-SSRS) score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or

at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The Sheehan Disability Scale (SDS) is a self-rated instrument used to measure the effect of the patient's symptoms on the following three items: work/school, social life, and family/home responsibilities. For each of the three items, scores range from 0 through 10. The number most representative of how much each area was disrupted by symptoms is marked along the line from 0 (not at all) to 10 (extremely). The three items or domains can be summarized to evaluate global functional impairment by adding the scores of each of the three items or domains, resulting in global SDS score ranges from 0 (unimpaired) to 30 (highly impaired).

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a Sheehan Disability Scale (SDS) score that is: for each item SDS (0-10 scale) at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 9; and for SDS total score at least about 5, at least 10, at least about 20, about 10-15, about 15-20, about 20-25, or about 25-30.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the SDS score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The Hamilton Rating Scale for Depression (HAM-D, HRSD, HDRS, or HAMD-17) is a clinician-rated, 17-item scale used to rate the subject's depressive state based on feelings of depression, guilt, suicidality, anxiety, agitation, level of insight, patterns of insomnia, loss of interest in work and other activities, weight loss, hypochondriasis, and degree of psychomotor retardation. It also can be used to identify genital, and somatic symptoms. Items are rated either on 0-2 scale or on 0-4 scale. A higher score is indicative of more severity. For example, HAM-D score level of depression of 10-13 is considered mild; 14-17 is considered mild to moderate; and >17 is considered moderate to severe.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a HAM-D score that is at least about 16, at least about 19, at least about 21, at least about 24, at least about 27, at least about 30, at least about 33, at least about 36, about 16-19, about 18-21, about 21-24, about 24-27, about 27-30, about 30-33, about 33-36, about 36-40, about 15-24, about 24-33, or about 33-40, or more than 40 prior to starting the treatment.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the HAM-D score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time. In some embodiments, the treatment effect is assessed weekly using the HAM-D.

Conversion from MADRS scores to HAM-D scores and vice versa may be accomplished using the table below.

Total scores		Change scores		Percentage change scores	
MADRS	HAMD	MADRS	HAMD	MADRS	HAMD
				−100	−98
				−98	−94
				−96	−92
3	3	−37	−27	−94	−90
4	4	−36	−26	−92	−88
5	4	−35	−25	−90	−86
6	5	−34	−25	−88	−84
7	6	−33	−24	−86	−83
8	7	−32	−23	−84	−81
9	7	−31	−23	−82	−80
10	8	−30	−22	−80	−79
11	9	−29	−22	−78	−77
12	9	−28	−21	−76	−75
13	10	−27	−20	−74	−74
14	11	−26	−20	−72	−73
15	12	−25	−19	−70	−72
16	12	−24	−18	−68	−70
17	13	−23	−18	−66	−67
18	14	−22	−17	−64	−65
19	15	−21	−16	−62	−62
20	16	−20	−16	−60	−61
21	16	−19	−15	−58	−59
22	17	−18	−14	−6	−57
23	18	−17	−14	−54	−56
24	19	−16	−13	−52	−54
25	19	−15	−12	−50	−52
26	20	−14	−12	−48	−50
27	21	−13	−11	−46	−48
28	22	−12	−10	−44	−47
29	23	−11	−9	−42	−45
30	23	−10	−9	−40	−43
31	24	−9	−8	−38	−41
32	25	−8	−7	−36	−39
33	25	−7	−6	−34	−37
34	26	−6	−6	−32	−35
35	27	−5	−5	−30	−33
36	28	−4	−4	−28	−31
37	29	−3	−3	−26	−29
38	29	−2	−2	−24	−27

-continued

Total scores		Change scores		Percentage change scores	
MADRS	HAMD	MADRS	HAMD	MADRS	HAMD
39	30	−1	−1	−22	−25
40	31	0	−1	−20	−23
41	32	1	0	−18	−21
42	33	2	1	−16	−19
43	34	3	2	−14	−17
44	35	4	2	−12	−15
45	35	5	3	−10	−13
46	36	6	4	−8	−11
47	37	7	4	−6	−9
48	37	8	5	−4	−7
49	38			−2	−5
50	38			0	−3
51	39			2	0
52	40			4	1
53	40			6	2
				8	4
				10	5
				12	7
				14	9
				16	10
				18	11
				20	13
				22	15
				24	17
				26	18
				28	19
				30	20
				32	21
				34	22
				36	24
				38	26
				40	28

Negative values mean improvement.

The Hamilton Anxiety Scale (HAM-A) is a clinician-administered scale which consists of 14 items, each rated on a five point scale ranging from 0 (not present) to 4 (very severe). The highest possible total score is 56, which represents the most severe form of anxiety; the lowest possible score is 0, which represents an absence of anxiety.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a Hamilton Anxiety Scale (HAM-A) score that is at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, about 20-25, about 25-30, about 30-35, about 35-40, about 40-45, about 45-50, about 50-56, about 25-35, about 35-45, about 45-56, about 25-40, or about 40-56.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the HAM-A score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) is a 7-item patient-rated scale used to measure cognitive and executive dysfunction in mood and anxiety disorders and was developed to assess clinically relevant cognitive and physical symptoms that could emerge or persist during long-term treatment for depression. Subjects grade the perceived quality of their physical and cognitive functioning. It is scored from 1-6 with increasing severity that individually evaluates 7 distinct items: motivation/enthusiasm, wakefulness/alertness, energy, focus/attention, recall, ability to find words, and sharpness/mental acuity. The physical dimension of the CPFQ assesses sleepiness and fatigue, and the cognitive dimension assesses apathy, inattention, forgetfulness, word-finding difficulties, and mental slowness. A higher score is indicative of more impairment.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the CPFQ score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the CPFQ-Cognitive subscales (items 4-7) score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

The Brief Psychiatric Rating Scale (BPRS) is a clinician-administered scale developed to measure psychiatric symptoms such as depression, anxiety, hallucinations, and unusual behavior. Each symptom is rated from 1 (not present) to 7 (extremely severe). Zero is entered if the item is not assessed and will be excluded from the analysis. The scale should be administered by a clinician who is knowledgeable concerning psychotic disorders and able to interpret the constructs used in the assessment. Factor 1 (Reality Distortion) items are Suspiciousness, Hallucinatory Behavior and Unusual Thought Content.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, a Brief Psychiatric Rating Scale (BPRS)-Factor 1 score that

is starting score: at least about 3, at least about 4, at least about 5, at least about 6, about 7, about 3-7, about 4-7, about 4-5, about 5-6, or about 6-7.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the BPRS-Factor 1 score that is at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, about 0.1-6, about 0.1-1, about 1-2, about 2-3, about 3-4, about 4-5, about 5-6, about 0.1-3, or about 3-6 as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g. for a type of depression, has, or is selected for having, a Beck Depression Inventory (BDI) score that is at least about 20, at least about 25, at least about 30, at least about 35, at least about 40, at least about 45, at least about 50, at least about 55, at least about 60, about 20-25, about 25-30, about 30-35, about 35-40, about 40-45, about 45-50, about 50-55, about 55-60, about 60-63, about 25-35, about 35-45, about 45-55, about 55-63, about 25-40, or about 40-63.

The Beck Depression Inventory (BDI, BDI-1A, BDI-II) is a 21-question multiple-choice self-report inventory about how the subject has been feeling in the last week. Each question had a set of four possible responses, ranging in intensity. When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the depression's severity. Higher total scores indicate more severe depressive symptoms. The standard cut-off scores were as follows: 0-9: indicates minimal depression; 10-18: indicates mild depression; 19-29: indicates moderate depression; and 30-63: indicates severe depression.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having a reduction in the BDI score that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

In some embodiments, the human being that is treated with a combination of dextromethorphan and bupropion, e.g., for a type of depression, has, or is selected for having, C Reactive Protein (CRP) levels that are at least 0.5 mg/L, at least 1 mg/L, at least 2 mg/L, or higher.

In some embodiments, administering the combination of dextromethorphan and bupropion results in the human being having an improvement in CRP level that is at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50% as compared to baseline or placebo. In some embodiments, the reduction is compared to baseline. In some embodiments, the reduction is compared to placebo.

Treatment effect may be assessed at any appropriate time, such as during weeks 1-2, weeks 1-3, weeks 1-4, weeks 1-5, weeks 1-6, weeks 4-6, weeks 6-8, weeks 8-12, weeks 12-16, at the beginning or at the end of week 1, at the beginning or at the end of week 2, at the beginning or at the end of week 3, at the beginning or at the end of week 4, at the beginning or at the end of week 5, at the beginning or at the end of week 6, at the beginning or at the end of week 7, at the beginning or at the end of week 8, at the beginning or at the end of week 9, at the beginning or at the end of week 10, at the beginning or at the end of week 11, at the beginning or at the end of week 12, at the beginning or at the end of week 13, at the beginning or at the end of week 14, at the beginning or at the end of week 15, at the beginning or at the end of week 16, or at any other time.

Conversion between some of the scores in some of the assessments above may be done according to the tables below.

Severity	IDS-C	IDS-SR	QIDS-C	QIDS-SR	HRSD 17	HRSD21	HRSD24	MADRS	BDI
0	0-3	0-3	0	0	0	0-1	0-1	0	0
0	4-5	4-5	1	1	1-2	2	2		
0	6	6	2	2	3	3	3-4		
0	7-8	7-8	3	3	4	4	5		
0	9-10	9-11	4	4	5-6	5-6	6-7		
0	11	12-13	5	5	7	7-8	8-9	6	9
1	12-15	14-16	6	6	8	9	10-11	7	10
1	16-17	17-18	7	7	9-10	10	12		
1	18-20	19-21	8	8	11	11-12	13-14		
1	21-22	22-23	9	9	12	13	15-16		
1	23	24-25	10	10	13	14-15	17-18	19	18
2	24-27	26-28	11	11	14-15	16	19	20	19

-continued

Severity	IDS-C	IDS-SR	QIDS-C	QIDS-SR	HRSD 17	HRSD21	HRSD24	MADRS	BDI
2	28-29	29-30	12	12	16	17	20-21		
2	30-32	31-33	13	13	17	18-19	22-23		
2	33-35	34-36	14	14	18-19	20-21	24-25		
2	36	37-38	15	15	18-19	22	26	34	29
3	37-39	39-40	16	16	20	23	27-28	35	30
3	40-41	41-43	17	17	21-22	24-25	29-30		
3	42-43	44-45	18	18	23	26	31-32		
3	44-45	46-47	19	19	24	27	33		
3	46	48	20	20	25	28	34		
4	47-51	49-53	21	21	26-27	29-31	35-38		
4	52-53	54-55	22	22	28	32	39		
4	54-56	56-58	23	23	29	33-34	40-41		
4	57-59	59-61	24	24	30-31	35-36	42-44		
4	60-62	62-24	25	25	32	37-38	45-46		
4	63-65	65-67	26	26	33-35	39-41	47-49		
4	66-84	68-84	27	27	36-52	42-64	50-75	60	63

[1]Severity of Depression.
0 = None,
1 = Mild,
2 = Moderate,
3 = Severe,
4 = Very Severe.

Severity	IDS-SR	QIDS-SR	HRSD 17	HRSD21	HRSD24
0	0-3	0	0	0-1	0-1
0	4-5	1	1-2	2	2
0	6	2	3	3	3-4
0	7-8	3	4	4	5
0	9-11	4	5-6	5-6	6-7
0	12-13	5	7	7-8	8-9
1	14-16	6	8	9	10-11
1	17-18	7	9-10	10	12
1	19-21	8	11	11-12	13-14
1	22-23	9	12	13	15-16
1	24-25	10	13	14-15	17-18
2	26-28	11	14-15	16	19
2	29-30	12	16	17	20-21
2	31-33	13	17	18-19	22-23
2	34-36	14	18-19	2-21	24-25
2	37-38	15	18-19	22	26
3	39-40	16	20	23	27-28
3	41-43	17	21-22	24-25	29-30
3	44-45	18	23	26	31-32
3	46-47	19	24	27	33
3	48	20	25	28	34
4	49-53	21	26-27	29-31	35-38
4	54-55	22	28	32	39
4	56-58	23	29	33-34	40-41
4	59-61	24	30-31	35-36	42-44
4	62-24	25	32	37-38	45-46
4	65-67	26	33-35	39-41	47-49
4	68-84	27	36-52	42-64	50-75

[1]Severity of Depression. 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Very Severe.

QIDS-SR16	IDS-SR30	HAM-D24	HAM-D21	HAM-D17
0	0-3	0-1	0-1	0
1	4-5	2	2	1-2
2	6	3-4	3	3
3	7-8	5	4	4
4	9-11	6-7	5-6	5-6
5	12-13	8-9	7-8	7
6	14-16	1-11	9	8
7	17-18	12	10	9-10
8	19-21	13-14	11-12	11
9	22-23	15-16	13	12
10	24-25	17-18	14-15	13
11	26-28	19	16	14-15

-continued

QIDS-SR16	IDS-SR30	HAM-D24	HAM-D21	HAM-D17
12	29-30	20-21	17	16
13	31-33	22-23	18-19	17
14	34-36	24-25	20-21	18-19
15	37-38	26	22	18-19
16	39-40	27-28	23	20
17	41-43	29-30	24-25	21-22
18	44-45	31-32	26	23
19	46-47	33	27	24
20	48	34	28	25
21	49-53	35-38	29-31	26-27
22	54-55	39	32	28
23	56-58	40-41	33-34	29
24	59-61	42-44	35-36	30-31
25	62-24	45-46	37-38	32
26	65-67	47-49	39-41	33-35
27	68-84	50-75	42-64	36-52

IDS-SR30	QIDS-SR16	HAM-D24	HAM-D21	HAM-D17
0-2	0	0	0	0
3	0	1	1	1
4-5	1	2-3	2	2
6	2	4	3	3
7	3	5	4	3
8	3	5	4	4
9	4	6	5	5
10	4	7	6	5
11	4	7	6	6
12	5	8	7	6
13	5	9	7	7
14	6	9	8	7
15	6	10	9	8
16	6	11	9	9
17	7	12	10	9
18	7	12	10	10
19	8	13	11	10
20	8	14	12	11
21	8	15	12	11
22	9	15	13	12
23	9	16	13	12
24	10	17	14	13
25	10	17	15	13
26	11	18	15	14
27	11	19	16	14

-continued

IDS-SR30	QIDS-SR16	HAM-D24	HAM-D21	HAM-D17
28	11	20	16	15
29	12	20	17	15
30	12	21	17	16
31	13	22	18	16
32	13	22	19	17
33	13	23	19	17
34	14	24	20	18
35	14	25	20	19
36	14	25	21	19
37-38	15	26	22	20
39-40	16	27-28	23	20
41	17	29	24	21
42-43	17	30	25	22
44-45	18	31-32	26	23
46-47	19	33	27	24
48	20	34	28	25
49-50	21	35	29	26
51-52	21	36-37	30	26
53	21	38	31	27
54-55	22	39	32	28
56-57	23	40	33	29
58	23	41	34	29
59	24	42-43	35	30
60-61	24	44	36	31
62	25	45	37	32
63-64	25	46	38	33
65	26	47	39	33
66	26	48	40	34
67	26	49	41	35
68	27	50	42	35
69-70	27	51	43	36
71	27	52	44	37
72	27	53-54	45	38
73-74	27	55	46	39
75-76	27	56	47-48	40
77-78	27	57-58	49-50	42-43
79-82	27	59-62	51-54	44-48
83-84	27	63-75	55-64	49-52

In some embodiments, the combination of dextromethorphan and bupropion is a novel and oral NMDA receptor antagonist with multimodal activity for the treatment of central nervous system (CNS) disorders. The dextromethorphan is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, also known as a glutamate receptor modulator, which is a novel mechanism of action that works differently than currently available therapies for depression.

The dextromethorphan is also a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion can increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. Both dextromethorphan and bupropion are nicotinic acetylcholine receptor antagonists, a mechanism that is relevant to nicotine dependence. Thus, the combination of dextromethorphan and bupropion provides a potentially new mechanism of action for smoking cessation treatment.

In some embodiments, the combination of dextromethorphan and bupropion may be used to treat nicotine addiction. In some embodiments, the combination of dextromethorphan and bupropion may be administered once daily or twice daily to a human being. In some embodiments, the combination of dextromethorphan and bupropion may be administered twice daily to a human being. In some embodiments, the combination of dextromethorphan and bupropion may be administered once daily or twice daily to a human being for at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6-months, about 6-12 months, about 1 year, about 2 years or longer. In some embodiments, the combination of dextromethorphan and bupropion may be administered twice daily to a human being for at least 1 week, at least 2 weeks, at least 3 weeks, or longer.

In some embodiments, the smoker may be, or may be selected for being, an ad-lib smoker. In some embodiments, the smoker may, or may be selected for, smoking 10 or more cigarettes daily on average, such as about 10, about 10-15, about 10-17, about 10-20, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 20-25, about 25-30, about 30-40, about 40-50 cigarettes, or more, before administration of the combination of dextromethorphan and bupropion.

In some embodiments, the combination of dextromethorphan and bupropion may be used to treat nicotine addiction, and the combination contains about 30-100 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 35 mg, about 35 mg, about 55 mg, about 65 mg, about 75 mg, about 85 mg, or about 95 mg of dextromethorphan in a free base form or a salt form. In some embodiments, the dextromethorphan is in an HBr salt form.

In some embodiments, the combination of dextromethorphan and bupropion may be used to treat nicotine addiction, wherein the combination contains about 100-200 mg, about 100-150 mg, about 150-200 mg, about 100-110 mg, about 110-120 mg, about 120-130 mg, about 130-140 mg, about 140-150 mg, about 150-160 mg, about 160-170 mg, about 170-180 mg, about 180-190 mg, about 190-200 mg, about 105 mg, about 115 mg, about 125 mg, about 135 mg, about 145 mg, about 150 mg, about 155-165 mg, about 165-175 mg, about 175-185 mg, or about 185-195 mg of bupropion in a free base form or a salt form. In some embodiments, the bupropion is in an HCl salt form.

In some embodiments, administration of the combination of dextromethorphan and bupropion to human beings results in the reduction of smoking intensity as measured using the number of cigarettes smoked per day, assessed via daily smoking diaries.

The treatment with the combination of dextromethorphan and bupropion to human beings results in at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, about 5-10%, about 10-15%, about 15-20%, about 20-25%, about 25-30%, 10-20%, about 20-30%, about 30-40%, about 40-50%, about 50-60%, about 60-80%, about 80-100%, about 20%, about 25% greater, about 30%, or about 50% reduction in the average number of cigarettes smoked per day as compared to bupropion alone over a period of time, such as 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 3 months, 4 months, 6 months, or longer.

The treatment with the combination of dextromethorphan and bupropion to human beings results in average reduction of at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, about 8-9, about 8-10, about 10-15, about 15-20, about 25, or more cigarettes per day.

The treatment with the combination of dextromethorphan and bupropion to human beings results in a greater proportion of smokers, such as at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, about 35%, about 50%, about 60%, about 60-80%, about 80-90%, about 90-100%, who experience a more than 50% reduction in expired carbon

monoxide levels, a biochemical marker of smoking intensity, as compared to those treated with bupropion alone.

The treatment with the combination of dextromethorphan and bupropion to human beings results in at least 1, or about 1-2 cigarettes fewer on the day of administration and at least 1, at least 2, about 1-2, or about 2-3 cigarettes fewer on the following day as compared to those who missed one or both doses of the combination of dextromethorphan and bupropion.

The treatment of smoking cessation with the combination of dextromethorphan and bupropion to human beings results in the magnitude of improvement over bupropion alone that is similar to the improvement over placebo reported for the approved smoking cessation treatment varenicline in studies with a similar design.

In some embodiments, an enhanced bioavailability of dextromethorphan, or a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, may be used as an adjunctive therapy for treatment of any condition recited herein, including TRD. For example, the adjunctive therapy could be used in combination with another antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, clomipramine, doxepin, fluoxetine, mianserin, imipramine, 2-chloroimipramine, amitriptyline, amoxapine, desipramine, protriptyline, trimipramine, nortriptyline, maprotiline, phenelzine, isocarboxazid, tranylcypromine, paroxetine, trazodone, citalopram, sertraline, aryloxy indanamine, benactyzine, escitalopram, fluvoxamine, venlafaxine, desvenlafaxine, duloxetine, mirtazapine, nefazodone, selegiline, sibutramine, milnacipran, tesofensine, brasofensine, moclobemide, rasagiline, nialamide, iproniazid, iproclozide, toloxatone, butriptyline, dosulepin, dibenzepin, iprindole, lofepramine, opipramol, norfluoxetine, dapoxetine, ketamine, etc., or a metabolite or prodrug of any of these compounds, or a pharmaceutically acceptable salt of any of these compounds.

In some embodiments, TRD may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds and may result in a reduction of depressive symptoms of at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, up to about 100%, or any other reduction in a range bounded by any of these values.

Psychiatric disorders that may be treated by enhanced plasma levels of dextromethorphan such as those achieved by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, include, but are not limited to, anxiety disorders, including but not limited to, phobias, generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive-compulsive disorder, and post-traumatic stress disorder (PTSD); mania, manic depressive illness, hypomania, unipolar depression, depression, stress disorders, somatoform disorders, personality disorders, psychosis, schizophrenia, delusional disorder, schizoaffective disorder, schizotypy, aggression, aggression in Alzheimer's disease, agitation, and agitation in Alzheimer's disease.

Agitation in Alzheimer's disease occurs as the disease progresses. Agitation may present itself as inappropriate verbal, emotional, and/or physical behaviors. Inappropriate behaviors may include, but are not limited to, incoherent babbling, inappropriate emotional response, demands for attention, threats, irritability, frustration, screaming, repetitive questions, mood swings, cursing, abusive language, physical outbursts, emotional distress, restlessness, shredding, sleeping disturbances, delusions, hallucinations, pacing, wandering, searching, rummaging, repetitive body motions, hoarding, shadowing, hitting, scratching, biting, combativeness, hyperactivity, and/or kicking.

In some embodiments, agitation in Alzheimer's disease may be treated by enhanced plasma levels of dextromethorphan or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds and may result in a reduction of agitation-related symptoms of at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, up to about 100%, or any other reduction in a range bounded by any of these values.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, and behavioral and psychological symptoms including agitation. AD is the most common form of dementia and afflicts an estimated 6 million individuals in the United States, a number that is anticipated to increase to approximately 14 million by 2050. Agitation is reported in up to 70% of patients with AD and is characterized by emotional distress, aggressive behaviors, disruptive irritability, and disinhibition. Managing agitation is a priority in AD. Agitation in patients with AD has been associated with increased caregiver burden, decreased functioning, accelerated cognitive decline, earlier nursing home placement, and increased mortality. There are currently no therapies approved by the FDA for the treatment of agitation in patients with AD.

Measures of treatment effect that may be improved by treatment with enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, Neuropsychiatric Inventory—Clinician (NPI-C) rating scale, overall and all domains; Neuropsychiatric Inventory—Clinician (NPI-C) rating scale Agitation domain; Cohen-Mansfield Agitation Inventory (CMAI); Cornell Scale for Depression in Dementia (CSDD); Neuropsychiatric Inventory (NPI Agitation/Aggression Domain); Cocomitant Medications (Frequency of using concomitant medications); Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL); Neuropsychiatric Inventory (NPI) Individual Domains and NPI Total Scores (range 0-144), including NPI-C Apathy domain, NPI Agitation/Aggression Caregiver Distress, Modified Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change Agitation (mADCS-CGIC Agitation), Patient Global Impression of Change (PGIC) (rated by caregiver), Dementia Quality of Life (DEMQOL), Quality of Life—Alzheimer's disease measure (QoL-AD), Zarit Burden Scale, Resource Utilization in Dementia (RUD), Alzheimer's Disease Assessment Scale—Cognitive Subscale (ADAS-Cog), Mini-mental State Examination (MMSE), Caregiver Strain Index (CSI), Individual Domain of the Neuropsychiatric Inventory (NPI),

Total Neuropsychiatric Inventory (NPI) Score, Neuropsychiatric Inventory (Agitation/Aggression Domain of NPI), Neuropsychiatric Inventory (Caregiver Distress for NPI Domains), etc.

Substance addiction abuse that may be treated by enhanced bioavailability or plasma levels of dextromethorphan or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, includes, but is not limited to, drug dependence, addiction to cocaine, psychostimulants (e.g., crack, cocaine, speed, meth), nicotine, alcohol, opioids, anxiolytic and hypnotic drugs, *cannabis* (marijuana), amphetamines, hallucinogens, phencyclidine, volatile solvents, and volatile nitrites. Nicotine addiction includes nicotine addiction of all known forms, such as smoking cigarettes, cigars and/or pipes, and addiction to chewing tobacco.

Cerebral function disorders that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, disorders involving intellectual deficits such as senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances of consciousness, coma, lowering of attention, speech disorders, voice spasms, Parkinson's disease, Lennox-Gastaut syndrome, autism, hyperkinetic syndrome, and schizophrenia. Cerebral function disorders also include disorders caused by cerebrovascular diseases including, but not limited to, stroke, cerebral infarction, cerebral bleeding, cerebral arteriosclerosis, cerebral venous thrombosis, head injuries, and the like where symptoms include disturbance of consciousness, senile dementia, coma, lowering of attention, and speech disorders.

Movement disorders that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, akathisia, akinesia, associated movements, athetosis, ataxia, ballismus, hemiballismus, bradykinesia, cerebral palsy, chorea, Huntington's disease, rheumatic chorea, Sydenham's chorea, dyskinesia, tardive dyskinesia, dystonia, blepharospasm, spasmodic torticollis, dopamine-responsive dystonia, Parkinson's disease, restless legs syndrome (RLS), tremor, essential tremor, and Tourette's syndrome, and Wilson's disease.

Dementias that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, Alzheimer's disease, Parkinson's disease, vascular dementia, dementia with Lewy bodies, mixed dementia, fronto-temporal dementia, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, Huntington's disease, Wernicke-Korsakoff Syndrome, and Pick's disease.

Motor neuron diseases that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy, primary lateral sclerosis (PLS), progressive muscular atrophy, post-polio syndrome (PPS), spinal muscular atrophy (SMA), spinal motor atrophies, Tay-Sach's disease, Sandoff disease, and hereditary spastic paraplegia.

Neurodegenerative diseases that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, Alzheimer's disease, prion-related diseases, cerebellar ataxia, spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), bulbar muscular atrophy, Friedrich's ataxia, Huntington's disease, Lewy body disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), multiple sclerosis (MS), multiple system atrophy, Shy-Drager syndrome, corticobasal degeneration, progressive supranuclear palsy, Wilson's disease, Menkes disease, adrenoleukodystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), muscular dystrophies, Charcot-Marie-Tooth disease (CMT), familial spastic paraparesis, neurofibromatosis, olivopontine cerebellar atrophy or degeneration, striatonigral degeneration, Guillain-Barré syndrome, and spastic paraplesia.

Seizure disorders that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, epileptic seizures, nonepileptic seizures, epilepsy, febrile seizures; partial seizures including, but not limited to, simple partial seizures, Jacksonian seizures, complex partial seizures, and epilepsia partialis continua; generalized seizures including, but not limited to, generalized tonic-clonic seizures, absence seizures, atonic seizures, myoclonic seizures, juvenile myoclonic seizures, and infantile spasms; and status epilepticus.

Types of headaches that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, but are not limited to, migraine, tension, and cluster headaches.

Other neurological disorders that may be treated by enhanced bioavailability or plasma levels of dextromethorphan, or by a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds include, Rett Syndrome, autism, tinnitus, disturbances of consciousness disorders, sexual dysfunction, intractable coughing, narcolepsy, cataplexy; voice disorders due to uncontrolled laryngeal muscle spasms, including, but not limited to, abductor spasmodic dysphonia, adductor spasmodic dysphonia, muscular tension dysphonia, and vocal tremor; diabetic neuropathy, chemotherapy-induced neurotoxicity, such as methotrexate neurotoxicity; incontinence including, but not limited, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

In some embodiments, a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupro-

pion, or a metabolite or prodrug of any of these compounds, may be used to treat pain, joint pain, pain associated with sickle cell disease, pseudobulbar affect, depression (including treatment resistant depression), disorders related to memory and cognition, schizophrenia, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Rhett's syndrome, seizures, cough (including chronic cough), etc.

In some embodiments, a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat treatment refractory depression.

In some embodiments, a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat allodynia.

In some embodiments, a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat treatment refractory hyperalgesia.

In some embodiments, a combination of dextromethorphan and an antidepressant such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat dermatitis.

Pain relieving properties of dextromethorphan may be enhanced by a method comprising co-administering dextromethorphan and an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, with dextromethorphan.

Pain relieving properties of bupropion may be enhanced by a method comprising co-administering dextromethorphan with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, ketamine or another NMDA receptor antagonist may be administered with an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, dextromethorphan and quinidine may be co-administered with an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

These methods may be used to treat, or provide relief to, any type of pain including, but not limited to, musculoskeletal pain, neuropathic pain, cancer-related pain, acute pain, nociceptive pain, inflammatory pain, arthritis pain, complex regional pain syndrome, etc.

In some embodiments, co-administering dextromethorphan with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat or reduce inflammation or inflammatory conditions, such as Crohn's disease, including pain associated with inflammation.

In some embodiments, co-administering dextromethorphan with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be used to treat psoriasis, cancer, viral infection, or as an adjuvant treatment for multiple myeloma.

Examples of musculoskeletal pain include low back pain (i.e., lumbosacral pain), primary dysmenorrhea, and arthritic pain, such as pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, axial spondyloarthritis including ankylosing spondylitis, pain associated with vertebral crush fractures, fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, transient osteoporosis, and transient osteoporosis of the hip, etc.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, is used to treat chronic musculoskeletal pain.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, may be administered to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component. Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor, and sensory changes.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, may be administered orally to relieve neuropathic pain.

Examples of neuropathic pain include diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, central pain, etc. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio- or chemo-therapy associated neuropathy, etc.

In some embodiments, a combination of dextromethorphan and an antidepressant, such as bupropion, may be administered to relieve fibromyalgia.

The term "treating", or "treatment" includes the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

Any antidepressant may be used in combination with dextromethorphan to improve the therapeutic properties of

dextromethorphan. Dextromethorphan and the antidepressant compound may be administered in separate compositions or dosage forms or may be administered in a single composition or dosage form comprising both.

A quinidine may be co-administered with dextromethorphan to provide enhanced plasma levels of dextromethorphan. For a combination of a quinidine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-1,000 mg, 1-10 mg, 10 mg, about 5 mg, about 4.5, about 1-3 mg, about 2-4 mg, about 3-5 mg, about 4-6 mg, about 5-7 mg, about 6-8 mg, about 7-9 mg, about 8-10 mg, about 9-11 mg, about 10-12 mg, about 4.5-5 mg, 20 mg, 30 mg, 30-100 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 10-30 mg, about 30-50 mg, about 50-70 mg, about 10-90 mg of the quinidine, or any dose in a range bounded by any of these values.

Antidepressant compounds that can be co-administered with dextromethorphan include, but are not limited to, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, clomipramine, doxepin, fluoxetine, mianserin, imipramine, 2-chloroimipramine, amitriptyline, amoxapine, desipramine, protriptyline, trimipramine, nortriptyline, maprotiline, phenelzine, isocarboxazid, tranylcypromine, paroxetine, trazodone, citalopram, sertraline, aryloxy indanamine, benactyzine, escitalopram, fluvoxamine, venlafaxine, desvenlafaxine, duloxetine, mirtazapine, nefazodone, selegiline, sibutramine, milnacipran, tesofensine, brasofensine, moclobemide, rasagiline, nialamide, iproniazid, iproclozide, toloxatone, butriptyline, dosulepin, dibenzepin, iprindole, lofepramine, opipramol, norfluoxetine, dapoxetine, ketamine, etc., or a metabolite or prodrug of any of these compounds, or a pharmaceutically acceptable salt of any of these compounds.

For a combination of a ketamine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.01-0.2 mg, about 0.2-0.4 mg, about 0.4-0.6 mg, about 0.6-0.8 mg, about 0.8-1 mg, about 1-1.2 mg, about 1.2-1.4 mg, about 1.4-1.6 mg, about 1.6-1.8 mg, about 1.8-2 mg, about 2-2.2 mg, about 2.2-2.4 mg, about 2.4-2.6 mg, about 2.6-2.8 mg, about 2.8-3 mg, about 3-3.2 mg, about 3.2-3.4 mg, about 3.4-3.6 mg, about 3.6-3.8 mg, about 3.8-4 mg, about 3.9-4.1 mg, about 4-4.2 mg, about 0.2-0.4 mg, about 0.2-0.6 mg, about 0.2-0.8 mg, about 0.2-1 mg, about 0.2-1.2 mg, about 0.2-1.4 mg, about 0.2-1.6 mg, about 0.2-1.8 mg, about 0.2-2.0 mg, 0.2-2.5 mg, about 0.2-3.0 mg, about 0.2-3.5 mg, about 0.2-4.0 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 10-500 mg, about 50-400 mg, about 50-300 mg, about 100-250 mg, about 1-10 mg, about 10-200 mg, about 10-150 mg, about 10-100 mg, about 10-180 mg, about 10-160 mg, about 10-140 mg, about 10-120 mg, about 10-100 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-350 mg, about 350-400 mg, about 25 mg, about 50 mg, about 100 mg, about 250 mg, of the ketamine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a tesofensine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.2 mg, about 0.1-0.3 mg, about 0.1-0.4 mg, about 0.1-0.5 mg, about 0.1-0.6 mg, about 0.1-0.7 mg, about 0.1-0.8 mg, about 0.1-0.9 mg, about 0.1-0.1 mg, about 0.1-0.12 mg, 0.01-0.2 mg, about 0.1-0.3 mg, about 0.2-0.4 mg, about 0.3-0.5 mg, about 0.4-0.6 mg, about 0.5-0.7 mg, about 0.6-0.8 mg, about 0.7-0.9 mg, about 0.8-1 mg, about 0.9-1.1 mg, of the tesofensine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a brasofensine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.01-0.2 mg, about 0.2-0.4 mg, about 0.4-0.6 mg, about 0.6-0.8 mg, about 0.8-1 mg, about 1-1.2 mg, about 1.2-1.4 mg, about 1.4-1.6 mg, about 1.6-1.8 mg, about 1.8-2 mg, about 2-2.2 mg, about 2.2-2.4 mg, about 2.4-2.6 mg, about 2.6-2.8 mg, about 2.8-3 mg, about 3-3.2 mg, about 3.2-3.4 mg, about 3.4-3.6 mg, about 3.6-3.8 mg, about 3.8-4 mg, about 3.9-4.1 mg, about 4-4.2 mg, about 0.2-0.4 mg, about 0.2-0.6 mg, about 0.2-0.8 mg, about 0.2-1 mg, about 0.2-1.2 mg, about 0.2-1.4 mg, about 0.2-1.6 mg, about 0.2-1.8 mg, about 0.2-2.0 mg, 0.2-2.5 mg, about 0.2-3.0 mg, about 0.2-3.5 mg, about 0.2-4.0 mg, of the brasofensine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a clomipramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 10-500 mg, about 50-400 mg, about 50-300 mg, about 100-250 mg, about 1-10 mg, about 10-200 mg, about 10-150 mg, about 10-100 mg, about 10-180 mg, about 10-160 mg, about 10-140 mg, about 10-120 mg, about 10-100 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-350 mg, about 350-400 mg, about 25 mg, about 50 mg, about 100 mg, about 250 mg, of the clomipramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a doxepin and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-500 mg, about 1-10 mg, about 1-40 mg, about 1-30 mg, about 1-20 mg, about 1-18 mg, about 1-16 mg, about 1-14 mg, about 1-12 mg, about 1-10 mg, about 10-150 mg, about 10-125 mg, about 10-100 mg, about 10-75 mg, about 10-70 mg, about 10-60 mg, about 10-50 mg, about 10-40 mg, about 10-30 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg,

about 300 mg, of the doxepin, or any dose in a range bounded by any of these values, may be administered.

For a combination of a fluoxetine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of a daily dose of about 1-10 mg, about 5-15 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 20 mg, about 60 mg, about 100 mg, about 150 mg, of the fluoxetine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a mianserin and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-300 mg, about 1-90 mg, about 1-60 mg, about 1-30 mg, about 1-25 mg, about 1-20 mg, about 1-15 mg, about 1-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 30 mg, about 60 mg, about 90 mg, about 120 mg, about 150 mg, of the mianserin, or any dose in a range bounded by any of these values, may be administered.

For a combination of a imipramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 5-150 mg, about 5-125 mg, about 5-100 mg, about 5-75 mg, about 5-60 mg, about 5-50 mg, about 5-40 mg, about 5-30 mg, about 5-25 mg, about 5-20 mg, about 5-15 mg, about 10-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, of the imipramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a 2-chloroimipramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the about 2-chloroimipramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of an amitriptyline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 5-100 mg, about 5-70 mg, about 5-60 mg, about 5-50 mg, about 5-40 mg, about 5-35 mg, about 5-30 mg, about 5-25 mg, about 5-20 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 10 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, of the amitriptyline, or any dose in a range bounded by any of these values, may be administered.

For a combination of an amoxapine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 10-20 mg, about 10-300 mg, about 10-250 mg, about 10-200 mg, about 10-150 mg, about 10-120 mg, about 10-100 mg, about 10-80 mg, about 10-60 mg, about 10-40 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 500-600 mg, about 600-700 mg, about 700-800 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, of the amoxapine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a desipramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 1-15 mg, about 10-20 mg, about 10-25 mg, about 10-30 mg, about 10-40 mg, about 10-50 mg, about 10-60 mg, about 10-70 mg, about 10-80 mg, about 10-90 mg, about 10-100 mg, about 10-120 mg, about 10-140 mg, about 10-150 mg, about 10-180 mg, about 10-200 mg, about 20-30 mg, about 20-40 mg, about 30-40 mg, about 40-50 mg, about 40-60 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 90-110 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 180-220 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 280-320 mg, about 300-350 mg, about 350-400 mg, about 100-200 mg, about 25-100 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 250 mg, of the desipramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a protriptyline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 5-100 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24

mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 15-60 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 20 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the protriptyline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a trimipramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 20-300 mg, about 1-10 mg, about 5-20 mg, about 5-25 mg, about 5-30 mg, about 5-35 mg, about 5-40 mg, about 5-45 mg, about 5-50 mg, about 5-55 mg, about 5-60 mg, about 5-65 mg, about 5-70 mg, about 5-75 mg, about 5-100 mg, about 5-125 mg, about 5-150 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 100-200 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 180-220 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 10 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, of the trimipramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a nortriptyline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 5-10 mg, about 5-20 mg, about 5-25 mg, about 5-30 mg, about 5-35 mg, about 5-40 mg, about 5-45 mg, about 5-50 mg, about 5-55 mg, about 5-60 mg, about 5-65 mg, about 5-70 mg, about 5-75 mg, about 5-100 mg, about 5-125 mg, about 5-150 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 20-30 mg, about 25-30 mg, about 30-35 mg, about 30-50 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-150 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 80-120 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 20 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the nortriptyline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a maprotiline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 5-10 mg, about 5-20 mg, about 5-25 mg, about 5-30 mg, about 5-35 mg, about 5-40 mg, about 5-45 mg, about 5-50 mg, about 5-55 mg, about 5-60 mg, about 5-65 mg, about 5-70 mg, about 5-75 mg, about 5-100 mg, about 5-125 mg, about 5-150 mg, about 10-15 mg, about 10-250 mg, about 10-75 mg, about 10-50 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 60-90 mg, about 65-70 mg, about 70-75 mg, about 75-80 mg, about 80-85 mg, about 80-120 mg, about 85-90 mg, about 90-100 mg, about 100-120 mg, about 100-150 mg, about 120-125 mg, about 125-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-225 mg, about 210-240 mg, about 200-250 mg, about 10 mg, about 25 mg, about 30 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 225 mg, of the maprotiline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a phenelzine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 5-10 mg, about 5-20 mg, about 5-25 mg, about 5-30 mg, about 5-35 mg, about 5-40 mg, about 5-45 mg, about 5-50 mg, about 5-55 mg, about 5-60 mg, about 5-65 mg, about 5-70 mg, about 5-75 mg, about 5-90 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 40-50 mg, about 45-50 mg, about 50-55 mg, about 50-70 mg, about 50-200 mg, about 55-60 mg, about 60-65 mg, about 60-90 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, 80-120 mg, about 90-100 mg, about 100-120 mg, about 100-150 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the phenelzine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a isocarboxazid and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-50 mg, about 2-55 mg, about 2-60 mg, about 5-10 mg, about 5-15 mg, about 10-15 mg, about 10-60 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 30-50 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 50-70 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the isocarboxazid, or any dose in a range bounded by any of these values, may be administered.

For a combination of a tranylcypromine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 1-30 mg, about 1-25 mg, about 1-20 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-50 mg, about 2-55 mg, about 2-60 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70

mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the tranylcypromine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a paroxetine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 1-50 mg, about 1-20 mg, about 1-15 mg, about 1-10 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-30 mg, about 2-40 mg, about 2-50 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 60 mg, about 100 mg, about 150 mg, of the paroxetine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a trazodone and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 10-20 mg, about 10-30 mg, about 10-40 mg, about 10-50 mg, about 10-60 mg, about 10-70 mg, about 10-80 mg, about 10-90 mg, about 10-100 mg, about 10-120 mg, about 10-140 mg, about 10-150 mg, about 10-180 mg, about 10-200 mg, about 10-250 mg, about 10-300 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the trazodone, or any dose in a range bounded by any of these values, may be administered.

For a combination of a citalopram and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 1-20 mg, about 1-15 mg, about 1-10 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 2-25 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 100 mg, about 150 mg, of the citalopram, or any dose in a range bounded by any of these values, may be administered.

For a combination of a sertraline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 1-50 mg, about 1-45 mg, about 1-40 mg, about 1-30 mg, about 1-20 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-16 mg, about 2-17 mg, about 2-18 mg, about 2-19 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-50 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-75 mg, about 75-80 mg, about 80-85 mg, about 85-90 mg, about 90-100 mg, about 100-120 mg, about 120-125 mg, about 125-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-300 mg, about 10 mg, about 25 mg, about 30 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 225 mg, of sertraline, or any dose in a range bounded by any of these values, may be administered.

For a combination of an aryloxy indanamine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the aryloxy indanamine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a benactyzine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the benactyzine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a escitalopram and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-12 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 5-10 mg, about 5-15 mg, about 10-15 mg, about 10-30 mg, about 15-20 mg, about 15-30 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-200 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 50 mg, of the escitalopram, or any dose in a range bounded by any of these values, may be administered.

For a combination of a fluvoxamine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of 50-300 mg, 1-10 mg, about 10-20 mg, about 10-30 mg, about 10-40 mg, about 10-50 mg, about 10-60 mg, about 10-70 mg, about 10-80 mg, about 10-90 mg, about 10-100 mg, about 10-120 mg, about 10-140 mg, about 10-150 mg, about 10-180 mg, about 10-200 mg, about 10-250 mg, about 10-300 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 90-110 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 180-220 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 240-260 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 280-320 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-500 mg, about 10 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, of the fluvoxamine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a venlafaxine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 5-20 mg, about 5-25 mg, about 5-30 mg, about 5-35 mg, about 5-40 mg, about 5-45 mg, about 5-50 mg, about 5-55 mg, about 5-60 mg, about 5-65 mg, about 5-70 mg, about 5-75 mg, about 5-100 mg, about 5-125 mg, about 5-150 mg, about 10-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 120-180 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 225, about 250 mg, about 375 mg, about 400 mg, about 600 mg, of the venlafaxine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a desvenlafaxine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-50 mg, about 2-75 mg, about 2-100 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 20-30 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 40-60 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 80-120 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 100 mg, about 150 mg, of the desvenlafaxine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a duloxetine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 2-21 mg, about 2-22 mg, about 2-23 mg, about 2-24 mg, about 2-25 mg, about 2-26 mg, about 2-27 mg, about 2-28 mg, about 2-29 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 2-60 mg, about 2-90 mg, about 2-120 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 20-40 mg, about 25-30 mg, about 30-35 mg, about 30-50 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 50-70 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 100 mg, about 120 mg, of the duloxetine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a mirtazapine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 2-5 mg, about 2-6 mg, about 2-7 mg, about 2-8 mg, about 2-9 mg, about 2-10 mg, about 2-11 mg, about 2-12 mg, about 2-13 mg, about 2-14 mg, about 2-15 mg, about 2-20 mg, about 2-25 mg, about 2-30 mg, about 2-35 mg, about 2-40 mg, about 2-45 mg, about 1-5 mg, about 5-10 mg, about 5-100 mg, about 10-15 mg, about 10-50 mg, about 15-20 mg, about 15-45 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 45 mg, about 60 mg, about 75 mg, of the mirtazapine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a nefazodone and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 10-20 mg, about 20-40 mg, about 20-50 mg, about 20-60 mg, about 20-70 mg, about 20-80 mg, about 20-90 mg, about 20-100 mg, about 20-120 mg, about 20-140 mg, about 20-160 mg, about 20-180 mg, about 20-200 mg, about 20-250 mg, about 20-300 mg, about 20-450 mg, about 20-600 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 80-120 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg,

about 160-180 mg, about 160-240 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-1000 mg, about 1000-1500 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the nefazodone, or any dose in a range bounded by any of these values, may be administered.

For a combination of a selegiline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.5-2 mg, about 2-5 mg, about 1-10 mg, about 1-9 mg, about 1-8 mg, about 1-7 mg, about 1-6 mg, about 1-5 mg, about 1-3 mg, about 3-5 mg, about 5-10 mg, about 5-15 mg, about 10-15 mg, about 15-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, of the selegiline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a sibutramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-5 mg, about 1-15 mg, about 1-10 mg, about 1-8 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 60 mg, about 100 mg, about 120 mg, of the sibutramine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a rasagiline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.3 mg, about 0.3-0.5 mg, about 0.3-0.7 mg, about 0.5-0.7 mg, about 0.5-1.5 mg, about 0.7-0.9 mg, about 0.9-1.0 mg, about 1.0-1.5 mg, about 1.5-2.0 mg, about 2.0-3.0 mg, about 0.1 mg, about 0.25 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 2 mg, of the rasagiline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a milnacipran and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-7.5 mg, about 7.5-12.5 mg, about 5-20 mg, about 5-100 mg, about 5-90 mg, about 5-80 mg, about 5-70 mg, about 5-60 mg, about 5-50 mg, about 5-40 mg, about 12.5-15 mg, about 15-20 mg, about 20-30 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 40-60 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 80-120 mg, about 100-120 mg, about 120-140 mg, about 140-160 mg, about 160-180 mg, about 180-200 mg, about 180-220 mg, about 200-300 mg, about 300-400 mg, about 7.5 mg, about 12.5 mg, about 25 mg, about 50 mg, about 75 mg, about 60 mg, about 100 mg, about 200 mg, of the milnacipran, or any dose in a range bounded by any of these values, may be administered.

For a combination of a moclobemide and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 1-10 mg, about 10-20 mg, about 20-25 mg, about 20-450 mg, about 20-300 mg, about 20-250 mg, about 20-200 mg, about 20-150 mg, about 20-100 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-320 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 430-470 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the moclobemide, or any dose in a range bounded by any of these values, may be administered.

For a combination of a nialamide and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the nialamide, or any dose in a range bounded by any of these values, may be administered.

For a combination of a iproniazid and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the iproniazid, or any dose in a range bounded by any of these values, may be administered.

For a combination of a iproclozide and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about

20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the iproclozide, or any dose in a range bounded by any of these values, may be administered.

For a combination of a toloxatone and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the toloxatone, or any dose in a range bounded by any of these values, may be administered.

For a combination of a butriptyline and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the butriptyline, or any dose in a range bounded by any of these values, may be administered.

For a combination of a dosulepin and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the dosulepin, or any dose in a range bounded by any of these values, may be administered.

For a combination of a dibenzepin and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the dibenzepin, or any dose in a range bounded by any of these values, may be administered.

For a combination of a iprindole and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the iprindole, or any dose in a range bounded by any of these values, may be administered.

For a combination of a lofepramine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about

450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the lofepramine, or any dose in a range bounded by any of these values, may be administered.

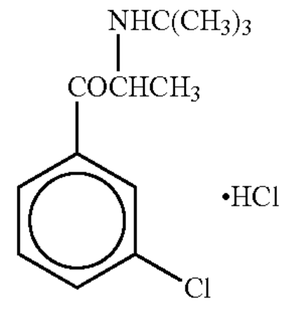
For a combination of a opipramol and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the opipramol, or any dose in a range bounded by any of these values, may be administered.

For a combination of a norfluoxetine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg, about 400 mg, about 600 mg, of the norfluoxetine, or any dose in a range bounded by any of these values, may be administered.

For a combination of a dapoxetine and a dextromethorphan (including deuterium-modified dextromethorphan, e.g. d6-dextromethorphan, and non-deuterium modified dextromethorphan), a daily dose of about 0.1-0.25 mg, about 0.25-0.5 mg, about 0.5-0.75 mg, about 0.75-1 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-40 mg, about 40-50 mg, about 50-60 mg, about 60-70 mg, about 70-80 mg, about 80-90 mg, about 90-100 mg, about 100-120 mg, about 120-140 mg, about 140-150 mg, about 150-160 mg, about 160-180 mg, about 180-200 mg, about 200-220 mg, about 220-240 mg, about 240-250 mg, about 250-260 mg, about 260-280 mg, about 280-300 mg, about 300-320 mg, about 320-350 mg, about 350-400 mg, about 400-450 mg, about 450-500 mg, about 500-550 mg, about 550-600 mg, about 600-650 mg, about 650-700 mg, about 700-800 mg, about 800-1000 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 250 mg, about 300 mg,

about 400 mg, about 600 mg, of the dapoxetine, or any dose in a range bounded by any of these values, may be administered.

Bupropion has the structure shown below (bupropion hydrochloride form shown).



Combining bupropion with dextromethorphan may provide greater efficacy, such as greater pain relief, than would otherwise be achieved by administering either component alone. In extensive metabolizers, dextromethorphan can be rapidly and extensively metabolized, yielding low systemic exposure even at high doses. Bupropion, besides possessing anti-depressant and analgesic properties, is an inhibitor of dextromethorphan metabolism. Bupropion is a dopamine and norepinephrine reuptake inhibitor. It can also be a nicotinic acetylcholine receptor antagonist, and it can modulate cytokines associated with inflammatory diseases. Bupropion can affect levels of tumor necrosis factor-alpha and interferon-gamma. Metabolites of bupropion, which include hydroxybupropion, threohydroxybupropion (also known as threohydrobupropion or threodihydrobupropion), and erythrohydroxybupropion (also known as erythrohydrobupropion or erythrodihydrobupropion), are also inhibitors of dextromethorphan metabolism. Thus, bupropion, including a form of bupropion that is rapidly converted in the body (such as a salt, hydrate, solvate, polymorph, etc.), is a prodrug of hydroxybupropion, threohydroxybupropion, and erythrohydroxybupropion. Prodrugs of bupropion can include N-methylbupropion and N-benzylbupropion.

As explained above, this inhibition may augment dextromethorphan plasma levels, resulting in additive or synergistic efficacy such as relief of neurological disorders including pain, depression, smoking cessation, etc. Thus, while inhibition of dextromethorphan metabolism is only one of many potential benefits of the combination, co-administration of dextromethorphan with bupropion may thereby enhance the efficacy of bupropion for many individuals. Co-administration of dextromethorphan with bupropion may enhance the analgesic properties of bupropion for many individuals. Co-administration of dextromethorphan with bupropion may also enhance the anti-depressant properties of bupropion for many individuals, including faster onset of action.

Another potential benefit of co-administration of dextromethorphan and bupropion is that it may be useful to reduce the potential for an adverse event, such as somnolence, associated with treatment by dextromethorphan. This may be useful, for example, in human patients at risk of experiencing the adverse event as a result of being treated with dextromethorphan.

Another potential benefit of co-administration of dextromethorphan and bupropion is that it may be useful to reduce the potential for an adverse event, such as seizure, associated with treatment by bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds. This may be useful, for example, in human patients at risk of experi-

encing the adverse event as a result of being treated with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

With respect to dextromethorphan, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, co-administration may reduce a central nervous system adverse event, a gastrointestinal event, or another type of adverse event associated with any of these compounds. Central nervous system (CNS) adverse events include, but are not limited to, nervousness, dizziness, sleeplessness, light-headedness, tremor, hallucinations, convulsions, CNS depression, fear, anxiety, headache, increased irritability or excitement, tinnitus, drowsiness, dizziness, sedation, somnolence, confusion, disorientation, lassitude, incoordination, fatigue, euphoria, nervousness, insomnia, sleeping disturbances, convulsive seizures, excitation, catatonic-like states, hysteria, hallucinations, delusions, paranoia, headaches and/or migraine, and extrapyramidal symptoms such as oculogyric crisis, torticollis, hyperexcitability, increased muscle tone, ataxia, and/or tongue protrusion.

Gastrointestinal adverse events include, but are not limited to, nausea, vomiting, abdominal pain, dysphagia, dyspepsia, diarrhea, abdominal distension, flatulence, peptic ulcers with bleeding, loose stools, constipation, stomach pain, heartburn, gas, loss of appetite, feeling of fullness in stomach, indigestion, bloating, hyperacidity, dry mouth, gastrointestinal disturbances, and gastric pain.

Co-administering dextromethorphan and an antidepressant, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, does not necessarily require that the two compounds be administered in the same dosage form. For example, the two compounds may be administered in a single dosage form, or they may be administered in two separate dosage forms. Additionally, the two compounds may be administered at the same time, but this is not required. The compounds can be given at different times as long as both are in a human body at the same time for at least a portion of the time that treatment by co-administration is being carried out.

Side effects of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, and/or dextromethorphan may be reduced by administering bupropion, hydroxybupropion, erythrohydroxybupropion, or threohydroxybupropion, with dextromethorphan. Examples of side effects that may be reduced include abnormal sensation of rotation and movement, agitation, arm weakness, bloating, blurred vision, burning sensation in the eyes, buzzing sound(s) in the ear(s), changes in vital signs (including, but not limited to, heart rate, respiratory rate, body temperature, and blood pressure), cold sensation, constipation, difficulty concentrating, difficulty sleeping, difficulty in falling asleep, difficulty urinating, difficulty with bowel movement, discomfort in the ear, discomfort in the eye, discomfort in the stomach, dizziness, dry lips, dry mouth, dry throat, dysmenorrhea, fatigue, feeling feverish, feeling heavy headed, feeling more agitated than usual, feeling more tired than usual, feeling tired, hand tremors, hand weakness, headache, heartburn, hot flashes, increased blood pressure, increased skin sensitivity, increased skin sensitivity at head and face, involuntary muscle contraction, involuntary muscle contractions all over the body, knee pain, leg weakness, lightheadedness, loose stool, loss of appetite, low back pain, menstrual disorder, metallic taste, more saliva than usual, mucosal dryness, nasal congestion, nausea, runny nose, sensation of light pressure sensation in the eyes, shivers when stretching or yawning, skin sensitivity, skin sensitivity in arm, face, and/or head, sleep difficulties, soft stools, stomach ache, stomach discomfort, sweaty hands and/or feet, throat irritation, throat pain, tinnitus, tremors, and/or weakness. Any of these side effects may also be referred to, or grouped, according to a corresponding, equivalent, or otherwise relevant term found in the Medical Dictionary for Regulatory Activities (MedRA).

In some embodiments, co-administration of a combination of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan results in both bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan contributing to the pain relieving properties of the combination. For example, the combination may have improved pain relieving properties as compared to bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, alone or compared to dextromethorphan alone, including potentially faster onset of action.

In some embodiments, the combination may have improved pain relieving properties of at least about 0.5%, at least about 1%, at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least 100%, up to about 500% or up to 1000%, about 0.5% to about 1000%, about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, about 100% to about 110%, about 110% to about 120%, about 120% to about 130%, about 130% to about 140%, about 140% to about 150%, about 150% to about 160%, about 160% to about 170%, about 170% to about 180%, about 180% to about 190%, about 190% to about 200%, or any amount of pain relief in a range bounded by, or between, any of these values, as compared to bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, alone.

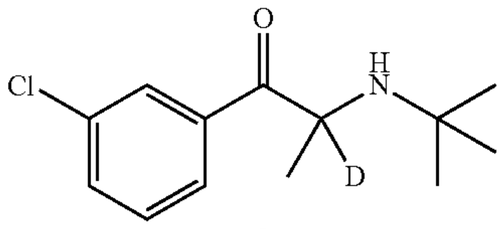
In some embodiments, the combination may have improved pain relieving properties of at least about 0.5%, at least about 1%, at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least 100%, up to about 500% or up to 1000%, about 0.5% to about 1000%, about 10% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, about 100% to about 110%, about 110% to about 120%, about 120% to about 130%, about 130% to about 140%, about 140% to about 150%, about 150% to about 160%, about 160% to about 170%, about 170% to about 180%, about 180% to about 190%, about 190% to about 200%, or any amount of pain relief in a range bounded by, or between, any of these values, as compared to as compared to dextromethorphan alone.

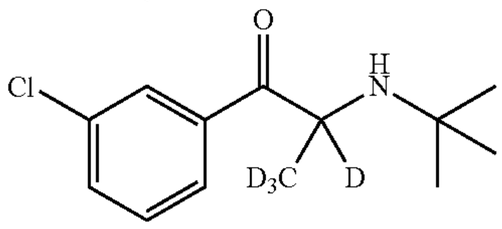
Unless otherwise indicated, any reference to a compound herein, such as dextromethorphan, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, by structure, name, or any other means, includes pharmaceutically acceptable salts; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; deuterium-modified compounds, such as deuterium modified dextromethorphan; or any chemical species that may

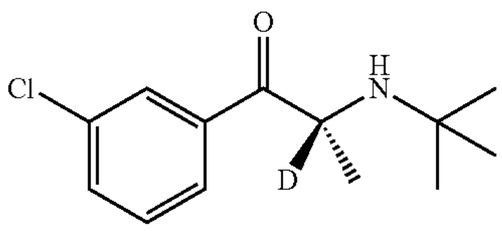
rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

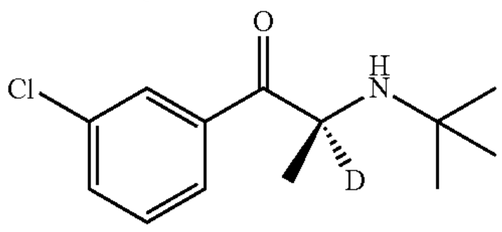
In some embodiments, an excess of one stereoisomer of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be administered. In other embodiments, an excess of the S-enantiomer (such as at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or enantiomerically pure S-enantiomer) or an excess of the R-enantiomer (such as at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 99% or enantiomerically pure R-enantiomer) of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds may be administered.

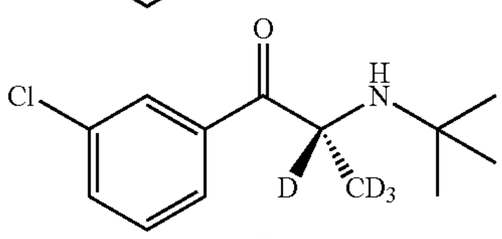
Examples of deuterium-enriched bupropion, and/or enantiopure deuterium-enriched bupropion include, but are not limited to, those shown below.

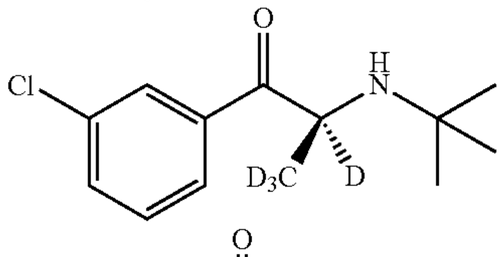


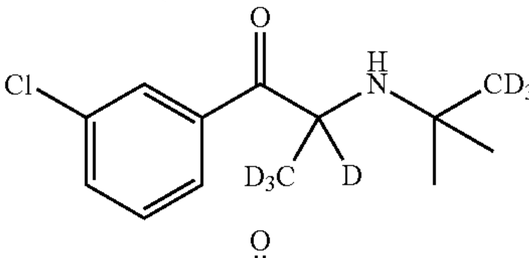


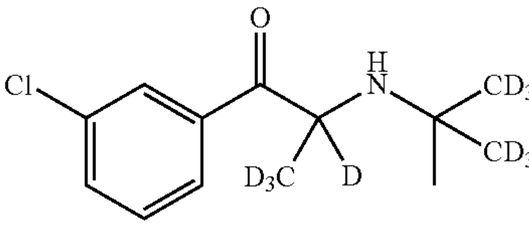












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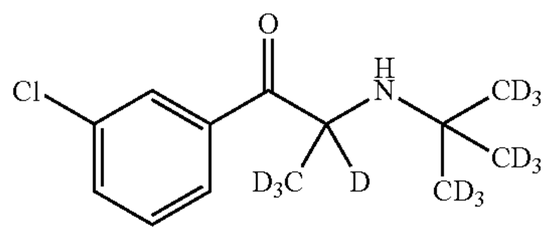

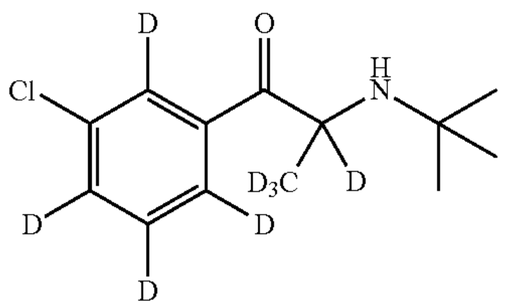

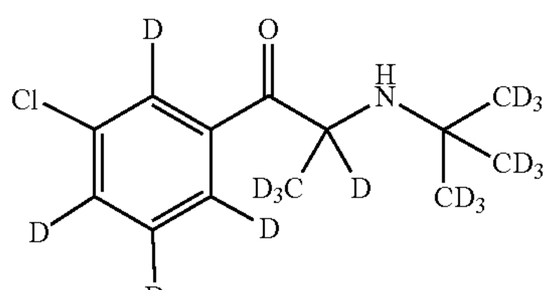

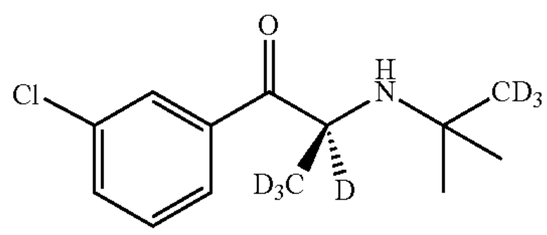

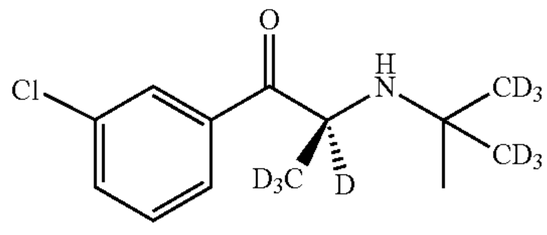

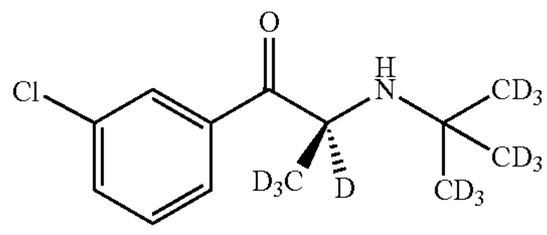

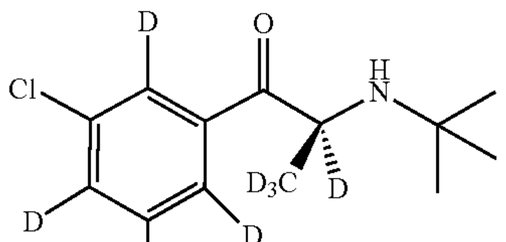

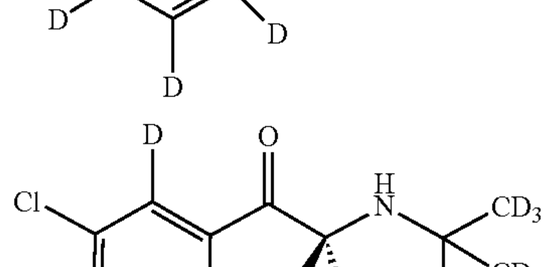

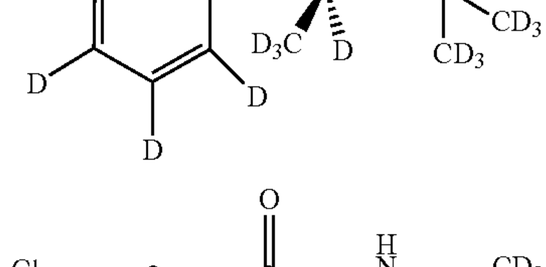

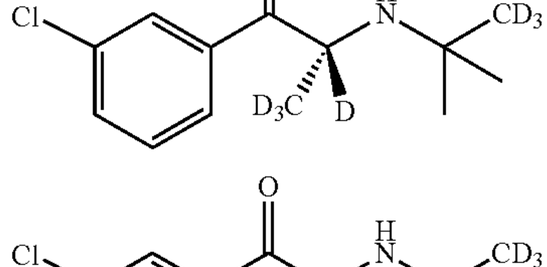

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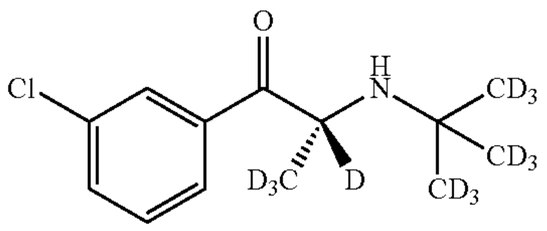
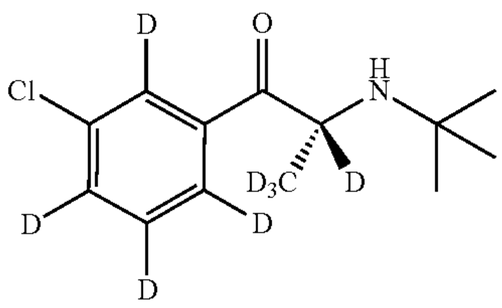
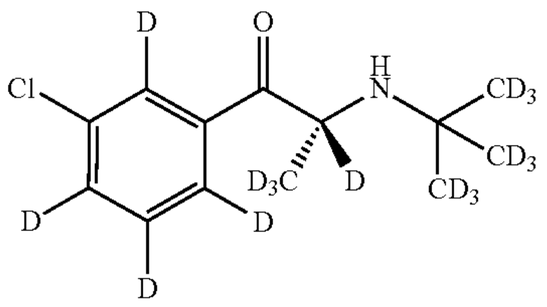
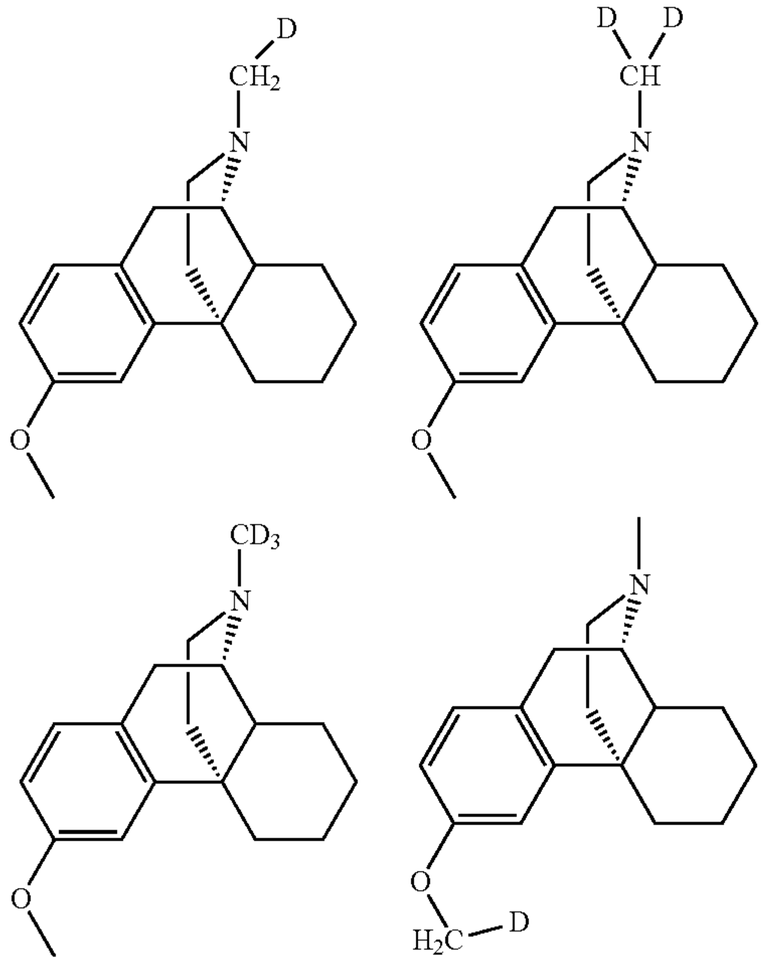






In some embodiments, both dextromethorphan and bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, a metabolite, or prodrug of any of these compounds are formulated to be immediate release, and in other embodiments both bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, a metabolite or prodrug of any of these compounds are formulated to be sustained release.

Examples of deuterium modified dextromethorphan include, but are not limited to, those shown below.



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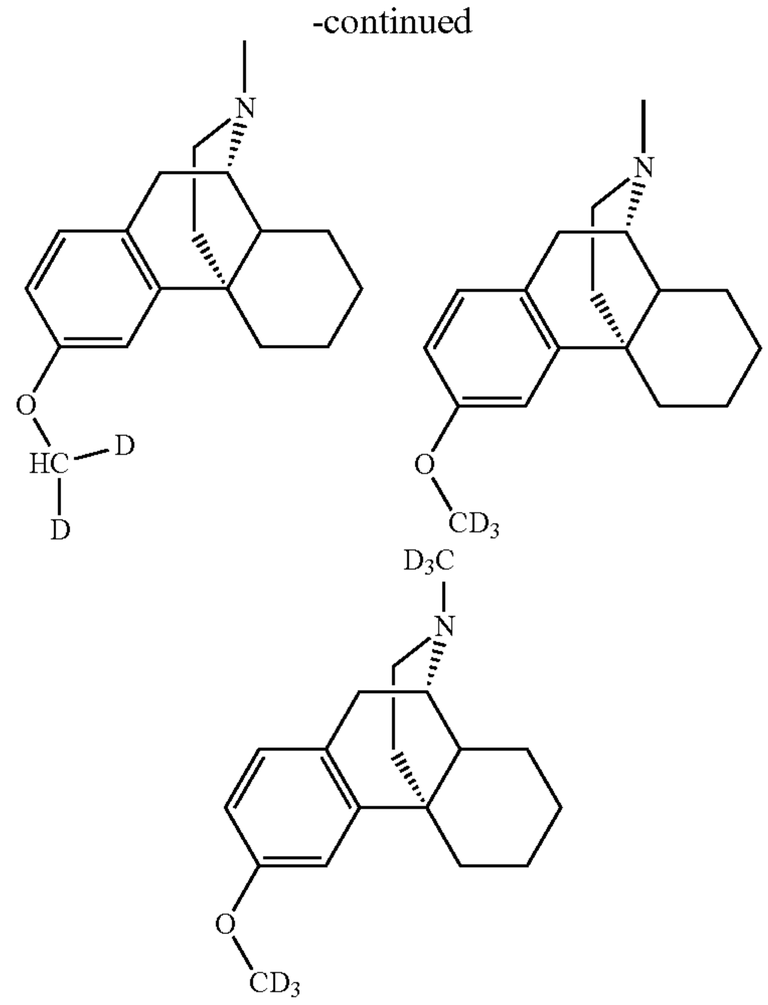

d6-dextromethorphan

A dosage form or a composition may be a blend or mixture of dextromethorphan and a compound that inhibits the metabolism of dextromethorphan, such as bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, either alone or within a vehicle. For example, dextromethorphan and bupropion may be dispersed within each other or dispersed together within a vehicle. A dispersion may include a mixture of solid materials wherein small individual particles are substantially one compound, but the small particles are dispersed within one another, such as might occur if two powders of two different drugs are blended with a solid vehicle material, and the blending is done in the solid form. In some embodiments, dextromethorphan and bupropion may be substantially uniformly dispersed within a composition or dosage form. Alternatively, dextromethorphan and bupropion may be in separate domains or phases within a composition or dosage form. For example, one drug may be in a coating and another drug may be in a core within the coating. For example, one drug may be formulated for sustained release and another drug may be formulated for immediate release.

Some embodiments include administration of a tablet that contains bupropion in a form that provides sustained release and dextromethorphan in a form that provides immediate release. While there are many ways that sustained release of bupropion may be achieved, in some embodiments, bupropion is combined with hydroxypropyl methylcellulose. For example, particles of bupropion hydrochloride could be blended with microcrystalline cellulose and hydroxypropyl methylcellulose (e.g., METHOCEL®) to form an admixture of blended powders. This could then be combined with immediate release dextromethorphan in a single tablet.

Dextromethorphan and/or an antidepressant, such as bupropion, hydroxybupropion, threohydroxybupropion and erythrohydroxybupropion, or a non-bupropion antidepressant (all of which are referred to collectively herein as "therapeutic compounds" for convenience) may be combined with a pharmaceutical carrier selected on the basis of

the chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington's Pharmaceutical Sciences,* 2005. The relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

Therapeutic compounds may be administered by any means that may result in the contact of the active agent(s) with the desired site or site(s) of action in the body of a patient. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. For example, they may be administered as the sole active agents in a pharmaceutical composition, or they can be used in combination with other therapeutically active ingredients.

Therapeutic compounds may be administered to a human patient in a variety of forms adapted to the chosen route of administration, e.g., orally, or parenterally. Parenteral administration in this respect includes administration by the following routes: intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, ophthalmic, sublingual, and buccal; topically including ophthalmic, dermal, ocular, rectal and nasal inhalation via insufflation, aerosol and rectal systemic.

The ratio of dextromethorphan to bupropion may vary. In some embodiments, the weight ratio of dextromethorphan to bupropion may be about 0.1 to about 10, about 0.1 to about 2, about 0.2 to about 1, about 0.1 to about 0.5, about 0.1 to about 0.3, about 0.2 to about 0.4, about 0.3 to about 0.5, about 0.5 to about 0.7, about 0.8 to about 1, about 0.2, about 0.3, about 0.4, about 0.45, about 0.6, about 0.9, or any ratio in a range bounded by, or between, any of these values. A ratio of 0.1 indicates that the weight of dextromethorphan is 1/10 that of bupropion. A ratio of 10 indicates that the weight of dextromethorphan is 10 times that of bupropion.

The amount of dextromethorphan in a therapeutic composition may vary. For example, some liquid compositions may comprise about 0.0001% (w/v) to about 50% (w/v), about 0.01% (w/v) to about 20% (w/v), about 0.01% to about 10% (w/v), about 0.001% (w/v) to about 1% (w/v), about 0.1% (w/v) to about 0.5% (w/v), about 1% (w/v) to about 3% (w/v), about 3% (w/v) to about 5% (w/v), about 5% (w/v) to about 7% (w/v), about 7% (w/v) to about 10% (w/v), about 10% (w/v) to about 15% (w/v), about 15% (w/v) to about 20% (w/v), about 20% (w/v) to about 30% (w/v), about 30% (w/v) to about 40% (w/v), or about 40% (w/v) to about 50% (w/v) of dextromethorphan.

Some liquid dosage forms may contain about 10 mg to about 500 mg, about 30 mg to about 350 mg, about 50 mg to about 200 mg, about 50 mg to about 70 mg, about 20 mg to about 50 mg, about 30 mg to about 60 mg, about 40 mg to about 50 mg, about 40 mg to about 55 mg, about 40 mg to about 42 mg, about 42 mg to about 44 mg, about 44 mg to about 46 mg, about 46 mg to about 48 mg, about 48 mg to about 50 mg, about 80 mg to about 100 mg, about 110 mg to about 130 mg, about 170 mg to about 190 mg, about 45 mg, about 60 mg, about 90 mg, about 120 mg, or about 180 mg of dextromethorphan, or any amount of dextromethorphan in a range bounded by, or between, any of these values.

Some solid compositions may comprise at least about 5% (w/w), at least about 10% (w/w), at least about 20% (w/w), at least about 50% (w/w), at least about 70% (w/w), at least about 80%, about 10% (w/w) to about 30% (w/w), about 10% (w/w) to about 20% (w/w), about 20% (w/w) to about 30% (w/w), about 30% (w/w) to about 40% (w/w), about 40% (w/w) to about 50% (w/w), about 50% (w/w) to about 80% (w/w), about 50% (w/w) to about 60% (w/w), about 70% (w/w) to about 80% (w/w), or about 80% (w/w) to about 90% (w/w) of dextromethorphan.

Some solid dosage forms may contain about 10 mg to about 500 mg, about 30 mg to about 350 mg, about 20 mg to about 50 mg, about 30 mg to about 60 mg, about 40 mg to about 50 mg, about 40 mg to about 42 mg, about 42 mg to about 44 mg, about 44 mg to about 46 mg, about 46 mg to about 48 mg, about 48 mg to about 50 mg, about 50 mg to about 200 mg, about 50 mg to about 70 mg, about 80 mg to about 100 mg, about 110 mg to about 130 mg, about 170 mg to about 190 mg, about 60 mg, about 90 mg, about 120 mg, or about 180 mg of dextromethorphan, or any amount of dextromethorphan in a range bounded by, or between, any of these values.

In some embodiments, the amount of dextromethorphan may range from about 0.1 mg/kg to about 20 mg/kg, about 0.75 mg/kg to about 7.5 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 0.1 mg/kg to about 3 mg/kg, about 0.3 mg/kg to about 0.9 mg/kg, about 0.3 mg/kg to about 1 mg/kg, about 0.6 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.8 mg/kg, about 0.75 mg/kg, about 0.4 mg/kg to about 1.5 mg/kg, about 1 mg/kg to about 2 mg/kg, about 10 mg/kg to about 20 mg/kg, about 12 mg/kg to about 17 mg/kg, about 15 mg/kg to about 20 mg/kg, about 1 mg/kg, about 1 mg/kg to about 10 mg/kg, or any value bounded by or in between these ranges based on the body weight of the patient.

The amount of bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, in a therapeutic composition may vary. If increasing the plasma level of dextromethorphan is desired, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, should be administered in an amount that increases the plasma level of dextromethorphan. For example, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, may be administered in an amount that results in a plasma concentration of dextromethorphan in the human being, on day 8, day 9, or day 10, that is at least about 2 times, at least about 5 times, at least about 10 times, at least about 15 times, at least about 20 times, at least about 30 times, at least about 40 times, at least about 50 times, at least about 60 times, at least about 70 times, or at least about 80 times, the plasma concentration of the same amount of dextromethorphan administered without bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, may be administered to a human being in an amount that results in a 12 hour area under the curve from the time of dosing (AUC_{0-12}), or average plasma concentration in the human being for the 12 hours following dosing (C_{avg}) of dextromethorphan, on day 8, day 9, or day 10, that is at least about 2 times, at least about 5 times, at least about 10 times, at least about 15 times, at least about 20 times, at least about 30 times, at least about 40 times, at least about 50 times, at least about 60 times, at least about 70 times, or at least about 80 times the plasma concentration of the same amount of dextromethorphan administered without bupropion,

hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds, may be administered to a human being in an amount that results in a maximum plasma concentration (C_{max}) of dextromethorphan in the human being, on day 8, day 9, or day 10, that is at least about 2 times, at least about 5 times, at least about 10 times, at least about 15 times, at least about 20 times, at least about 30 times, or at least about 40 times the plasma concentration of the same amount of dextromethorphan administered without bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a metabolite or prodrug of any of these compounds.

For co-administration of bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, an increase in the dextromethorphan plasma level can occur on the first day that bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered, as compared to the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds. For example, the dextromethorphan plasma level on the first day that bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 times, at least about at least 2 times, at least about 2.5 times, at least about 3 times, at least about 4 times, at least about 5 times, at least about 6 times at least about 7 times, at least about 8 times, at least about 9 times, or at least about 10 times the level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan AUC on the first day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least twice the AUC that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan AUC_{0-12} on the first day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 15 ng·hr/mL, at least about 17 ng·hr/mL, at least about 19 ng·hr/mL, at least about 20 ng·hr/mL, at least about 22 ng·hr/mL, at least about 23 ng·hr/mL, at least about 24 ng·hr/mL, at least about 25 ng·hr/mL, at least about 26 ng·hr/mL, at least about 27 ng·hr/mL, at least about 28 ng·hr/mL, at least about 29 ng·hr/mL, at least about 30 ng·hr/mL, at least about 31 ng·hr/mL, at least about 32 ng·hr/mL, at least about 33 ng·hr/mL, at least about 34 ng·hr/mL, at least about 35 ng·hr/mL, at least about 36 ng·hr/mL, at least about 37 ng·hr/mL, at least about 38 ng·hr/mL, at least about 39 ng·hr/mL, at least about 40 ng·hr/mL, at least about 41 ng·hr/mL, at least about 42 ng·hr/mL, at least about 43 ng·hr/mL, at least about 44 ng·hr/mL, at least about 45 ng·hr/mL, at least about 46 ng·hr/mL, at least about 47 ng·hr/mL, at least about 48 ng·hr/mL, at least about 49 ng·hr/mL, at least about 50 ng·hr/mL, at least about 51 ng·hr/mL, at least about 52 ng·hr/mL, at least about 53 ng·hr/mL, at least about 54 ng·hr/mL, at least about 55 ng·hr/mL, at least about 56 ng·hr/mL, at least about or 56.7 ng·hr/mL, and may be up to 10,000 ng·hr/mL.

In some embodiments, the dextromethorphan AUC_{0-12} on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 40 ng·hr/mL, at least about 50 ng·hr/mL, at least about 60 ng·hr/mL, at least about 70 ng·hr/mL, at least about 80 ng·hr/mL, at least about 90 ng·hr/mL, at least about 100 ng·hr/mL, at least about 150 ng·hr/mL, at least about 200 ng·hr/mL, at least about 250 ng·hr/mL, at least about 300 ng·hr/mL, at least about 350 ng·hr/mL, at least about 400 ng·hr/mL, at least about 450 ng·hr/mL, at least about 500 ng·hr/mL, at least about 550 ng·hr/mL, about 500 ng·hr/mL to about 600 ng·hr/mL, about 500 ng·hr/mL to about 550 ng·hr/mL, about 500 ng·hr/mL to about 525 ng·hr/mL, about 525 ng·hr/mL to about 600 ng·hr/mL, at least about 600 ng·hr/mL, at least about 650 ng·hr/mL, at least about 700 ng·hr/mL, at least about 750 ng·hr/mL, at least about 800 ng·hr/mL, about 800 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 875 ng·hr/mL, about 875 ng·hr/mL to about 900 ng·hr/mL, about 900 ng·hr/mL to about 1,000 ng·hr/mL, about 1,000 ng·hr/mL to about 1,100 ng·hr/mL, about 1,100 ng·hr/mL to about 1,200 ng·hr/mL, about 1,200 ng·hr/mL to about 1,300 ng·hr/mL, about 1,300 ng·hr/mL to about 1,400 ng·hr/mL, about 1,400 ng·hr/mL to about 1,500 ng·hr/mL, about 1,500 ng·hr/mL to about 1,600 ng·hr/mL, about 1,600 ng·hr/mL to about 1,700 ng·hr/mL, about 1,700 ng·hr/mL to about 1,800 ng·hr/mL, about 1,800 ng·hr/mL to about 2,000 ng·hr/mL, at least about 850 ng·hr/mL, at least about 900 ng·hr/mL, at least about 950 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1050 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1150 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1250 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1350 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1450 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1550 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1625 ng·hr/mL, at least about 1650 ng·hr/mL, at least about 1675 ng·hr/mL, or at least about 1686.3 ng·hr/mL, and, in some embodiments, may be up to about 50,000 ng·hr/mL.

In some embodiments, the dextromethorphan AUC_{0-24} on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 50 ng·hr/mL, at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at

least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 1850 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 2950 ng·hr/mL, or at least about 2975.3 ng·hr/mL, and, in some embodiments, may be up to about 100,000 ng·hr/mL.

In some embodiments, the dextromethorphan $AUC_{0\text{-}inf}$ on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 3000 ng·hr/mL, at least about 3100 ng·hr/mL, at least about 3200 ng·hr/mL, at least about 3300 ng·hr/mL, at least about 3400 ng·hr/mL, at least about 3500 ng·hr/mL, at least about 3600 ng·hr/mL, at least about 3700 ng·hr/mL, at least about 3800 ng·hr/mL, at least about 3900 ng·hr/mL, at least about 4000 ng·hr/mL, at least about 4100 ng·hr/mL, at least about 4200 ng·hr/mL, at least about 4300 ng·hr/mL, at least about 4400 ng·hr/mL, at least about 4500 ng·hr/mL, at least about 4600 ng·hr/mL, at least about 4700 ng·hr/mL, at least about 4800 ng·hr/mL, at least about 4900 ng·hr/mL, at least about 5000 ng·hr/mL, at least about 5100 ng·hr/mL, at least about 5200 ng·hr/mL, at least about 5300 ng·hr/mL, at least about 5400 ng·hr/mL, at least about 5500 ng·hr/mL, at least about 5600 ng·hr/mL, at least about 5700 ng·hr/mL, at least about 5800 ng·hr/mL, at least about 5900 ng·hr/mL, at least about 6000 ng·hr/mL, at least about 6100 ng·hr/mL, at least about 6200 ng·hr/mL, at least about 6300 ng·hr/mL, at least about 6400 ng·hr/mL, at least about 6500 ng·hr/mL, at least about 6600 ng·hr/mL, at least about 6700 ng·hr/mL, at least about 6800 ng·hr/mL, at least about 6900 ng·hr/mL, at least about 7000 ng·hr/mL, at least about 7100 ng·hr/mL, at least about 7150 ng·hr/mL, at least about 7200 ng·hr/mL, or at least about 7237.3 ng·hr/mL, and, in some embodiments, may be up to about 100,000 ng·hr/mL.

In some embodiments, the dextromethorphan $AUC_{0\text{-}12}$ on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 40 ng·hr/mL, at least about 50 ng·hr/mL, at least about 60 ng·hr/mL, at least about 70 ng·hr/mL, at least about 80 ng·hr/mL, at least about 90 ng·hr/mL, at least about 100 ng·hr/mL, at least about 150 ng·hr/mL, at least about 200 ng·hr/mL, at least about 250 ng·hr/mL, at least about 300 ng·hr/mL, at least about 350 ng·hr/mL, at least about 400 ng·hr/mL, at least about 450 ng·hr/mL, at least about 500 ng·hr/mL, at least about 550 ng·hr/mL, about 500 ng·hr/mL to about 600 ng·hr/mL, about 500 ng·hr/mL to about 550 ng·hr/mL, about 500 ng·hr/mL to about 525 ng·hr/mL, about 525 ng·hr/mL to about 600 ng·hr/mL, at least about 600 ng·hr/mL, at least about 650 ng·hr/mL, at least about 700 ng·hr/mL, at least about 750 ng·hr/mL, at least about 800 ng·hr/mL, about 800 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 875 ng·hr/mL, about 875 ng·hr/mL to about 900 ng·hr/mL, about 900 ng·hr/mL to about 1,000 ng·hr/mL, about 1,000 ng·hr/mL to about 1,100 ng·hr/mL, about 1,100 ng·hr/mL to about 1,200 ng·hr/mL, about 1,200 ng·hr/mL to about 1,300 ng·hr/mL, about 1,300 ng·hr/mL to about 1,400 ng·hr/mL, about 1,400 ng·hr/mL to about 1,500 ng·hr/mL, about 1,500 ng·hr/mL to about 1,600 ng·hr/mL, about 1,600 ng·hr/mL to about 1,700 ng·hr/mL, about 1,700 ng·hr/mL to about 1,800 ng·hr/mL, about 1,800 ng·hr/mL to about 2,000 ng·hr/mL, at least about 850 ng·hr/mL, at least about 900 ng·hr/mL, at least about 950 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1050 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1150 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1250 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1350 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1450 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1550 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1625 ng·hr/mL, at least about 1650 ng·hr/mL, at least about 1675 ng·hr/mL, or at least about 1686.3 ng·hr/mL, and, in some embodiments, may be up to about 50,000 ng·hr/mL.

In some embodiments, the dextromethorphan $AUC_{0\text{-}24}$ on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 50 ng·hr/mL, at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 1850 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 2950 ng·hr/mL, or at least about 2975.3 ng·hr/mL, and, in some embodiments, may be up to about 100,000 ng·hr/mL.

In some embodiments, the dextromethorphan $AUC_{0\text{-}inf}$ on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at

least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 3000 ng·hr/mL, at least about 3100 ng·hr/mL, at least about 3200 ng·hr/mL, at least about 3300 ng·hr/mL, at least about 3400 ng·hr/mL, at least about 3500 ng·hr/mL, at least about 3600 ng·hr/mL, at least about 3700 ng·hr/mL, at least about 3800 ng·hr/mL, at least about 3900 ng·hr/mL, at least about 4000 ng·hr/mL, at least about 4100 ng·hr/mL, at least about 4200 ng·hr/mL, at least about 4300 ng·hr/mL, at least about 4400 ng·hr/mL, at least about 4500 ng·hr/mL, at least about 4600 ng·hr/mL, at least about 4700 ng·hr/mL, at least about 4800 ng·hr/mL, at least about 4900 ng·hr/mL, at least about 5000 ng·hr/mL, at least about 5100 ng·hr/mL, at least about 5200 ng·hr/mL, at least about 5300 ng·hr/mL, at least about 5400 ng·hr/mL, at least about 5500 ng·hr/mL, at least about 5600 ng·hr/mL, at least about 5700 ng·hr/mL, at least about 5800 ng·hr/mL, at least about 5900 ng·hr/mL, at least about 6000 ng·hr/mL, at least about 6100 ng·hr/mL, at least about 6200 ng·hr/mL, at least about 6300 ng·hr/mL, at least about 6400 ng·hr/mL, at least about 6500 ng·hr/mL, at least about 6600 ng·hr/mL, at least about 6700 ng·hr/mL, at least about 6800 ng·hr/mL, at least about 6900 ng·hr/mL, at least about 7000 ng·hr/mL, at least about 7100 ng·hr/mL, at least about 7150 ng·hr/mL, at least about 7200 ng·hr/mL, or at least about 7237.3 ng·hr/mL, and, in some embodiments, may be up to about 100,000 ng·hr/mL.

In some embodiments, the dextromethorphan AUC_{0-12} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 40 ng·hr/mL, at least about 50 ng·hr/mL, at least about 60 ng·hr/mL, at least about 70 ng·hr/mL, at least about 80 ng·hr/mL, at least about 90 ng·hr/mL, at least about 100 ng·hr/mL, at least about 150 ng·hr/mL, at least about 200 ng·hr/mL, at least about 250 ng·hr/mL, at least about 300 ng·hr/mL, at least about 350 ng·hr/mL, at least about 400 ng·hr/mL, at least about 450 ng·hr/mL, at least about 500 ng·hr/mL, at least about 550 ng·hr/mL, about 500 ng·hr/mL to about 600 ng·hr/mL, about 500 ng·hr/mL to about 550 ng·hr/mL, about 500 ng·hr/mL to about 525 ng·hr/mL, about 525 ng·hr/mL to about 600 ng·hr/mL, at least about 600 ng·hr/mL, at least about 650 ng·hr/mL, at least about 700 ng·hr/mL, at least about 750 ng·hr/mL, at least about 800 ng·hr/mL, about 800 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 900 ng·hr/mL, about 850 ng·hr/mL to about 875 ng·hr/mL, about 875 ng·hr/mL to about 900 ng·hr/mL, about 900 ng·hr/mL to about 1,000 ng·hr/mL, about 1,000 ng·hr/mL to about 1,100 ng·hr/mL, about 1,100 ng·hr/mL to about 1,200 ng·hr/mL, about 1,200 ng·hr/mL to about 1,300 ng·hr/mL, about 1,300 ng·hr/mL to about 1,400 ng·hr/mL, about 1,400 ng·hr/mL to about 1,500 ng·hr/mL, about 1,500 ng·hr/mL to about 1,600 ng·hr/mL, about 1,600 ng·hr/mL to about 1,700 ng·hr/mL, about 1,700 ng·hr/mL to about 1,800 ng·hr/mL, about 1,800 ng·hr/mL to about 2,000 ng·hr/mL, at least about 850 ng·hr/mL, at least about 900 ng·hr/mL, at least about 950 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1050 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1150 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1250 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1350 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1450 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1550 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1625 ng·hr/mL, at least about 1650 ng·hr/mL, at least about 1675 ng·hr/mL, or at least about 1686.3 ng·hr/mL, and, in some embodiments, may be up to about 50,000 ng·hr/mL.

In some embodiments, the dextromethorphan AUC_{0-24} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 50 ng·hr/mL, at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 1850 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 2950 ng·hr/mL, or at least about 2975.3 ng·hr/mL, and, in some embodiments, may be up to about 100,000 ng·hr/mL.

In some embodiments, the dextromethorphan AUC_{0-inf} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 75 ng·hr/mL, at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 300 ng·hr/mL, at least about 400 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1000 ng·hr/mL, at least about 1100 ng·hr/mL, at least about 1200 ng·hr/mL, at least about 1300 ng·hr/mL, at least about 1400 ng·hr/mL, at least about 1500 ng·hr/mL, at least about 1600 ng·hr/mL, at least about 1700 ng·hr/mL, at least about 1800 ng·hr/mL, at least about 1900 ng·hr/mL, at least about 2000 ng·hr/mL, at least about 2100 ng·hr/mL, at least about 2200 ng·hr/mL, at least about 2300 ng·hr/mL, at least about 2400 ng·hr/mL, at least about 2500 ng·hr/mL, at least about 2600 ng·hr/mL, at least about 2700 ng·hr/mL, at least about 2800 ng·hr/mL, at least about 2900 ng·hr/mL, at least about 3000 ng·hr/mL, at least about 3100 ng·hr/mL, at least about 3200 ng·hr/mL, at least about 3300 ng·hr/mL, at least about 3400 ng·hr/mL, at least about 3500 ng·hr/mL, at least about 3600 ng·hr/mL, at least about 3700 ng·hr/mL, at least about 3800 ng·hr/mL, at least about 3900 ng·hr/mL, at least about 4000 ng·hr/mL, at least about 4100 ng·hr/mL, at least about 4200 ng·hr/mL, at least about 4300 ng·hr/mL, at least about 4400 ng·hr/mL, at least about 4500 ng·hr/mL, at least about 4600 ng·hr/mL, at least about 4700 ng·hr/mL, at least about 4800 ng·hr/mL, at least about 4900 ng·hr/mL, at least about 5000 ng·hr/mL, at least about 5100 ng·hr/mL, at least about 5200 ng·hr/mL, at least about 5300 ng·hr/mL, at

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In some embodiments, the dextromethorphan C_{max} on the first day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least twice the C_{max} that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan C_{max} on the first day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.0 ng/mL, at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 2.5 ng/mL, at least about 3.0 ng/mL, at least about 3.1 ng/mL, at least about 3.2 ng/mL, at least about 3.3 ng/mL, at least about 3.4 ng/mL, at least about 3.5 ng/mL, at least about 3.6 ng/mL, at least about 3.7 ng/mL, at least about 3.8 ng/mL, at least about 3.9 ng/mL, at least about 4.0 ng/mL, at least about 4.1 ng/mL, at least about 4.2 ng/mL, at least about 4.3 ng/mL, at least about 4.4 ng/mL, at least about 4.5 ng/mL, at least about 4.6 ng/mL, at least about 4.7 ng/mL, at least about 4.8 ng/mL, at least about 4.9 ng/mL, at least about 5.0 ng/mL, at least about 5.1 ng/mL, at least about 5.2 ng/mL, at least about 5.3 ng/mL, at least about 5.4 ng/mL, at least about 5.5 ng/mL, at least about 5.6 ng/mL, at least about 5.7 ng/mL, at least about 5.8 ng/mL, at least about 5.9 ng/mL, at least about 6.0 ng/mL, at least about 6.1 ng/mL, at least about 6.2 ng/mL, at least about 6.3 ng/mL, at least about 6.4 ng/mL, at least about 6.5 ng/mL, at least about 6.6 ng/mL, at least about 6.7 ng/mL, at least about 6.8 ng/mL, at least about 6.9 ng/mL, at least about 7.0 ng/mL, at least about 7.1 ng/mL, at least about 7.2 ng/mL, at least about 7.3 ng/mL, at least about 7.4 ng/mL, at least about 7.5 ng/mL, at least about 7.6 ng/mL, at least about 7.7 ng/mL, at least about 7.8 ng/mL, at least about 7.9 ng/mL, at least about 8.0 ng/mL, at least about 8.1 ng/mL, at least about 8.2 ng/mL, at least about 8.3 ng/mL, at least about 8.4 ng/mL, at least about 8.5 ng/mL, at least about 8.6 ng/mL, or at least about 8.7 ng/mL, and, in some embodiments, may be up to about 1000 ng·hr/mL.

In some embodiments, the dextromethorphan C_{max} on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be about 50 ng/mL to about 60 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, at least about 145 ng/mL, at least about 150 ng/mL, at least about 155 ng/mL, or at least about 158.1 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{max} on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be about 50 ng/mL to about 60 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, at least about 145 ng/mL, at least about 150 ng/mL, at least about 155 ng/mL, or at least about 158.1 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{max} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite

or prodrug of any of these compounds, is administered may be about 50 ng/mL to about 60 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, at least about 145 ng/mL, at least about 150 ng/mL, at least about 155 ng/mL, or at least about 158.1 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered in an amount that results in a C_{avg} of dextromethorphan, over the period between two separate and consecutive administrations of dextromethorphan, that is at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, or at least about 140.5 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL. For example, if dextromethorphan is administered at 8 am and at 8 pm on day 1, and no dextromethorphan is administered after 8 am and before 8 pm on day 1, the period between two separate and consecutive administrations of dextromethorphan is from immediately after 8 am to immediately before 8 pm on day 1.

In some embodiments, the dextromethorphan C_{avg} on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, or at least about 140.5 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL. The C_{avg} values given above can be for the period between two separate and consecutive administrations of dextromethorphan, or if dextromethorphan is administered only once on Day 8, the C_{avg} can be for 12 hours after the first dose of dextromethorphan.

In some embodiments, the dextromethorphan C_{avg} on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least

about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, or at least about 140.5 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL. The C_{avg} values given above can be for the period between two separate and consecutive administrations of dextromethorphan, or if dextromethorphan is administered only once on Day 9, the C_{avg} can be for 12 hours after the first dose of dextromethorphan.

In some embodiments, the dextromethorphan C_{avg} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 120 ng/mL, at least about 125 ng/mL, at least about 130 ng/mL, at least about 135 ng/mL, at least about 140 ng/mL, or at least about 140.5 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, about 170 ng/mL to about 200 ng/mL, and, in some embodiments, may be up to about 10,000 ng/mL. The C_{avg} values given above can be for the period between two separate and consecutive administrations of dextromethorphan, or if dextromethorphan is administered only once on Day 10, the C_{avg} can be for 12 hours after the first dose of dextromethorphan.

The dextromethorphan fluctuation index values FI (%) can be determined by equation:

$$FI(\%) = \frac{(C_{max} - C_{min})}{C_{avg}} \times 100.$$

In some embodiments, the dextromethorphan FI (%) on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold or at least 2-fold as compared to dextromethorphan that is administered for eight days without plasma level enhancement, such as by co-administration of dextromethorphan with of bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold or at least 2-fold as compared to dextromethorphan that is administered for nine days without plasma level enhancement, such as by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan FI (%) on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold or at least 2-fold as compared to dextromethorphan that is administered for ten days without plasma level enhancement, such as by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan FI (%) on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is less than 100%, less than 50%, less than 40%, less than 30%, about 20-50%, about 20-40%, about 20-30%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextromethorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is less than 100%, less than 50%, less than 40%, less than 30%, about 20-50%, about 20-40%, about 20-30%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextromethorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite

or prodrug of any of these compounds, is less than 100%, less than 50%, less than 40%, less than 30%, about 20-50%, about 20-40%, about 20-30%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextrorphan FI (%) on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 6-fold as compared to dextromethorphan that is administered for eight days without plasma level enhancement, such as by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextrorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 6-fold as compared to dextromethorphan that is administered for nine days without plasma level enhancement, such as by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextrorphan FI (%) on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is reduced by at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, or at least 6-fold as compared to dextromethorphan that is administered for ten days without plasma level enhancement, such as by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextrorphan FI (%) on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is less than 100%, less than 70%, less than 60%, less than 50%, about 30-70%, about 30-60%, about 30-50%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextrorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is less than 100%, less than 70%, less than 60%, less than 50%, about 30-70%, about 30-60%, about 30-50%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextrorphan FI (%) on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is less than 100%, less than 70%, less than 60%, less than 50%, about 30-70%, about 30-60%, about 30-50%, or any FI (%) value in a range bounded by any of these values.

In some embodiments, the dextromethorphan trough level (e.g. plasma level 12 hours after administration; also referred herein as "Cn,") on the first day that bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least twice the trough level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds.

In some embodiments, the dextromethorphan C_{min} on the first day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 0.8 ng/mL, at least about 0.9 ng/mL, at least about 1.0 ng/mL, at least about 1.1 ng/mL, at least about 1.2 ng/mL, at least about 1.3 ng/mL, at least about 1.4 ng/mL, at least about 1.5 ng/mL, at least about 1.6 ng/mL, at least about 1.7 ng/mL, at least about 1.8 ng/mL, at least about 1.9 ng/mL, at least about 2.0 ng/mL, at least about 2.1 ng/mL, at least about 2.2 ng/mL, at least about 2.3 ng/mL, at least about 2.4 ng/mL, at least about 2.5 ng/mL, or at least about 2.5 ng/mL, and may be up to about 100 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the fifth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, or at least about 80.9 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the sixth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, or at least about 102.2 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the seventh day that the dextromethorphan plasma level is

enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, or at least about 110.6 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the eighth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 119.3 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, or about 170 ng/mL to about 200 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the ninth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 119.3 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, or about 170 ng/mL to about 200 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, the dextromethorphan C_{min} on the tenth day that the dextromethorphan plasma level is enhanced, for example by co-administration of dextromethorphan with bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered may be at least about 1.5 ng/mL, at least about 2.0 ng/mL, at least about 3.0 ng/mL, at least about 4.0 ng/mL, at least about 5.0 ng/mL, at least about 6.0 ng/mL, at least about 7.0 ng/mL, at least about 8.0 ng/mL, at least about 9.0 ng/mL, at least about 10 ng/mL, at least about 15 ng/mL, at least about 20 ng/mL, at least about 25 ng/mL, at least about 30 ng/mL, at least about 35 ng/mL, at least about 40 ng/mL, at least about 45 ng/mL, at least about 50 ng/mL, at least about 55 ng/mL, at least about 60 ng/mL, at least about 65 ng/mL, at least about 70 ng/mL, at least about 75 ng/mL, at least about 80 ng/mL, at least about 85 ng/mL, at least about 90 ng/mL, at least about 95 ng/mL, at least about 100 ng/mL, at least about 105 ng/mL, at least about 110 ng/mL, at least about 115 ng/mL, at least about 119.3 ng/mL, about 20 ng/mL to about 30 ng/mL, about 30 ng/mL to about 40 ng/mL, about 40 ng/mL to about 50 ng/mL, about 50 ng/mL to about 55 ng/mL, about 55 ng/mL to about 60 ng/mL, about 80 ng/mL to about 90 ng/mL, about 80 ng/mL to about 85 ng/mL, about 85 ng/mL to about 90 ng/mL, about 90 ng/mL to about 95 ng/mL, about 95 ng/mL to about 100 ng/mL, about 100 ng/mL to about 105 ng/mL, about 105 ng/mL to about 110 ng/mL, about 110 ng/mL to about 115 ng/mL, about 115 ng/mL to about 120 ng/mL, about 120 ng/mL to about 130 ng/mL, about 130 ng/mL to about 135 ng/mL, about 135 ng/mL to about 140 ng/mL, about 140 ng/mL to about 145 ng/mL, about 145 ng/mL to about 150 ng/mL, about 150 ng/mL to about 155 ng/mL, about 155 ng/mL to about 160 ng/mL, about 160 ng/mL to about 170 ng/mL, or about 170 ng/mL to about 200 ng/mL, and may be up to about 10,000 ng/mL.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, is administered on the first day of at least two days of treatment with dextromethorphan, wherein a decrease in the dextrorphan plasma level occurs on the first day that bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds,

and dextromethorphan are co-administered, as compared to the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds. For example, the dextrorphan plasma level on the first day may be reduced by at least 5% as compared to the dextrorphan plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, are co-administered with dextromethorphan for at least five consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the fifth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for five consecutive days. For example, the dextromethorphan plasma level on the fifth day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be at least 5 times, at least 10 times, at least 20 times, at least 40 times, at least 50 times, at least 60 times, at least 65 times, or up to about 500 times, the level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for five consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan, are co-administered for at least six consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the sixth day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for six consecutive days. For example, the dextromethorphan plasma level on the sixth day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 60 times, at least 70 times, at least 75 times, or up to about 500 times, the level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for six consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan, are co-administered for at least seven consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the seventh day, the dextromethorphan plasma level is higher than the dextromethorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for seven consecutive days. For example, the dextromethorphan plasma level on the seventh day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 70 times, at least 80 times, at least 90 times, or up to about 500 times, the level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for seven consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan, are co-administered for at least eight consecutive days, wherein, on the eighth day, dextromethorphan has a plasma level, for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours, after co-administering bupropion with dextromethorphan that is at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 60 times, at least 70 times, at least 80 times, at least 90 times, at least 100 times, or up to about 1,000 times, the plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for eight consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan are co-administered for at least eight consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the eighth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for eight consecutive days. For example, the dextrorphan plasma level on the eighth day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, as compared to the dextrorphan plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for eight consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan, are co-administered for at least nine consecutive days, wherein, on the ninth day, dextromethorphan has a plasma level, for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours, after co-administering bupropion with dextromethorphan that is at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 60 times, at least 70 times, at least 80 times, at least 90 times, at least 100 times, or up to about 1,000 times, the plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for nine consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan are co-administered for at least nine

consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the ninth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for nine consecutive days. For example, the dextrorphan plasma level on the ninth day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, as compared to the dextrorphan plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for nine consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan, are co-administered for at least ten consecutive days, wherein, on the tenth day, dextromethorphan has a plasma level, for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours, after co-administering bupropion with dextromethorphan that is at least 5 times, at least 10 times, at least 20 times, at least 30 times, at least 50 times, at least 60 times, at least 70 times, at least 80 times, at least 90 times, at least 100 times, or up to about 1,000 times, the plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for ten consecutive days.

In some embodiments, bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, and dextromethorphan are co-administered for at least ten consecutive days, to a human being in need of treatment with dextromethorphan, wherein, on the tenth day, the dextrorphan plasma level is lower than the dextrorphan plasma level that would have been achieved by administering the same amount of dextromethorphan administered without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for ten consecutive days. For example, the dextrorphan plasma level on the tenth day (for example at 0 hours, 1 hour, 3 hours, 6 hours, or 12 hours after administration) may be reduced by at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%, as compared to the dextrorphan plasma level that would be achieved by administering the same amount of dextromethorphan without bupropion, hydroxybupropion, threohydroxybupropion, erythrohydroxybupropion, or a metabolite or prodrug of any of these compounds, for ten consecutive days.

In some embodiments, bupropion may be administered to a human being in an amount that results in an AUC_{0-12} of bupropion in the human being, on day 8, that is at least about 100 ng·hr/mL, at least about 200 ng·hr/mL, at least about 500 ng·hr/mL, at least about 600 ng·hr/mL, at least about 700 ng·hr/mL, at least about 800 ng·hr/mL, at least about 900 ng·hr/mL, at least about 1,000 ng·hr/mL, at least about 1,200 ng·hr/mL, at least 1,600 ng·hr/mL, or up to about 15,000 ng·hr/mL.

In some embodiments, bupropion may be administered to a human being in an amount that results in a C_{avg} of bupropion in the human being, on day 8, that is at least about 10 ng/mL, at least about 20 ng/mL, at least about 40 ng/mL, at least about 50 ng/mL, at least about 60 ng/mL, at least about 70 ng/mL, at least about 80 ng/mL, at least about 90 ng/mL, at least about 100 ng/mL, at least 120 ng/mL, or up to about 1,500 ng/mL.

In some embodiments, bupropion may be administered to a human being in an amount that results in a C_{max} of bupropion in the human being, on day 8, that is at least about 10 ng/mL, at least about 20 ng/mL, at least about 50 ng/mL, at least about 90 ng/mL, at least about 100 ng/mL, at least about 110 ng/mL, at least about 120 ng/mL, at least about 130 ng/mL, at least about 140 ng/mL, at least 200 ng/mL, or up to about 1,500 ng/mL.

Some liquid compositions may comprise about 0.0001% (w/v) to about 50% (w/v), about 0.01% (w/v) to about 20% (w/v), about 0.01% to about 10% (w/v), about 1% (w/v) to about 3% (w/v), about 3% (w/v) to about 5% (w/v), about 5% (w/v) to about 7% (w/v), about 5% (w/v) to about 15% (w/v), about 7% (w/v) to about 10% (w/v), about 10% (w/v) to about 15% (w/v), about 15% (w/v) to about 20% (w/v), about 20% (w/v) to about 30% (w/v), about 30% (w/v) to about 40% (w/v), or about 40% (w/v) to about 50% (w/v) of bupropion, or any amount of bupropion in a range bounded by, or between, any of these values.

Some liquid dosage forms may contain about 10 mg to about 1000 mg, about 50 mg to about 1000 mg, about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 40 mg to about 90 mg, about 200 mg to about 300 mg, about 70 mg to about 95 mg, about 100 mg to about 200 mg, about 100 mg to about 110 mg, about 105 mg to about 200 mg, about 110 mg to about 140 mg, about 180 mg to about 220 mg, about 280 mg to about 320 mg, about 105 mg, about 200 mg, about 150 mg, or about 300 mg of bupropion, e.g. bupropion chloride, or any amount of bupropion in a range bounded by, or between, any of these values.

Some solid compositions may comprise at least about 5% (w/w), at least about 10% (w/w), at least about 20% (w/w), at least about 50% (w/w), at least about 70% (w/w), at least about 80%, about 10% (w/w) to about 30% (w/w), about 10% (w/w) to about 20% (w/w), about 20% (w/w) to about 30% (w/w), about 30% (w/w) to about 50% (w/w), about 30% (w/w) to about 40% (w/w), about 40% (w/w) to about 50% (w/w), about 50% (w/w) to about 80% (w/w), about 50% (w/w) to about 60% (w/w), about 70% (w/w) to about 80% (w/w), or about 80% (w/w) to about 90% (w/w) of bupropion, or any amount of bupropion in a range bounded by, or between, any of these values.

Some solid dosage forms may contain about 10 mg to about 1000 mg, about 50 mg to about 1000 mg, about 10 mg to about 50 mg, about 50 mg to about 100 mg, about 40 mg to about 90 mg, about 200 mg to about 300 mg, about 70 mg to about 95 mg, about 100 mg to about 200 mg, about 100 mg to about 120 mg, about 105 mg to about 200 mg, about 90 mg to about 120 mg, about 100 mg to about 110 mg, about 110 mg to about 140 mg, about 50 mg to about 150 mg, about 180 mg to about 220 mg, about 280 mg to about 320 mg, about 105 mg, about 200 mg, about 150 mg, or about 300 mg of bupropion, e.g. bupropion chloride, or any amount of bupropion in a range bounded by, or between, any of these values.

In some embodiments, bupropion is administered at a dose that results in a bupropion plasma level of about 0.1 μM to about 10 μM, about 0.1 μM to about 5 μM, about 0.2 μM to about 3 μM, about 0.1 μM to about 1 μM, about 0.2 μM to about 2 μM, about 1 μM to about 10 μM, about 1 μM to about 5 μM, about 2 μM to about 3 μM, or about 2.8 μM to about 3 μM, about 1.5 μM to about 2 μM, about 4.5 μM to about 5 μM, about 2.5 μM to about 3 μM, about 1.8 μM,

about 4.8 μM, about 2.9 μM, about 2.8 μM, or any plasma level in a range bounded by, or between, any of these values.

In some embodiments, bupropion, hydroxybupropion, or a prodrug of hydroxybupropion, is administered at a dose that results in a hydroxybupropion plasma level of about 0.1 μM to about 10 μM, about 0.1 μM to about 5 μM, about 0.2 μM to about 3 μM, about 0.1 μM to about 1 μM, about 0.2 μM to about 2 μM, 1 μM to about 10 μM, about 1 μM to about 5 μM, about 2 μM to about 3 μM, or about 2.8 μM to about 3 μM, about 1.5 μM to about 2 μM, about 4.5 μM to about 5 μM, about 2.5 μM to about 3 μM, about 1.8 μM, about 4.8 μM, about 2.9 μM, about 2.8 μM, or any plasma level in a range bounded by, or between, any of these values.

In some embodiments, bupropion, hydroxybupropion, or a prodrug of hydroxybupropion, may be administered to a human being in an amount that results in an $AUC_{0\text{-}12}$ of hydroxybupropion in the human being, on day 8, that is at least about 3,000 ng·hr/mL, at least about 7,000 ng·hr/mL, at least about 10,000 ng·hr/mL, at least about 15,000 ng·hr/mL, at least about 20,000 ng·hr/mL, at least about 30,000 ng·hr/mL, up to about 50,000 ng·hr/mL, up to about 150,000 ng·hr/mL, or any AUC in a range bounded by, or between, any of these values.

In some embodiments, bupropion, hydroxybupropion, or a prodrug of hydroxybupropion, may be administered to a human being in an amount that results in a C_{max} of hydroxybupropion in the human being, on day 8, that is at least about 300 ng/mL, at least about 700 ng/mL, at least about 1,000 ng/mL, at least about 1,500 ng/mL, at least about 2,000 ng/mL, at least about 4,000 ng/mL, up to about 10,000 ng/mL, up to about 50,000 ng/mL, or any C_{max} in a range bounded by, or between, any of these values.

In some embodiments, bupropion, hydroxybupropion, or a prodrug of hydroxybupropion, may be administered to a human being in an amount that results in a C_{avg} of hydroxybupropion in the human being, on day 8, that is at least about 200 ng/mL, at least about 300 ng/mL, at least about 700 ng/mL, at least about 1,000 ng/mL, at least about 1,500 ng/mL, at least about 2,000 ng/mL, at least about 4,000 ng/mL, up to about 10,000 ng/mL, up to about 50,000 ng/mL, or any C_{avg} in a range bounded by, or between, any of these values.

In some embodiments, bupropion, threohydroxybupropion, or a prodrug of threohydroxybupropion, is administered at a dose that results in a threohydroxybupropion plasma level of about 0.1 μM to about 10 μM, about 0.1 μM to about 5 μM, about 0.2 μM to about 3 μM, about 0.1 μM to about 1 μM, about 0.2 μM to about 2 μM, about 1 μM to about 10 μM, about 1 μM to about 5 μM, about 2 μM to about 3 μM, or about 2.8 μM to about 3 μM, about 1.5 μM to about 2 μM, about 4.5 μM to about 5 μM, about 2.5 μM to about 3 μM, about 1.8 μM, about 4.8 μM, about 2.9 μM, about 2.8 μM, or any plasma level in a range bounded by, or between, any of these values.

In some embodiments, bupropion, threohydroxybupropion, or a prodrug of threohydroxybupropion, may be administered to a human being in an amount that results in an $AUC_{0\text{-}12}$ of threohydroxybupropion in the human being, on day 8, that is at least about 1,000 ng·hr/mL, at least about 2,000 ng·hr/mL, at least about 4,000 ng·hr/mL, at least about 5,000 ng·hr/mL, at least about 8,000 ng·hr/mL, up to about 10,000 ng·hr/mL, up to about 40,000 ng·hr/mL, or any AUC in a range bounded by, or between, any of these values.

In some embodiments, bupropion, threohydroxybupropion, or a prodrug of threohydroxybupropion, may be administered to a human being in an amount that results in a C_{max} of threohydroxybupropion in the human being, on day 8, that is at least about 100 ng/mL, at least about 200 ng/mL, at least about 400 ng/mL, at least about 500 ng/mL, at least about 600 ng/mL, at least about 800 ng/mL, up to about 2,000 ng/mL, up to about 10,000 ng/mL, or any C_{max} in a range bounded by, or between, any of these values.

In some embodiments, bupropion, threohydroxybupropion, or a prodrug of threohydroxybupropion, may be administered to a human being in an amount that results in a C_{avg} of threohydroxybupropion in the human being, on day 8, that is at least about 100 ng/mL, at least about 300 ng/mL, at least about 400 ng/mL, at least about 600 ng/mL, at least about 800 ng/mL, up to about 2,000 ng/mL, up to about 10,000 ng/mL, or any C_{avg} in a range bounded by, or between, any of these values.

In some embodiments, bupropion, erythrohydroxybupropion, or a prodrug of erythrohydroxybupropion, is administered at a dose that results in an erythrohydroxybupropion plasma level of about 0.1 μM to about 10 μM, about 0.1 μM to about 5 μM, about 0.2 μM to about 3 μM, about 0.1 μM to about 1 μM, about 0.2 μM to about 2 μM, about 1 μM to about 10 μM, about 1 μM to about 5 μM, about 2 μM to about 3 μM, or about 2.8 μM to about 3 μM, about 1.5 μM to about 2 μM, about 4.5 μM to about 5 μM, about 2.5 μM to about 3 μM, about 1.8 μM, about 4.8 μM, about 2.9 μM, about 2.8 μM, or any plasma level in a range bounded by, or between, any of these values.

In some embodiments, bupropion, erythrohydroxybupropion, or a prodrug of erythrohydroxybupropion, may be administered to a human being in an amount that results in an $AUC_{0\text{-}12}$ of erythrohydroxybupropion in the human being, on day 8, that is at least about 200 ng·hr/mL, at least about 400 ng·hr/mL, at least about 700 ng·hr/mL, at least about 1,000 ng·hr/mL, at least about 1,500 ng·hr/mL, at least about 3,000 ng·hr/mL, up to about 5,000 ng·hr/mL, up to about 30,000 ng·hr/mL, or any plasma level in a range bounded by, or between, any of these values.

In some embodiments, bupropion, erythrohydroxybupropion, or a prodrug of erythrohydroxybupropion, may be administered to a human being in an amount that results in a C_{max} of erythrohydroxybupropion in the human being, on day 8, that is at least about 30 ng/mL, at least about 60 ng/mL, at least about 90 ng/mL, at least about 100 ng/mL, at least about 150 ng/mL, at least about 200 ng/mL, at least about 300 ng/mL, up to about 1,000 ng/mL, or any C in a range bounded by, or between, any of these values.

In some embodiments, bupropion, erythrohydroxybupropion, or a prodrug of erythrohydroxybupropion, may be administered to a human being in an amount that results in a C_{avg} of erythrohydroxybupropion in the human being, on day 8, that is at least about 20 ng/mL, at least about 30 ng/mL, at least about 50 ng/mL, at least about 80 ng/mL, at least about 90 ng/mL, at least about 100 ng/mL, at least about 150 ng/mL, at least about 200 ng/mL, at least about 300 ng/mL, up to about 1,000 ng/mL, up to about 5,000 ng/mL, or any C_{avg} in a range bounded by, or between, any of these values.

For compositions comprising both dextromethorphan and bupropion, some liquids may comprise about 0.0001% (w/v) to about 50% (w/v), about 0.01% (w/v) to about 20% (w/v), about 0.01% to about 10% (w/v), about 1% (w/v) to about 3% (w/v), about 3% (w/v) to about 5% (w/v), about 5% (w/v) to about 7% (w/v), about 5% (w/v) to about 15% (w/v), about 7% (w/v) to about 10% (w/v), about 10% (w/v) to about 15% (w/v), about 15% (w/v) to about 20% (w/v), about 20% (w/v) to about 30% (w/v), about 30% (w/v) to about 40% (w/v), about 40% (w/v) to about 50% (w/v) of

dextromethorphan and bupropion combined, or any amount in a range bounded by, or between, any of these values.

Some solid compositions may comprise at least about 5% (w/w), at least about 10% (w/w), at least about 20% (w/w), at least about 50% (w/w), at least about 70% (w/w), at least about 80%, about 10% (w/w) to about 30% (w/w), about 10% (w/w) to about 20% (w/w), about 20% (w/w) to about 30% (w/w), about 30% (w/w) to about 50% (w/w), about 30% (w/w) to about 40% (w/w), about 40% (w/w) to about 50% (w/w), about 50% (w/w) to about 80% (w/w), about 50% (w/w) to about 60% (w/w), about 70% (w/w) to about 80% (w/w), about 80% (w/w) to about 90% (w/w) of dextromethorphan and bupropion combined, or any amount in a range bounded by, or between, any of these values.

In some embodiments, the weight ratio of dextromethorphan to bupropion in a single composition or dosage form may be about 0.1 to about 2, about 0.2 to about 1, about 0.1 to about 0.3, about 0.2 to about 0.4, about 0.3 to about 0.5, about 0.5 to about 0.7, about 0.8 to about 1, about 0.2, about 0.3, about 0.4, about 0.45, about 0.6, about 0.9, or any ratio in a range bounded by, or between, any of these values.

A therapeutically effective amount of a therapeutic compound may vary depending upon the circumstances. For example, a daily dose of dextromethorphan may in some instances range from about 0.1 mg to about 1000 mg, about 40 mg to about 1000 mg, about 20 mg to about 600 mg, about 60 mg to about 700 mg, about 100 mg to about 400 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, about 45 mg to about 50 mg, about 50 mg to about 55 mg, about 55 mg to about 60 mg, about 20 mg to about 60 mg, about 60 mg to about 100 mg, about 100 mg to about 200 mg, about 100 mg to about 140 mg, about 160 mg to about 200 mg, about 200 mg to about 300 mg, about 220 mg to about 260 mg, about 300 mg to about 400 mg, about 340 mg to about 380 mg, about 400 mg to about 500 mg, about 500 mg to about 600 mg, about 15 mg, about 30 mg, about 60 mg, about 120 mg, about 180 mg, about 240 mg, about 360 mg, or any daily dose in a range bounded by, or between, any of these values. Dextromethorphan may be administered once daily; or twice daily or every 12 hours, three times daily, four times daily, or six times daily in an amount that is about half, one third, one quarter, or one sixth, respectively, of the daily dose.

A daily dose of bupropion, may in some instances range from about 10 mg to about 1000 mg, about 50 mg to about 600 mg, about 100 mg to about 2000 mg, about 50 mg to about 100 mg, about 70 mg to about 95 mg, about 100 mg to about 200 mg, about 105 mg to about 200 mg, about 100 mg to about 150 mg, about 150 mg to about 300 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 200 mg about 300 mg, about 300 mg to about 400 mg, about 400 mg to about 500 mg, about 400 mg to about 600 mg, about 360 mg to about 440 mg, about 560 mg to about 640 mg, or about 500 mg to about 600 mg, about 100 mg, about 150 mg, about 200 mg, about 300 mg, about 400 mg, about 600 mg, or any daily dose in a range bounded by, or between, any of these values. Bupropion may be administered once daily; or twice daily or every 12 hours, or three times daily in an amount that is about half or one third, respectively, of the daily dose.

In some embodiments: 1) about 50 mg/day to about 100 mg/day, about 100 mg/day to about 150 mg/day, about 150 mg/day to about 300 mg/day, about 150 mg/day to about 200 mg/day, about 200 mg/day to about 250 mg/day, about 250 mg/day to about 300 mg/day of bupropion, or about 300 mg/day to about 500 mg/day of bupropion; and/or 2) about 15 mg/day to about 60 mg/day, about 15 mg/day to about 30 mg/day, about 30 mg/day to about 45 mg/day, about 45 mg/day to about 60 mg/day, about 60 mg/day to about 100 mg/day, about 80 mg/day to about 110 mg/day, about 100 mg/day to about 150 mg/day, or about 100 mg/day to about 300 mg/day of dextromethorphan, are administered to a human being in need thereof.

In some embodiments, about 150 mg/day of bupropion and about 30 mg/day of dextromethorphan, about 150 mg/day of bupropion and about 60 mg/day of dextromethorphan, about 150 mg/day of bupropion and about 90 mg/day of dextromethorphan, about 150 mg/day of bupropion and about 120 mg/day of dextromethorphan, about 200 mg/day of bupropion and about 30 mg/day of dextromethorphan, about 200 mg/day of bupropion and about 60 mg/day of dextromethorphan, about 200 mg/day of bupropion and about 90 mg/day of dextromethorphan, about 200 mg/day of bupropion and about 120 mg/day of dextromethorphan, about 300 mg/day of bupropion and about 30 mg/day of dextromethorphan, about 300 mg/day of bupropion and about 60 mg/day of dextromethorphan, about 300 mg/day of bupropion and about 90 mg/day of dextromethorphan, or about 300 mg/day of bupropion and about 120 mg/day of dextromethorphan is administered to the human being.

In some embodiments, about 100 mg/day of bupropion and about 15 mg/day of dextromethorphan is administered to the human being for 1, 2, or 3 days, followed by about 200 mg/day of bupropion and about 30 mg/day of dextromethorphan. In some embodiments, about 100 mg/day of bupropion and about 30 mg/day of dextromethorphan is administered to the human being for 1, 2, or 3 days, followed by about 200 mg/day of bupropion and about 60 mg/day of dextromethorphan.

In some embodiments, about 75 mg/day of bupropion and about 15 mg/day of dextromethorphan is administered to the human being for 1, 2, or 3 days, followed by about 150 mg/day of bupropion and about 30 mg/day of dextromethorphan. In some embodiments, about 75 mg/day of bupropion and about 30 mg/day of dextromethorphan is administered to the human being for 1, 2, or 3 days, followed by about 150 mg/day of bupropion and about 60 mg/day of dextromethorphan.

An antidepressant compound, such as bupropion, may be administered for as long as needed to treat a neurological condition, such as pain, depression, or cough. In some embodiments, an antidepressant compound, such as bupropion, and dextromethorphan are administered at least once a day, such as once daily or twice daily, for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 8 days, at least 9 days, or at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 30 days, at least 35 days, at least 42 days, at least 60 days, at least 90 days, at least 180 days, at least 365 days, or longer.

In some embodiments, co-administration of dextromethorphan with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, may occur once a day for about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more days prior to co-administering dextromethorphan with bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds twice a day.

Therapeutic compounds may be formulated for oral administration, for example, with an inert diluent or with an edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated

directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

Tablets, troches, pills, capsules, and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn starch, or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid, and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose, or saccharin; or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as a coating, for example, tablets, pills, or capsules may be coated with shellac, sugar, or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. It may be desirable for material in a dosage form or pharmaceutical composition to be pharmaceutically pure and substantially nontoxic in the amounts employed.

Some compositions or dosage forms may be a liquid or may comprise a solid phase dispersed in a liquid.

Therapeutic compounds may be formulated for parental or intraperitoneal administration. Solutions of the active compounds as free bases or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also have an oil dispersed within, or dispersed in, glycerol, liquid polyethylene glycols, and mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

In some embodiments, the human being or the patient is, or is selected for being, Black or African American.

In some embodiments, the human being or the patient is, or is selected for being, white.

In some embodiments, the human being or the patient is, or is selected for being, Asian.

In some embodiments, the human being or the patient is, or is selected for being, Native Hawaiian or other Pacific Islander.

In some embodiments, the human being or the patient is, or is selected for being, Hispanic or Latino.

In some embodiments, the human being or the patient is, or is selected for being, Native American or Alaska Native.

In some embodiments, the human being or the patient is not, or is selected for not being, Hispanic or Latino.

Specifically Contemplated Embodiments

The following are examples of embodiments that are specifically contemplated by the inventor:

Embodiment 1. A method of treating pain or a neurological disorder comprising delivering an enhanced plasma level or bioavailability of dextromethorphan or administering a therapeutically effective amount of a combination of dextromethorphan and an antidepressant compound, to a person in need thereof.

Embodiment 2. A method of treating pain comprising administering a combination of an antidepressant compound and dextromethorphan to a human being in need thereof.

Embodiment 3. A method of enhancing the pain relieving properties of dextromethorphan, comprising co-administering dextromethorphan and an antidepressant compound.

Embodiment 4. A method of increasing dextromethorphan plasma levels in a human being that is an extensive metabolizer of dextromethorphan, comprising co-administering an antidepressant compound to the human being receiving a treatment that includes administration of dextromethorphan.

Embodiment 5. A method of inhibiting the metabolism of dextromethorphan, comprising administering an antidepressant compound to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as the antidepressant compound.

Embodiment 6. A method of increasing the metabolic lifetime of dextromethorphan, comprising administering an antidepressant compound to a human being, wherein the human being is an extensive metabolizer of dextromethorphan, and wherein dextromethorphan is present in the body of the human being at the same time as the antidepressant compound.

Embodiment 7. A method of correcting extensive metabolism of dextromethorphan, comprising administering an antidepressant compound to a human being in need thereof.

Embodiment 8. A method of improving pain relieving properties of dextromethorphan comprising administering an antidepressant compound in conjunction with administration of dextromethorphan to a human being in need of treatment for pain.

Embodiment 9. A method of improving antitussive properties of dextromethorphan comprising administering an antidepressant compound in conjunction with administration of dextromethorphan to a human being in need of treatment for cough.

Embodiment 10. A method of treating cough comprising administering a combination of an antidepressant compound and dextromethorphan to a human being in need thereof.

Embodiment 11. A method of improving a therapeutic property of dextromethorphan comprising administering an antidepressant compound in conjunction with administration of dextromethorphan to a human being in need of treatment for a neurological disorder.

Embodiment 12. A method of treating a neurological disorder comprising administering a combination of an antidepressant compound and dextromethorphan to a human being in need thereof.

Embodiment 13. A method of treating a neurological disorder comprising administering an antidepressant compound and dextromethorphan to a human being in need thereof, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 14. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, wherein the dextromethorphan and the antidepressant compound are administered in separate dosage forms.

Embodiment 15. A pharmaceutical composition comprising a therapeutically effective amount of dextromethorphan, a therapeutically effective amount of an antidepressant compound, and a pharmaceutically acceptable excipient.

Embodiment 16. An oral dosage form comprising at least 20 mg of dextromethorphan and an effective amount of an antidepressant compound to inhibit the metabolism of dextromethorphan in a human being that is an extensive metabolizer of dextromethorphan.

Embodiment 17. The oral dosage form of embodiment 16, wherein about 30 mg to about 350 mg of dextromethorphan is present in the dosage form.

Embodiment 18. The oral dosage form of embodiment 16 or 17, wherein about 100 mg to about 400 mg of bupropion is present in the dosage form.

Embodiment 19. The oral dosage form of any of embodiments 16, 17, or 18, comprising an amount of bupropion that results in a bupropion plasma level of about 0.1 μM to about 10 μM when the oral dosage form is administered to a human being.

Embodiment 20. The oral dosage form of embodiment 19, comprising an amount of bupropion that results in a bupropion plasma level of about 0.1 μM to about 2 μM when the oral dosage form is administered to a human being.

Embodiment 21. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or 13, wherein bupropion is administered at a dose that results in a bupropion plasma level of about 0.1 μM to about 10 μM.

Embodiment 22. The method of any preceding embodiment, such as embodiment 21, wherein bupropion is administered at a dose that results in a bupropion plasma level of about 0.3 μM to about 1 μM.

Embodiment 23. The method, composition, or dosage form of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, wherein the antidepressant compound is bupropion or a metabolite thereof.

Embodiment 24. The method, composition, or dosage form of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, wherein the antidepressant compound is bupropion.

Embodiment 25. The method, composition, or dosage form of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17, wherein the antidepressant compound is clomipramine, doxepin, fluoxetine, mianserin, imipramine, 2-chloroimipramine, amitriptyline, amoxapine, desipramine, protriptyline, trimipramine, nortriptyline, maprotiline, phenelzine, isocarboxazid, tranylcypromine, paroxetine, trazodone, citalopram, sertraline, aryloxy indanamine, benactyzine, escitalopram, fluvoxamine, venlafaxine, desvenlafaxine, duloxetine, mirtazapine, nefazodone, selegiline, ketamine, or a pharmaceutically acceptable salt thereof

Embodiment 26. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 21, 22, 23, 24, or 25, wherein dextromethorphan is administered to the human being for the treatment of cough.

Embodiment 27. A method of treating a neurological disorder comprising administering about 150 mg/day to about 300 mg/day of bupropion and about 30 mg/day to about 120 mg/day of dextromethorphan to a human being in need thereof.

Embodiment 28. A method of treating a neurological disorder comprising administering bupropion and dextromethorphan to a human being in need thereof, wherein the bupropion and dextromethorphan are administered at least once a day for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 29. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, or 27, wherein bupropion is administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 30. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, or 28, wherein dextromethorphan is administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 31. The method of any preceding embodiment, such as embodiment 28, 29, or 30, wherein bupropion is administered in an amount that results in a plasma concentration of dextromethorphan in the human being, on day 8, that is at least 10 times the plasma concentration of the same amount of dextromethorphan administered without bupropion.

Embodiment 32. The method of any preceding embodiment, such as embodiment 28, 29, 30, or 31, wherein bupropion is administered in an amount that results in an AUC_{0-12} of hydroxybupropion, on day 8, that is at least about 3000 ng·hr/mL.

Embodiment 33. The method of any preceding embodiment, such as embodiment 28, 29, 30, 31, or 32, wherein bupropion is administered in an amount that results in an AUC_{0-12} of erythrohydroxybupropion, on day 8, that is at least about 400 ng·hr/mL.

Embodiment 34. The method of any preceding embodiment, such as embodiment 28, 29, 30, 31, 32, or 33, wherein bupropion is administered in an amount that results in an AUC_{0-12} of threohydroxybupropion, on day 8, that is at least about 2000 ng·hr/mL.

Embodiment 35. The method, composition, or dosage form of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 26, 27, 28, 29, 30, 31, 32, 33, or 34, wherein the weight ratio of dextromethorphan to bupropion is about 0.1 to about 0.5.

Embodiment 36. The method of any preceding embodiment, such as embodiment 27, 28, 29, 30, 31, 32, 33, 34, or 35, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 37. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein about 150 mg/day of bupropion and about 30 mg/day of dextromethorphan is administered to the human being.

Embodiment 38. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein about 150 mg/day of bupropion and about 60 mg/day of dextromethorphan is administered to the human being.

Embodiment 39. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein about 200 mg/day of bupropion and about 30 mg/day of dextromethorphan is administered to the human being.

Embodiment 40. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein about 100 mg/day of bupropion and about 15 mg/day of dextromethorphan is administered to the human being for about 1 to about 3 days, followed by about 200 mg/day of bupropion and about 30 mg/day of dextromethorphan.

Embodiment 41. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36, wherein about 200 mg/day of bupropion and about 60 mg/day of dextromethorphan is administered to the human being.

Embodiment 42. The method of any preceding embodiment, such as embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35,

or 36, wherein about 100 mg/day of bupropion and about 30 mg/day of dextromethorphan is administered to the human being for about 1 to about 3 days, followed by about 200 mg/day of bupropion and about 60 mg/day of dextromethorphan.

Embodiment 43. The method of any preceding embodiment, such as embodiment 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, or 42, wherein dextromethorphan is administered to the human being for the treatment of pain.

Embodiment 44. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises post-operative pain, cancer pain, arthritic pain, lumbosacral pain, musculoskeletal pain, central multiple sclerosis pain, nociceptive pain, or neuropathic pain.

Embodiment 45. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises musculoskeletal pain, neuropathic pain, cancer-related pain, acute pain, or nociceptive pain.

Embodiment 46. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises post-operative pain.

Embodiment 47. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises cancer pain.

Embodiment 48. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises arthritic pain.

Embodiment 49. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises lumbosacral pain.

Embodiment 50. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises musculoskeletal pain.

Embodiment 51. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises neuropathic pain.

Embodiment 52. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises nociceptive pain.

Embodiment 53. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises chronic musculoskeletal pain.

Embodiment 54. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with rheumatoid arthritis.

Embodiment 55. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with juvenile rheumatoid arthritis.

Embodiment 56. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with osteoarthritis.

Embodiment 57. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with an axial spondyloarthritis.

Embodiment 58. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with ankylosing spondylitis.

Embodiment 59. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with diabetic peripheral neuropathy.

Embodiment 60. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with post-herpetic neuralgia.

Embodiment 61. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with trigeminal neuralgia.

Embodiment 62. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with monoradiculopathies.

Embodiment 63. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with phantom limb pain.

Embodiment 64. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with central pain.

Embodiment 65. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises cancer-related pain.

Embodiment 66. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with lumbar nerve root compression.

Embodiment 67. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with spinal cord injury.

Embodiment 68. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with post-stroke pain.

Embodiment 69. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with central multiple sclerosis pain.

Embodiment 70. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with HIV-associated neuropathy.

Embodiment 71. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with radio-therapy associated neuropathy.

Embodiment 72. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with chemo-therapy associated neuropathy.

Embodiment 73. The method of any preceding embodiment, such as embodiment 43, wherein the pain comprises dental pain.

Embodiment 74. The method of any preceding embodiment, such as embodiment 43, wherein the pain is associated with primary dysmenorrhea.

Embodiment 75. The method of any preceding embodiment, such as embodiment 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, or 74, wherein 90 mg/day of dextromethorphan is administered to the human being.

Embodiment 76. The method of any preceding embodiment, such as embodiment 75, wherein 45 mg of dextromethorphan is administered twice a day to the human being.

Embodiment 77. The method of any preceding embodiment, such as embodiment 75 or 76, wherein 150 mg/day of bupropion is administered to the human being.

Embodiment 78. The method of any preceding embodiment, such as embodiment 75 or 76, wherein 180 mg/day of bupropion is administered to the human being.

Embodiment 79. The method of any preceding embodiment, such as embodiment 75 or 76, wherein 200 mg/day of bupropion is administered to the human being.

Embodiment 80. The method of any preceding embodiment, such as embodiment 75 or 76, wherein 300 mg/day of bupropion is administered to the human being.

Embodiment 81. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, with dextromethorphan to the human being, wherein the threohydroxybupropion, hydroxybupropion, erythrohy-

droxybupropion, bupropion, or a prodrug thereof, is administered in an amount that results in an AUC_{0-12} of dextromethorphan that is at least about 40 ng·hr/mL.

Embodiment 82. The method of any preceding embodiment, such as embodiment 81, wherein the AUC_{0-12} of dextromethorphan is at least about 50 ng·hr/mL.

Embodiment 83. The method of any preceding embodiment, such as embodiment 81 or 82, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 84. The method of any preceding embodiment, such as embodiment 81, 82, or 83, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 85. The method of any preceding embodiment, such as embodiment 81, 82, 83, or 84, wherein the threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 86. The method of any preceding embodiment, such as embodiment 85, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 87. The method of any preceding embodiment, such as embodiment 85 or 86, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 400 ng·hr/mL.

Embodiment 88. The method of any preceding embodiment, such as embodiment 85, 86, or 87, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 800 ng·hr/mL.

Embodiment 89. The method of any preceding embodiment, such as embodiment 85, 86, 87, or 88, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 1500 ng·hr/mL.

Embodiment 90. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, or 89, wherein the AUC_{0-24} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 91. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, or 90, wherein the AUC_{0-24} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 1500 ng·hr/mL.

Embodiment 92. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, 90, or 91, wherein the AUC_{0-24} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 2900 ng·hr/mL.

Embodiment 93. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, 90, 91, or 92, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 94. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, 90, 91, 92, or 93, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 1500 ng·hr/mL.

Embodiment 95. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, 90, 91, 92, 93, or 94, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 3500 ng·hr/mL.

Embodiment 96. The method of any preceding embodiment, such as embodiment 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, or 95, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 5000 ng·hr/mL.

Embodiment 97. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, with dextromethorphan to the human being, wherein the threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, is administered in an amount that results in a C_{max} of dextromethorphan that is at least about 6 ng/mL.

Embodiment 98. The method of any preceding embodiment, such as embodiment 97, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 99. The method of any preceding embodiment, such as embodiment 97 or 98, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 100. The method of any preceding embodiment, such as embodiment 97, 98, or 99, wherein the threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 101. The method of any preceding embodiment, such as embodiment 100, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 20 ng/mL.

Embodiment 102. The method of any preceding embodiment, such as embodiment 100 or 101, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 60 ng/mL.

Embodiment 103. The method of any preceding embodiment, such as embodiment 100, 101, or 102, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 120 ng/mL.

Embodiment 104. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, with dextromethorphan to the human being, wherein the threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, is administered in an amount that results in a C_{avg} of dextromethorphan over a 12 hour period, after one administration, that is at least about 5 ng/mL.

Embodiment 105. The method of any preceding embodiment, such as embodiment 104, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 106. The method of any preceding embodiment, such as embodiment 104 or 105, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 107. The method of any preceding embodiment, such as embodiment 104, 105, or 106, wherein the threohydroxybupropion, hydroxybupropion, erythrohydroxybupropion, bupropion, or a prodrug thereof, and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 108. The method of any preceding embodiment, such as embodiment 107, wherein the C_{avg} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 20 ng/mL.

Embodiment 109. The method of any preceding embodiment, such as embodiment 107 or 108, wherein the C_{avg} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 70 ng/mL.

Embodiment 110. The method of any preceding embodiment, such as embodiment 107, 108, or 109, wherein the C_{avg} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 120 ng/mL.

Embodiment 111. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, with dextromethorphan to the human being,

wherein the bupropion or a prodrug thereof is administered in an amount that results in an AUC_{0-12} of dextromethorphan that is at least about 40 ng·hr/mL.

Embodiment 112. The method of any preceding embodiment, such as embodiment 111, wherein the AUC_{0-12} of dextromethorphan is at least about 50 ng·hr/mL.

Embodiment 113. The method of any preceding embodiment, such as embodiment 111 or 112, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 114. The method of any preceding embodiment, such as embodiment 111, 112, or 113, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 115. The method of any preceding embodiment, such as embodiment 111, 112, 113, or 114, wherein the bupropion or a prodrug thereof is co-administered with dextromethorphan at least daily for at least two consecutive days.

Embodiment 116. The method of any preceding embodiment, such as embodiment 115, wherein the bupropion or a prodrug thereof and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 117. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 118. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 800 ng·hr/mL.

Embodiment 119. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-12} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 1500 ng·hr/mL.

Embodiment 120. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-24} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 121. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-24} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 1500 ng·hr/mL.

Embodiment 122. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 100 ng·hr/mL.

Embodiment 123. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 3500 ng·hr/mL.

Embodiment 124. The method of any preceding embodiment, such as embodiment 116, wherein the AUC_{0-inf} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 5000 ng·hr/mL.

Embodiment 125. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, with dextromethorphan to the human being, wherein the bupropion or a prodrug thereof is administered in an amount that results in a C_{max} of dextromethorphan that is at least about 6 ng/mL.

Embodiment 126. The method of any preceding embodiment, such as embodiment 125, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 127. The method of any preceding embodiment, such as embodiment 125 or 126, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 128. The method of any preceding embodiment, such as embodiment 126, 127, or 128, wherein the bupropion or a prodrug thereof is co-administered with dextromethorphan at least daily for at least two consecutive days.

Embodiment 129. The method of any preceding embodiment, such as embodiment 128, wherein the bupropion or a prodrug thereof and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 130. The method of any preceding embodiment, such as embodiment 129, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 10 ng/mL.

Embodiment 131. The method of any preceding embodiment, such as embodiment 129, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 60 ng/mL.

Embodiment 132. The method of any preceding embodiment, such as embodiment 129, wherein the C_{max} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 120 ng/mL.

Embodiment 133. A method of increasing dextromethorphan plasma levels in a human being, comprising co-administering bupropion, hydroxybupropion, erythrohydroxybupropion, threohydroxybupropion, or a prodrug of any of these compounds, with dextromethorphan to the human being, wherein the bupropion or a prodrug thereof is administered in an amount that results in a C_{avg} of dextromethorphan, over the period between two separate and consecutive administrations of dextromethorphan, that is at least about 5 ng/mL.

Embodiment 134. The method of any preceding embodiment, such as embodiment 134, wherein the bupropion or a prodrug thereof is administered in an amount that results in a C_{avg} of dextromethorphan, over the period between two separate and consecutive administrations of dextromethorphan, that is at least about 60 ng/mL.

Embodiment 135. The method of any preceding embodiment, such as embodiment 134, wherein the human being is in need of treatment with dextromethorphan.

Embodiment 136. The method of any preceding embodiment, such as embodiment 134 or 135, wherein the human being is an extensive metabolizer of dextromethorphan.

Embodiment 137. The method of any preceding embodiment, such as embodiment 134, 135, or 136, wherein the bupropion or a prodrug thereof is co-administered with dextromethorphan at least daily for at least two consecutive days.

Embodiment 138. The method of any preceding embodiment, such as embodiment 137, wherein the bupropion or a prodrug thereof and dextromethorphan are administered to the human being at least daily for at least 8 days, at least 9 days, or at least 10 days.

Embodiment 139. The method of any preceding embodiment, such as embodiment 138, wherein the C_{avg} of dextromethorphan on Day 8, Day 9, or Day 10 is at least about 8 ng/mL, wherein the C_{avg} is for the period between two separate and consecutive administrations of dextromethorphan, or

if dextromethorphan is administered only once on Day 8, Day 9, or Day 10, the C_{avg} is for 12 hours after the first dose of dextromethorphan on Day 8, Day 9, or Day 10.

Embodiment 140. The method of any preceding embodiment, such as embodiment 138, wherein the C_{avg} of dex-

tromethorphan on Day 8, Day 9, or Day 10 is at least about 120 ng/mL, wherein the C_{avg} is for the period between two separate and consecutive administrations of dextromethorphan, or

if dextromethorphan is administered only once on Day 8, Day 9, or Day 10, the Ca, for 12 hours after the first dose of dextromethorphan on Day 8, Day 9, or Day 10.

Embodiment 141. A method of improving the efficacy of bupropion in treating depression, comprising: orally administering about 90 mg to about 125 mg of a bupropion in combination with about 0.3 mg/kg to about 1 mg/kg of a dextromethorphan, once or twice a day for at least 23 days, to a human being suffering from depression, wherein orally administering the bupropion in combination with the dextromethorphan is more effective in treating depression than orally administering the same dosage regimen of bupropion without dextromethorphan.

Embodiment 142. The method of embodiment 141, wherein about 0.6 mg/kg to about 0.8 mg/kg of the dextromethorphan is orally administered once or twice a day.

Embodiment 143. The method of embodiment 141, wherein about 45 mg of the dextromethorphan is orally administered once or twice a day.

Embodiment 144. The method of embodiment 141, wherein about 100 mg to about 120 mg of the bupropion is orally administered once or twice a day.

Embodiment 145. The method of embodiment 142, wherein about 105 mg of the bupropion is orally administered once or twice a day.

Embodiment 146. The method of embodiment 141, wherein the dextromethorphan and the bupropion are orally administered for at least 35 days.

Embodiment 147. The method of embodiment 141, wherein the human being is suffering from treatment-resistant depression.

Embodiment 148. The method of embodiment 141, wherein the dextromethorphan is orally administered in a dosage form that provides immediate release of the dextromethorphan.

Embodiment 149. The method of embodiment 143, wherein the dextromethorphan is orally administered in a dosage form that provides immediate release of the dextromethorphan.

Embodiment 150. The method of embodiment 141, wherein the bupropion is orally administered in a dosage form that provides sustained release of the bupropion.

Embodiment 151. The method of embodiment 145, wherein the bupropion is orally administered in a dosage form that provides sustained release of the bupropion.

Embodiment 152. The method of embodiment 150, wherein about 105 mg of the bupropion is orally administered once or twice a day in a dosage form that provides sustained release of the bupropion.

Embodiment 153. The method of embodiment 152, wherein the bupropion and the dextromethorphan are orally administered together in a single dosage form that is orally administered once or twice a day.

Embodiment 154. The method of embodiment 153, wherein the dextromethorphan and the bupropion are orally administered for at least 5 weeks.

Embodiment 155. The method of embodiment 141, wherein the human being is suffering from major depressive disorder.

Embodiment 156. The method of embodiment 154, wherein the bupropion comprises an enantiomeric excess of an R-enantiomer.

Embodiment 157. The method of embodiment 154, wherein the bupropion comprises an enantiomeric excess of an S-enantiomer.

Embodiment 158. The method of embodiment 141, wherein the dextromethorphan comprises a deuterium-modified dextromethorphan.

Embodiment 159. The method of embodiment 141, wherein the human being is currently suffering from depression and has previously been unsuccessfully treated with at least two antidepressants.

Embodiment 160. A method of treating treatment-resistant depression comprising:

selecting a human being suffering from depression who has previously been unsuccessfully treated with at least one antidepressant; and

orally administering a dextromethorphan-bupropion combination treatment once or twice a day to the human being for at least about five weeks;

wherein the dextromethorphan-bupropion combination treatment comprises about 40 mg to about 70 mg of a dextromethorphan and about 100 mg to about 140 mg of a bupropion.

Embodiment 161. The method of embodiment 160, wherein the bupropion comprises an enantiomeric excess of an enantiomer.

Embodiment 162. The method of embodiment 160, wherein the dextromethorphan comprises a deuterium-modified dextromethorphan.

Embodiment 163. The method of embodiment 160, wherein the dextromethorphan-bupropion combination treatment comprises about 40 mg to about 50 mg of the dextromethorphan.

Embodiment 164. The method of embodiment 160, wherein the dextromethorphan-bupropion combination treatment comprises about 100 mg to about 110 mg of the bupropion.

Embodiment 165. The method of embodiment 163, wherein the dextromethorphan-bupropion combination treatment comprises about 100 mg to about 110 mg of the bupropion.

Embodiment 166. The method of embodiment 165, wherein the dextromethorphan and the bupropion are orally administered in a single dosage form that provides immediate release for the dextromethorphan and sustained release for the bupropion.

Embodiment 167. The method of embodiment 166, further comprising orally administering the dextromethorphan-bupropion combination treatment once a day for about 1, 2, 3, 4, 5, 6, or 7 days prior to orally administering the dextromethorphan-bupropion combination treatment twice a day to the human being for at least about five weeks.

Embodiment 168. The method of embodiment 167, wherein the dextromethorphan-bupropion combination treatment comprises about 45 mg of the dextromethorphan.

Embodiment 169. The method of embodiment 168, wherein the dextromethorphan-bupropion combination treatment comprises about 105 mg of the bupropion.

Embodiment 170. The method of embodiment 160, wherein the antidepressant is duloxetine.

Embodiment 171. A method of rapidly relieving the symptoms of depression, comprising administering a combination of bupropion and dextromethorphan once daily or twice daily to a human being in need thereof, wherein the human being experiences a therapeutic effect within 2 weeks of the first day that the combination of bupropion and dextromethorphan is administered.

Embodiment 172. A method of treating depression, comprising administering a combination of bupropion and dex-

tromethorphan once daily or twice daily to a human being in need thereof, wherein the human being is of Asian descent.

Embodiment 173. Use of a combination of bupropion and dextromethorphan in the manufacture of a medicament for rapidly relieving the symptoms of depression, wherein the medicament is administered once daily or twice daily to achieve a therapeutic effect within 2 weeks of the first day that the medicament is administered.

Embodiment 174. Use of a combination of bupropion and dextromethorphan in the manufacture of a medicament for the treatment of a depression, wherein the medicament is administered once daily or twice daily to a human being of Asian descent.

Embodiment 175. The method of embodiment 171 or 172 or the use of embodiment 173 or 174, wherein the human being is of Japanese descent.

Embodiment 176. The method of embodiment 171 or 172 or the use of embodiment 173 or 174, wherein the human being is of Chinese descent.

Embodiment 177. The method of embodiment 171 or 172 or the use of embodiment 173 or 174, wherein the human being is of Korean descent.

Embodiment 178. The method or the use of embodiment 171, 172, 173, 174, 175, 176, or 177, wherein about 105 mg of bupropion hydrochloride, or a molar equivalent amount of: 1) another salt form of bupropion or a 2) free base form of bupropion, is orally administered once daily or twice daily.

Embodiment 179. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, or 178, wherein about 44 mg to about 46 mg of dextromethorphan hydrobromide, or a molar equivalent amount of: 1) another salt form of dextromethorphan or a 2) free base form of dextromethorphan, is orally administered once daily or twice daily.

Embodiment 180. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, or 179, wherein the human being has previously had an inadequate response to at least one antidepressant therapy.

Embodiment 181. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, or 180, wherein the depression is major depressive disorder.

Embodiment 182. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, or 181, wherein the depression is treatment resistant depression.

Embodiment 183. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, or 182, wherein the combination of bupropion and dextromethorphan is administered once daily or twice daily for at least 30 days.

Embodiment 184. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, or 182, wherein the combination of bupropion and dextromethorphan is administered once daily or twice daily for at least 42 days.

Embodiment 185. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, or 184, wherein administration of the combination of bupropion and dextromethorphan results in the MADRS score reduced by at least about 10% as compared with baseline.

Embodiment 186. The method or the use of embodiment 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, or 184, wherein administration of the combination of bupropion and dextromethorphan results in the MADRS score reduced by at least about 10% as compared with placebo.

Embodiment 187. A method of treating nicotine addiction associated with smoking tobacco comprising administering a combination of a bupropion and a dextromethorphan daily for at least 21 consecutive days to a person suffering from nicotine addiction, wherein the person is an ad-lib tobacco smoker, wherein a total amount of 200 mg to 250 mg of bupropion and 80 mg to 140 mg of dextromethorphan are administered to the person daily, and wherein the method is more effective than administering the same amount of bupropion alone.

Embodiment 188. The method of embodiment 187, wherein the administration of the combination of the bupropion and the dextromethorphan resulted in at least 10% greater reduction in an intensity of the nicotine self-administration as compared to bupropion alone as measured by the reduction in the average number of cigarettes smoked per day.

Embodiment 189. The method of embodiment 187, wherein the administration of the combination of the bupropion and the dextromethorphan resulted in at least 15% greater reduction in an intensity of the nicotine self-administration as compared to bupropion alone as measured by the reduction in the average number of cigarettes smoked per day.

Embodiment 190. The method of embodiment 187, wherein the administration of the combination of the bupropion and the dextromethorphan resulted in at least 20% greater reduction in an intensity of the nicotine self-administration as compared to bupropion alone as measured by the reduction in the average number of cigarettes smoked per day.

Embodiment 191. The method of embodiment 187, wherein the administration of the combination of the bupropion and the dextromethorphan resulted in at least 10% greater reduction in expired carbon monoxide levels as compared to bupropion alone.

The method of embodiment 1, wherein the person taking a medication of the combination of the bupropion and the dextromethorphan twice a day in 2 equal amount of divided doses resulted in greater reduction in an intensity of the nicotine self-administration on the day or following day of the administration than the person taking only one of the 2 divided doses or not taking the medication of the combination.

Embodiment 192. The method of embodiment 187, wherein the combination of the bupropion and the dextromethorphan is administered to the person daily for at least 42 consecutive days.

Embodiment 193. The method of embodiment 187, wherein about 105 mg of the bupropion is administered to the person twice daily.

Embodiment 194. The method of embodiment 187, wherein about 200 mg to about 250 mg of the bupropion is administered daily to the person in two divided doses.

Embodiment 195. The method of embodiment 187, wherein about 90 mg of the dextromethorphan is administered to the person daily.

Embodiment 196. The method of embodiment 187, wherein about 45 mg of the dextromethorphan in each dose is administered to the person twice daily.

Embodiment 197. The method of embodiment 1, wherein about 40 mg to about 50 mg of the dextromethorphan in each dose is administered to the person twice daily.

Embodiment 198. The method of embodiment 187, wherein about 45 mg of the dextromethorphan and about 105 mg of bupropion are administered to the person twice daily.

Embodiment 199. The method of embodiment 187, wherein the weight ratio of dextromethorphan to bupropion is about 0.1 to about 0.5.

Embodiment 200. The method of embodiment 187, wherein the weight ratio of dextromethorphan to bupropion is about 0.4 to about 0.5.

Embodiment 201. The method of embodiment 187, wherein, to the person addicted to nicotine, the method is more effective than administering the dextromethorphan alone.

Embodiment 202. The method of embodiment 187, wherein about 105 mg of the bupropion is administered to the person once daily for three days, followed by administering 105 mg of the bupropion in each dose twice daily to the person for at least 21 days.

Embodiment 203. The method of embodiment 202, wherein, to the person addicted to nicotine, the method is more effective, as measured on day 24 of treatment, than a control method, wherein the control method consists of administering 105 mg of the bupropion alone to the person once daily for three days, followed by administering 105 mg of the bupropion alone in each dose twice daily to the person for 21 days.

Embodiment 204. The method of embodiment 187, wherein about 105 mg of the bupropion is administered to the person once daily for three days, followed by administering 105 mg of the bupropion in each dose twice daily to the person for at least 39 days.

Embodiment 205. The method of embodiment 204, wherein, to the person addicted to nicotine, the method is more effective, as measured on day 42 of treatment, than a control method, wherein the control method consists of administering 105 mg of the bupropion alone to the person once daily for three days, followed by administering 105 mg of the bupropion alone in each dose twice daily to the person for 39 days.

Embodiment 206. The method of embodiment 204, wherein, to the person addicted to nicotine, the method is more effective, as measured on day 42 of treatment, than a control method, wherein the control method consists of administering 105 mg of the bupropion alone to the person once daily for three days, followed by administering 105 mg of the bupropion alone in each dose twice daily to the person for 39 days.

Embodiment 207. The method of embodiment 187, wherein about 45 mg of the dextromethorphan is administered to the person once daily for three days, followed by administering 45 mg of the dextromethorphan in each dose twice daily to the person for at least 21 days.

Embodiment 208. The method of embodiment 198, wherein the method is more effective, as measured on day 21 of treatment, than a control method, wherein the control method consists of administering 105 mg of the bupropion alone to the person twice daily to the person for 21 days.

Embodiment 209. The method of embodiment 187, wherein the bupropion has an enantiomeric excess of the R-enantiomer that is at least 90%.

Embodiment 210. The method of embodiment 187, wherein the bupropion has an enantiomeric excess of the S-enantiomer that is at least 90%.

Embodiment 211. The method of embodiment 187, wherein the bupropion is deuterium enriched.

Embodiment 212. The method of embodiment 187, wherein the dextromethorphan is deuterium enriched.

EXAMPLES

Example 1

Fifteen human subjects were randomized into one of two treatment groups receiving either dextromethorphan (DM) alone, or DM in combination with bupropion, as shown in Table 1 below.

TABLE 1

Study Design

Group	Dose Levels Bupropion/DM	Dosing Regimen	Duration	Total Subjects
A	0 mg/60 mg	DM: Twice daily, Days 1-8	Days 1-8	8
B	150 mg/60 mg	Bupropion: Once daily, Days 1-3; Twice daily, Days 4-8 DM: Twice daily, Days 1-8	Days 1-8	7

All subjects were extensive, including ultra-rapid, metabolizers of dextromethorphan as determined by CYP2D6 genetic testing. Dextromethorphan was dosed at 12-hour intervals on Days 1-8, with a final morning dose on Day 8. Bupropion was dosed once daily on Days 1-3, and at 12-hour intervals thereafter, with a final morning dose on Day 8.

Plasma samples were collected for concentration analysis of dextromethorphan, total dextrorphan, bupropion, hydroxybupropion, erythrohydroxybupropion, and threohydroxybupropion on days 1 and 8. Plasma samples for determination of trough concentrations of dextromethorphan were obtained approximately 12 hours after dosing on days 1, 5, 6, and 8.

Concentrations of dextromethorphan, total dextrorphan (unconjugated and glucuronide forms), bupropion, hydroxybupropion, erythrohydroxybupropion, and threohydroxybupropion, were determined using LC-MS/MS. Pharmacokinetic parameters were calculated.

Phenotypic determination of dextromethorphan metabolizer status was performed by calculating the dextromethorphan/dextrorphan metabolic ratio as described in Jurica et al. *Journal of Clinical Pharmacy and Therapeutics,* 2012, 37, 486-490. Plasma concentrations of dextromethorphan and dextrorphan 3 hours after dosing were used, with a dextromethorphan/dextrorphan ratio of 0.3 or greater indicating a poor metabolizer phenotype.

Results

Plasma concentrations of dextromethorphan were significantly increased with bupropion administration, as illustrated in FIG. **1** and Table 2.

TABLE 2

Mean Day 8 Dextromethorphan Plasma Concentrations (ng/mL)

Time (hours)	Dextromethorphan (Group A)	Dextromethorphan + Bupropion (Group B)
0	1.2	110.6
1	2.4	129.3
2	3.6	153.9
3	3.6	151.6
4	3.3	149.1
6	2.5	150.0
8	1.9	144.4
12	1.1	119.3
24	0.4	95.3
36	0.1	69.0

The AUC of dextromethorphan was significantly increased with administration of bupropion as show in FIGS. **2-4**. As shown in FIG. **5** and Table 2A, administration of bupropion with dextromethorphan resulted in an approximately 60-fold, 80-fold, and 175-fold increase in mean dextromethorphan AUC_{0-12}, AUC_{0-24}, and AUC_{0-inf}, respec-

tively on Day 8 as compared to administration of dextromethorphan alone. As shown in FIG. **6** and Table 2B, the increase in dextromethorphan AUC occurred as early as Day 1 (an approximate 3-fold increase in AUC_{0-12}).

TABLE 2A

Day 8 Values

	Dextromethorphan (Group A)	Dextromethorphan + Bupropion (Group B)
AUC_{0-12} (ng * hr/mL)	28.1	1,686.3
AUC_{0-24} (ng * hr/mL)	37.1	2,975.3
AUC_{0-inf} (ng * hr/mL)	41.2	7,237.3
C_{max} (ng/mL)	3.8	158.1
C_{min} (ng/mL)	1.1	119.3
C_{avg} (ng/m L)	2.3	140.5

TABLE 2B

Day 1 Values

	Dextromethorphan (Group A)	Dextromethorphan + Bupropion (Group B)
AUC_{0-12} (ng * hr/mL)	20.1	56.5
C_{max} (ng/mL)	3.0	8.7

Trough plasma concentrations (also referred to as "minimum mean plasma concentrations" or "C_{min}") of dextromethorphan were significantly increased with administration of bupropion as illustrated in FIG. **7** and Tables 2A and 3. Administration of bupropion with dextromethorphan resulted in an approximately 105-fold increase in mean trough plasma concentration of dextromethorphan on Day 8 as compared to administration of dextromethorphan alone.

Mean average plasma concentrations (C_{avg}) of dextromethorphan on Day 8 increased approximately 60-fold with bupropion administration as compared to administration of dextromethorphan alone, as illustrated in Table 2A. Maximum mean plasma concentrations (C_{max}) were also significantly increased as illustrated in FIG. **8** and Table 2A.

TABLE 3

Mean Trough Dextromethorphan Plasma Concentrations (ng/mL)

	Dextromethorphan (Group A)	Dextromethorphan + Bupropion (Group B)	Fold Change
Day 1	0.7	2.5	3.5
Day 5	1.2	80.9	70
Day 6	1.3	102.2	78
Day 7	1.2	110.6	94
Day 8	1.1	119.3	105

The T_{max} and elimination half-life ($T_{1/2\ el}$) of dextromethorphan were significantly increased with administration of bupropion on Day 8. The increase of $T_{1/2\ el}$ shows that the metabolic lifetime of dextromethorphan was increased. Administration of bupropion with dextromethorphan resulted in a mean T_{max} of 3.6 hours, compared to 2.3 hours for dextromethorphan alone. Administration of bupropion with dextromethorphan resulted in a mean $T_{1/2\ el}$ of 27.7 hours, compared to 6.6 hours for dextromethorphan alone.

Plasma concentrations of dextrorphan were significantly decreased with bupropion administration, as illustrated in FIG. **9** and Table 4.

TABLE 4

Mean Day 8 Dextrorphan Plasma Concentrations (ng/mL)

Time (hours)	Dextromethorphan (Group A)	Dextromethorphan + Bupropion (Group B)
0	132.4	165.3
1	688.9	190.7
2	959.1	214.9
3	778.1	214.4
4	594.9	205.1
6	324.7	172.5
8	189.6	159.6
12	74.8	152.8
24	12.2	133.0
36	0.1	107.6

As shown in FIGS. **10-11**, there was an approximate 78% reduction in mean dextrorphan C_{max}, and an approximate 55% reduction in mean dextrorphan AUC_{0-12} on Day 8 with administration of bupropion.

Phenotypic determination of dextromethorphan metabolizer status showed that no subjects in either treatment arm were poor metabolizers on Day 1. On Day 8 however, 100% of subjects treated with bupropion had converted to poor metabolizer status as compared to 0% of subjects treated with dextromethorphan alone. The mean plasma dextromethorphan/dextrorphan metabolic ratio increased from 0.01 on Day 1 to 0.71 on Day 8 with bupropion administration. The mean ratio in the group administered DM alone was 0.00 on Day 1 and remained unchanged on Day 8.

On Day 8, average plasma concentrations of bupropion, hydroxybupropion, erythrohydroxybupropion, and threohydroxybupropion were at least 10 ng/mL, 200 ng/mL, 20 ng/mL, and 100 ng/mL, respectively after bupropion administration.

As used in this section, the term "fold change" or "fold increase" refers to the ratio of a value for bupropion with dextromethorphan to the same value for dextromethorphan alone (i.e., the value for bupropion with dextromethorphan divided by the same value for dextromethorphan alone).

Example 2

The ability of various antidepressant compounds to inhibit the metabolism of dextromethorphan was examined using human liver microsomes. Each antidepressant compound was incubated at seven increasing concentrations (0.1-100 μM) in duplicate with human liver microsomes (0.5 mg/mL) in the presence of dextromethorphan (5 μM) at 37° C. The assay was performed in the presence of 2 mM NADPH in 100 mM potassium phosphate (pH 7.4) containing 5 mM magnesium chloride, in a 200 μL assay final volume.

After optimal incubation at 37° C., the reactions were terminated by addition of methanol containing internal standard for analytical quantification. The quenched samples were incubated at 4° C. for 10 minutes and centrifuged at 4° C. for 10 minutes. The supernatant was removed, and the metabolite of dextromethorphan (dextrorphan) was analyzed by LC-MS/MS. A decrease in the formation of the metabolite compared to vehicle control was used to calculate an IC_{50} value (the test concentration which produces 50% inhibition of dextromethorphan metabolism) for each antidepressant compound, with a lower IC_{50} indicating greater potency.

The results are summarized in Table 5 below, and the corresponding potencies are depicted in FIG. **12**.

TABLE 5

Potency of Various Antidepressant Compounds for Inhibition of the Metabolism of Dextromethorphan in Human Liver Microsomes

Test Compound	Mean IC_{50} (μM)
Desvenlafaxine	97.3
Venlafaxine	27.7
Escitaloprann	17.1
Citalopram	14.1
(2S,3S)-Hydroxybupropion	12.5
Bupropion	9.1
(R,R)-Hydroxybupropion	8.2
Fluvoxamine	6.5
Sertraline	5.1
(S)-Duloxetine	4.1
Threohydroxybupropion	3.9
Erythrohydroxybupropion	1.4

Example 3

Phase 2 Clinical Trial Design:

The Phase 2 clinical trial with the administration of a combination of dextromethorphan and bupropion (DM/BU) was a randomized, double-blind, active-controlled, multicenter, U.S. trial with 80 adult patients with confirmed diagnosis of moderate to severe major depressive disorder (MDD), who received a twice daily dose for a 6-week treatment period. Dose groups (1:1 randomization) included DM/BU (45 mg dextromethorphan/105 mg bupropion) with 43 patients, or active comparator bupropion (105 mg) with 37 patients. Among these patients, 23% of them had received prior first line treatment for depression. The clinical trial had extensive quality control measures.

The Primary Endpoint:

The changes from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score over the 6-week treatment period were calculated at each time point and averaged.

FIG. **13** and Table A shows the changes in MADRS total score over the time during the 6-week dosing period for the subjects administered bupropion (BU) or the combination of dextromethorphan and bupropion (DM/BU).

TABLE A

Primary Endpoint	DM + BU	BU	P-Value
Change in MADRS Total Score over 6-week period (averaged)	−13.7	−8.8	<0.001
Change in MADRS Total Score at week 6	−17.2	−12.1	0.013

The Secondary Endpoints:

Table B listed the secondary endpoints with P-values.

TABLE B

Secondary Endpoint	P-Value*
MADRS Total Score Change Weeks 1-2	0.01
% Achieving Remission on MADRS at Week 2	0.004
% Achieving Remission on MADRS at Week 6	0.004
MADRS-6 Change at Week 6	0.007
% of Responders on MADRS-6	0.014
(≥50% reduction from baseline) at Week 6	
Clinical Global Impression-Improvement (CGI-I) at Week 1	0.045
CGI-I at Week 6	0.051
Clinical Global Impression-Severity (CGI-S) at Week 6	0.028

*P-values are for DM/BU versus active comparator bupropion (BU). Multiple secondary endpoints favored DM/BU.

FIG. **14** shows the percent of subjects achieving remission (as determined by MADRS≤10) over the time during the 6-week dosing period for the subjects administered bupropion (BU) or the combination of dextromethorphan and bupropion (DM/BU).

Safety:

The clinical study showed that the administration of the DM/BU was safe and well tolerated with similar rates of adverse events in the DM/BU and bupropion arms. No serious adverse events were observed. There was no meaningful difference between the two treatment arms in discontinuations due to adverse events. The most commonly reported adverse events in the DM/BU arm were nausea, dizziness, dry mouth, decreased appetite, and anxiety. The DM/BU was not associated with psychotomimetic effects, weight gain, or increased sexual dysfunction.

Summary:

Statistically significant improvements on MADRS and secondary efficacy endpoints for DM/BU in patients with MDD were achieved. Early and sustained separation from active comparator bupropion were observed. The administration of DM/BU was safe and well-tolerated with no psychotomimetic effects, weight gain, or increased sexual dysfunction

Thus, DM/BU demonstrated significant and rapid antidepressant activity with a favorable safety profile in the clinical trial in MDD.

Results:

FIGS. **13** and **14** are prepared based on the results of the US clinical trials with 80 adult patients having depression with 43 patients treated with the combination of 45 mg of DM and 105 mg of BU, and 37 patients treated with 105 mg of BU alone who received a twice daily dose for the 6-week treatment period. Among these patients, 23% of them had received prior first line treatment for depression.

As shown in FIG. **13** and Table A, the MADRS total score (depression rating scale) was significantly reduced with the combination of DM and BU than that of BU alone even at the first week of the treatment. At week 6, administration of the combination DM/BU reduced the MADRS total score by about 42% as compared to bupropion alone.

As shown in FIG. **14**, even in as early as the second week of the treatment, the remission rate for the combination of DM/BU is significantly higher than that for the comparator BU alone (about 8 times) with about 20% higher remission rate. At week 6 of the treatment, the administration of combination DM/BU resulted in about 30% higher remission rate than that of the comparator BU alone.

The above clinical study showed that the administration of the combination of bupropion with dextromethorphan (DM/BU) provides greater efficacy than would otherwise be achieved by administering bupropion alone. This clinical study demonstrated that the combination of dextromethorphan and bupropion has an additive or synergistic efficacy in treating depression.

Example 4: Product Kit

In some embodiments, a product kit comprises a combination of dextromethorphan and bupropion, for treating depression, wherein the product kit contains a dosage form containing about 30 mg to about 60 mg of dextromethorphan and about 100 mg to about 200 mg of bupropion, and wherein administration of the dosage form once daily or twice daily results in greater efficacy in the human being than that for administering bupropion alone. In some embodiments, the product kit contains 45 mg of dextromethorphan and 105 mg of bupropion.

In some embodiments, a product kit comprises an oral sustained release delivery system for dextromethorphan, comprising bupropion; dextromethorphan; and a water soluble vehicle in a dosage form, wherein the dosage form contains about 30 mg to about 60 mg of dextromethorphan and about 100 mg to about 200 mg of bupropion, and wherein the use of the dosage form once or twice daily for at least eight days results in the increase of elimination half-life ($T_{1/2}$) of dextromethorphan than that for administration dextromethorphan alone on the eighth day.

Example 5

Nearly 40 million American adults smoke and around 70% of them report that they want to quit. Tobacco use results in approximately 500,000 premature deaths each year in the U.S. alone, according to the Centers for Disease Control and Prevention. Smoking is the single largest cause of premature deaths worldwide accounting for an estimated almost 20% of all deaths in developed countries [Dani J A and Heinemann S (1996) Neuron 16:5, pp. 905-8]. Direct health care and lost productivity costs as a result of smoking total nearly $300 billion a year in the U.S. alone. It is estimated that only 3 to 5% of cigarette smokers who attempt to quit without assistance are successful for 6-12 months, and the relapse rate remains above 80% even with current treatments [Hughes J R, et al. (2004) Addiction 99:1, pp. 29-38]. As the vast majority of smokers who attempt to quit fail to do so highlighting the need for new approaches. The combination of dextromethorphan and bupropion (DM/BU) has the potential to address this condition due to the novel mechanisms of action of DM/BU.

The dextromethorphan component of DM/BU is a sigma-1 receptor agonist, nicotinic acetylcholine receptor antagonist, and inhibitor of the serotonin and norepinephrine transporters. The bupropion component of DM/BU serves to increase the bioavailability of dextromethorphan, and is a norepinephrine and dopamine reuptake inhibitor, and a nicotinic acetylcholine receptor antagonist. Both components of DM/BU are nicotinic acetylcholine receptor antagonists, a mechanism that is relevant to nicotine dependence. Thus, DM/BU provides a potentially new mechanism of action for smoking cessation treatment.

Phase 2 Clinical Trial Design:

The clinical trial was a Phase 2, randomized, double-blind, active-controlled study to evaluate the efficacy and safety of DM/BU for smoking cessation treatment. A total of 58 smokers were randomized in a 1:1 ratio to receive either DM/BU (45 mg dextromethorphan/105 mg bupropion) (n=31), or the active comparator bupropion (105 mg) (n=27), twice daily, and assessed over a 3-week period. Enrolled subjects were daily smokers using 10 or more cigarettes per day. The average number of cigarettes smoked per day at baseline was 20 for DM/BU and 17 for the bupropion treatment groups.

The Primary Endpoint:

The primary outcome measure was the change in smoking intensity, measured using the number of cigarettes smoked per day, assessed via daily smoking diaries.

Reduction in ad-lib smoking was selected as the primary endpoint in this trial because it has been shown to correlate with smoking abstinence.

Safety:

Medication adherence was similar between the study arms for both the morning dose (97.1% for DM/BU and 96.6% for bupropion) and the evening dose (76.3% for DM/BU and 79.4% for bupropion). In the study, DM/BU was safe and well tolerated with no serious adverse events. The most commonly reported side effects were headache, dry mouth, and insomnia/vivid dreams, with similar incidences in both treatment arms.

Results:

Treatment with DM/BU resulted in a 25% greater reduction in the average number of cigarettes smoked per day over the 3-week period, the prespecified primary endpoint, as compared to bupropion (average reductions of 8.49 and 6.79 cigarettes per day for DM/BU and bupropion, respectively, p=0.0016).

Consistent with this finding, a greater proportion of smokers receiving DM/BU experienced a more than 50% reduction in expired carbon monoxide levels, a biochemical marker of smoking intensity, as compared to those treated with bupropion (52.0% for DM/BU versus 30.4% for bupropion, p=0.15).

In addition, the human subjects who took DM/BU as prescribed on a given day smoked 1.0 fewer cigarette on the day of medication use of DM/BU (p=0.026) and 1.2 fewer cigarettes on the following day (p=0.008) as compared to those who missed one or both doses of DM/BU.

Summary:

The treatment with DM/BU achieves the prespecified primary endpoint in Phase 2 Trial in Smoking Cessation. The treatment with DM/BU demonstrated statistically significant reduction in daily smoking compared to the active comparator bupropion alone (p=0.0016). The findings in this phase 2 clinical trial are notable because DM/BU was compared to bupropion, which is an approved treatment for smoking cessation.

Furthermore, it is worth noting that the improvement of DM/BU over bupropion observed in this clinical trial in human beings is similar in magnitude to the improvement over placebo reported for the approved smoking cessation treatment varenicline in studies with a similar design. Varenicline is a prescription medication used to treat smoking addiction. This medication is the first approved nicotinic receptor partial agonist. Specifically, varenicline is a partial agonist of the alpha4/beta2 subtype of the nicotinic acetylcholine receptor.

Example 6

A Phase 3, randomized, double-blind, multicenter, placebo-controlled clinical trial of the combination of dextromethorphan (DM) and bupropion (BU or BUP) in patients with major depressive disorder (MDD) was conducted in the U.S. A total of 327 patients with a confirmed diagnosis of moderate to severe MDD were randomized in a 1:1 ratio to receive 45 mg dextromethorphan/105 mg bupropion (DM/BU) (n=163), or placebo (n=164) once daily for the first 3 days (day 1, day 2, and day 3) and twice daily thereafter (starting day 4) for a total of 6 weeks.

Baseline inclusion criteria included: Male or female 18-65 years of age, meeting DSM-5 criteria for current MDD without psychotic features, a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of at least 25, and CGI-S score of at least 4. Exclusion criteria included: a history of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment of, during the current episode or in the past 6 months, Schizophrenia, bipolar disorder, obsessive compulsive disorder, and Psychiatric symptoms secondary to any other general medical condition.

Patient demographics and baseline characteristics are shown in Table 6 below:

TABLE 6

	45 mg DM/105 mg BU	Placebo
Age (years)	42.1 (12.71)	41.1 (13.78)
Female Gender, n (%)	98 (60.1%)	117 (71.3%)
Race, n (%)		
White	88 (54.0%)	92 (56.1%)
Black or African American	61 (37.4%)	55 (33.5%)
Asian	9 (5.5%)	8 (4.9%)
Other or Not Reported	5 (3.1%)	9 (5.5%)
BMI (mg/kg^2)	29.2 (5.59)	29.4 (5.66)
MADRS Total Score	33.6 (4.43)	33.2 (4.36)
CGI-S Score	4.6 (0.59)	4.6 (0.57)

Data are mean (SD) unless otherwise stated.

Abbreviations: BMI = Body Mass Index; BU = Bupropion; CGI-S = Clinical Global Impression—Severity; DM = Dextromethorphan; MADRS = Montgomery-Asberg Depression Rating Scale

Demographics and baseline characteristics were similar across both treatment groups. Study completion rates were greater than 75% in both treatment groups.

The primary endpoint of the study was the change from baseline in the MADRS total score at Week 6. Secondary endpoints included MADRS change at Weeks 1 and 2, remission, response, Clinical Global Impression—Improvement (CGI-I), Clinical Global Impression—Severity (CGI-S), Patient Global Impression—Improvement (PGI-I), MADRS-6, Sheehan Disability Scale (SDS), other quality of life measures, safety, and tolerability. P-values were calculated based on least square mean estimates.

DM/BU met the primary endpoint and rapidly and significantly improved symptoms of depression. Specifically, DM/BU demonstrated rapid, durable, and statistically significant improvement in depressive symptoms as measured by MADRS total score compared to placebo (p=0.002 on primary endpoint). DM/BU demonstrated a highly statistically significant reduction in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared to placebo at Week 6, with mean reductions from baseline of 16.6 points for DM/BU and 11.9 points for placebo (p=0.002).

Additionally, a statistically significant improvement was observed at Week 1, or only 4 days after the start of twice daily dosing. As depicted in FIG. **15**, statistically significant improvements at Week 1 were observed for MADRS total score, with a reduction in MADRS total score of 7.3 points for DM/BU compared to the reduction of 4.9 points for placebo (key secondary endpoint, p=0.007), with statistical significance for this measure maintained at all time points thereafter (e.g., Week 2, 3, 4, 5, or 6). Statistically significant improvements for Patient Global Impression—Improvement (PGI-I) (p=0.008); Clinical Global Impression—Severity (CGI-S) (p=0.013); Clinical Global Impression—Improvement (CGI-I) (p=0.035); Quick Inventory of Depressive Symptomatology—Self-Rated (QIDS-SR-16) (p=0.016); Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF) (p=0.031); and other endpoints were also observed at Week 1 and at every time point thereafter (e.g. Week 2, 3, 4, 5, or 6).

As shown in FIG. **16**, response, defined as a 250% improvement in the MADRS total score, was seen at Week 6 in 54.0% of patients who received DM/BU, compared to 34.0% of patients who received placebo (p<0.001).

As shown in FIG. **17**, rates of remission from depression (defined as MADRS≤10) were statistically significantly greater for DM/BU compared to placebo at Week 2 (p=0.013) and at every time point thereafter (e.g., Week 3, 4, or 6), being achieved by 39.5% of DM/BU patients compared to 17.3% of placebo patients at Week 6 (p<0.001).

DM/BU was also associated with a statistically significant reduction in functional impairment, as measured by the Sheehan Disability Scale (SDS), compared to placebo at Week 2 (p=0.003), and at every time point thereafter (p=0.002, at Week 6).

On all secondary endpoints including the following, DM/BU demonstrated statistically significant improvement at Week 6 compared to placebo, reflecting increasing treatment effects over time: clinical response on the MADRS total score (defined as 250%) (p<0.001); PGI-I (p=0.007); CGI-S (p=0.002); CGI-I (p=0.016); QIDS-SR-16 (p=0.001); Sheehan Disability Scale (SDS) (p=0.002); and Q-LES-Q-SF (p=0.011).

DM/BU was well tolerated in the phase 3 clinical trial. The most commonly reported adverse events in the DM/BU arm were dizziness, nausea, headache, diarrhea, somnolence, and dry mouth. There was one serious adverse event in the DM/BU arm which was deemed by the investigator not to be study-drug related. The rates of discontinuation due to adverse events were low in both treatment groups (6.2% for DM/BU and 0.6% for placebo). Treatment with DM/BU was not associated with psychotomimetic effects or weight gain.

Example 7

A Phase 3, randomized, double-blind, active controlled trial was conducted to assess the efficacy and safety of DM/BU in the treatment of treatment resistant depression (TRD). Patients with major depressive disorder (MDD) who had previously failed one or two antidepressant treatments were treated in an open-label fashion with 150 mg bupropion twice daily (300 mg total daily dose) (n=799, n represents of number of patients) during a 6-week lead-in period. Patients who failed to respond to bupropion during this lead-in period were randomized in a 1:1 ratio to treatment with bupropion at this same total daily dose (n=156), or to treatment with DM/BU (45 mg dextromethorphan/105 mg bupropion) twice daily (90 mg dextromethorphan/210 mg bupropion total daily dose) (n=156), for 6 weeks. Inclusion criteria for the open-label period included males or females 18-65 years of age, a history of inadequate response to 1 or 2 prior antidepressant treatments, established by the Antidepressant Treatment Response Questionaire (ATRQ), and a Hamilton Depression Rating Scale (HAMD-17) total score of ≤18. Inclusion criteria for the double-blind period included inadequate response to 2 or 3 prior antidepressant treatments, including open-label period failure. Exclusion criteria included a history of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation, or any experimental central nervous system treatment during the current episode or in the past 6 months, schizophrenia,

bipolar disorder, obsessive compulsive disorder, psychiatric symptoms secondary to any other general medical condition.

Demographics and baseline characteristics are shown in Table 7 below. Study completion rates were similar across both treatment groups, 89% for dextromethorphan/bupropion and 94% for bupropion.

TABLE 7

Demographics and Baseline Characteristics

	Dextromethorphan(45 mg)/Bupropion (105 mg)	Bupropion (150 mg)
Age (years)	44.3 (12.19)	45.1 (12.56)
Female Gender, n (%)	101 (65.6%)	97 (62.6%)
Race, n (%)		
White	100 (64.9%)	106 (68.4%)
Black or African American	41 (26.6%)	39 (25.2%)
Asian	2 (1.3%)	6 (3.9%)
Other or Not Reported	11 (7.1%)	4 (2.6%)
BMI (mg/kg^2)	29.9 (5.85)	29.5 (5.64)
MADRS Total Score	33.4 (5.61)	33.2 (5.17)
CGI-S Score	4.6 (0.61)	4.6 (0.54)

Data are mean (SD) unless otherwise stated

Abbreviations: BMI = Body Mass Index; CGI-S = Clinical Global Impression—Severity; MADRS = Montgomery-Åsberg Depression Rating Scale

The change in depressive symptoms overtime was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Quick Inventory of Depressive Symptomatology—Self-Rated (QIDS-SR-16). The primary endpoint was the change from baseline in the MADRS after 6 weeks of treatment. The key secondary endpoints were the change from baseline in the MADRS after 1 week of treatment, after 2 weeks of treatment, the average change over entire 6-week double-blind treatment period, and the Sheehan Disability Scale (SDS). Other pre-specified secondary efficacy variables included the Cognitive subscale of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ), and the Hamilton Anxiety Scale (HAM-A).

As shown in FIG. **18**, DM/BU rapidly and significantly improved symptoms in patients with TRD as measured by MADRS averaged over the entire 6-week treatment period, a key secondary endpoint, with mean reductions of 8.6 for DM/BU (n=154) versus 6.7 for bupropion (n=155) (p=0.031). The rapid onset of action with DM/BU treatment was demonstrated with statistically significant mean MADRS reductions at Week 1, the earliest time point measured, of 5.2 versus 3.6 respectively for DM/BU and bupropion (p=0.02), and at Week 2 of 8.0 versus 6.1 respectively for DM/BU and bupropion (p=0.035), both time points being key secondary endpoints. At Week 6 (primary endpoint), DM/BU demonstrated a numerically greater improvement in MADRS, with mean reductions of 11.6 for DM/BU versus 9.4 for bupropion (p=0.117), but did not reach statistical significance on the Week 6.

As shown in FIG. **19**, DM/BU rapidly and significantly improved depressive symptoms in patients with TRD as measured by the Quick Inventory of Depressive Symptomatology—Self-Rated (QIDS-SR-16) averaged over the entire 6-week treatment period, with mean reductions of 3.3 for DM/BU versus 2.3 for bupropion (p=0.013).

As shown in FIG. **20**, rates of remission from depression (defined as QIDS-SR-16≤5) were statistically significantly greater for DM/BU compared to bupropion at Week 1 (p=0.001) and at every time point evaluated thereafter, being achieved by 18.2% of DM/BU patients compared to 8.2% of bupropion patients at Week 6 (p=0.012).

As shown in FIG. **21**, DM/BU significantly improved cognitive function in patients with TRD as compared to bupropion, assessed using the Cognitive subscale of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) (p=0.011). Cognitive dysfunction is well documented in the different phases of major depression, and plays an important role in functional recovery from major depression. The improvement in cognitive function with DM/BU was rapid as compared to bupropion, reaching statistical significance as early as Week 2 (p=0.01) and at every time point evaluated thereafter. The Cognitive subscale of the CPFQ assesses sharpness/mental acuity, and the ability to focus/maintain attention, to remember/recall information, and to find words. Statistical significance for the superiority of DM/BU versus bupropion was also achieved for the entire CPFQ (p=0.014), which assesses physical in addition to cognitive functioning.

DM/BU rapidly and significantly reduced anxiety symptoms in patients with TRD as compared to bupropion, assessed using the Hamilton Anxiety Scale (HAM-A) (p=0.009). DM/BU demonstrated numerical improvement versus the active comparator bupropion for all other efficacy variables assessed.

DM/BU was well tolerated in the trial. The most commonly reported adverse events in the DM/BU arm were dizziness and nausea. The rates of discontinuation due to adverse events were low in both treatment groups (2.6% for DM/BU and 1.9% for bupropion). There were three serious adverse events in the DM/BU arm, consisting of migraine; overdose; and suicidal ideation, which occurred more than one week after the cessation of treatment. Treatment with DM/BU was not associated with psychotomimetic effects, weight gain, or sexual dysfunction. Adverse events are listed in Table 8 below.

TABLE 8

Treatment-Emergent Adverse Events

	Double-blind Period[b] DM/BU (N = 154)	Double-blind Period[b] BU (N = 156)	Open-label Period BU (n = 310)
Any TEAE[a]	67 (43.5%)	61 (39.1%)	135 (43.5)
Dizziness	13 (8.4%)	0	9 (2.9%)
Nausea	8 (5.2%)	3 (1.9%)	22 (7.1%)
Dry mouth	6 (3.9%)	3 (1.9%)	13 (4.2%)
Headache	4 (2.6%)	7 (4.5%)	14 (4.5%)
Insomnia	3 (1.9%)	5 (3.2%)	19 (6.1%)
Constipation	3 (1.9%)	3 (1.9%)	13 (4.2%)
Anxiety	2 (1.3%)	0	11 (3.5%)
Irritability	0	2 (1.3%)	10 (3.2%)

Abbreviations: AE = adverse event. Data presented as number of subjects (% of subjects)

[a]Treatment-emergent AEs occurring in ≥3 subjects during the open-label period or ≥5% of subjects during the double-blind period are reported.

[b]In double-blind period, treatment-emergent AE is defined as any AE with an onset on or after date of randomization and prior to or on visit 9 date or period 2 early termination date.

Example 8

A Phase 2/3 randomized, double-blind, controlled, multicenter, U.S. clinical trial was conducted to evaluate the efficacy and safety of DM/BU in patients with agitation associated with Alzheimer's disease. A total of 366 patients with a diagnosis of probable Alzheimer's disease and clinically meaningful agitation associated with their disease were randomized, initially in a 1:1:1 ratio, to receive DM/BU (dextromethorphan/bupropion, dose escalated from 30 mg/105 mg once daily in the first week, to 30 mg/105 mg twice daily in the second week, to 45 mg/105 mg twice daily

thereafter), bupropion (dose escalated from 105 mg once daily in the first week to 105 mg twice daily thereafter), or matching placebo, for 5 weeks. An independent data monitoring committee performed an interim futility analysis and recommended no further randomization to the bupropion arm. Subsequently, patients were randomized in a 1:1 ratio to receive DM/BU or placebo. Total patients randomized were 159, 49, and 158 to the DM/BU, bupropion, and placebo arms, respectively. The mean Cohen-Mansfield Agitation Inventory (CMAI) total scores at baseline were 60.8, 66.1, and 59.3, respectively for the DM/BU, bupropion, and placebo groups. The minimum score on the CMAI is 29, corresponding to the total absence of symptoms, with higher scores corresponding to greater agitation. The primary endpoint of the study was the change from baseline in the CMAI total score at Week 5. P-values were calculated based on least square mean estimates.

Inclusion criteria included male or female 65-90 years of age, diagnosis of probable Alzheimer's disease, according to the 2011 NIA-AA criteria, diagnosis of agitation, according to the IPA provisional definition of agitation, MMSE score between 10 and 24, an NPI-AA score ≥4, and community dwelling. Exclusion criterial included dementia of non-Alzheimer's type and current use of a selective serotonin reuptake inhibitor and/or a serotonin and norepinephrine inhibitor (SSRI/SNRI). Demographics and baseline characteristics are shown in Table 9 below.

TABLE 9

Demographics and Baseline Characteristics

	DM/BU (n = 152)	Bupropion (n = 49)	Placebo (n = 156)
Age (years)	75.2 (5.71)	76.4 (6.13)	75.1 (5.96)
Female Gender, n (%)	86 (56.6%)	22 (44.9%)	91 (58.3%)
Race, n (%)			
White	136 (89.5%)	43 (87.8%)	128 (82.1%)
Black or African American	11 (7.2%)	5 (10.2%)	25 (16.0%)
Asian	1 (0.7%)	0	1 (0.6%)
Other or Not Reported	4 (2.6%)	1 (2.0%)	2 (1.3%)
CMAI Score	60.7 (17.40)	66.1 (19.65)	59.4 (15.60)
CGI-S (agitation)	4.2 (0.77)	4.4 (0.82)	4.2 (0.65)
NPI-A/A Score	7.2 (2.17)	6.9 (2.45)	6.8 (2.07)
MMSE	18.7 (3.76)	17.8 (4.19)	18.8 (3.70)

mITT population. Data are mean (SD) unless otherwise stated.

Abbreviations: BMI = Body Mass Index; BU = bupropion; CGI-S = Clinical Global Impression—Severity; CMAI = Cohen-Mansfield Agitation Inventory; DM = dextromethorphan; mITT = modified intent to treat; MMSE = Mini-mental state examination; NPI-A/A = Neuropsychiatric Inventory—Agitation and Aggressive domain.

As shown in FIG. **22**, DM/BU met the primary endpoint by demonstrating a statistically significant mean reduction in the Cohen Mansfield Agitation Inventory (CMAI) total score compared to placebo at Week 5, with mean reductions from baseline of 15.4 points for DM/BU (n=152), 10.0 for BU 9n=49), and 11.5 points for placebo (n=156) (p=0.010).

As shown in FIG. **23**, These results represent a mean percentage reduction of CMAI from baseline of 48% for DM/BU versus 38% for placebo. The CMAI is a 29-item caregiver-rated scale that assesses the frequency of agitation-related behaviors in patients with dementia, including excessive motor activity such as pacing and restlessness, verbal aggression such as screaming and shouting, and physical aggression such as grabbing, pushing, and hitting. DM/BU was also statistically superior to bupropion on the CMAI total score (p<0.001) at week 5, demonstrating component contribution.

DM/BU rapidly improved agitation symptoms. DM/BU numerically separated from placebo at Week 2 with a mean reduction from baseline in the CMAI total score of 11.5 points for DM/BU compared to 8.7 points for placebo (p=0.069).

DM/BU demonstrated a statistically significant mean reduction from baseline in the CMAI total score of 13.8 points for DM/BU compared to 9.7 points for placebo at Week 3 (p=0.007), with statistical significance for this measure maintained thereafter.

As shown in FIG. **24**, a statistically significantly greater proportion of patients achieved a clinical response on the CMAI, defined as a 30% or greater improvement from baseline, with DM/BU as compared to placebo (73% versus 57%, p=0.005). These results were consistent with clinicians' global assessments of change measured using the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation (mADCS-CGIC). DM/BU demonstrated statistically significantly greater improvement in agitation as compared to placebo on this measure (p=0.036).

DM/BU was safe and well tolerated in the trial. The most commonly reported adverse events in the DM/BU arm were somnolence (8.2% for DM/BU versus 4.1% for bupropion and 3.2% for placebo), dizziness (6.3%, 10.2%, 3.2%, for DM/BU, bupropion, and placebo arms respectively), and diarrhea (4.4%, 6.1%, 4.4%, for DM/BU, bupropion, and placebo arms respectively). The rates of discontinuation due to adverse events were 1.3%, 2.0%, and 1.3% in the DM/BU, bupropion, and placebo arms, respectively. Serious adverse events were reported in 3.1% of patients treated with DM/BU, compared to 8.2% of bupropion, and 5.7% of placebo-treated patients. No serious adverse events were deemed to be related to study drug in any treatment arm. There was one death in the placebo arm, one in the bupropion arm, and none in the DM/BU arm. There was no evidence of cognitive decline for patients treated with DM/BU as shown by the Mini-Mental State Examination (MMSE), a widely utilized measure of general cognitive function. Treatment with DM/BU was not associated with sedation. Adverse events are listed in Table 10 below.

TABLE 10

Treatment-Emergent Adverse Event

	DM/BU (n = 159)	Bupropion (n = 49)	Placebo (n = 158)
Subjects with any TEAE	70 (44.0%)	30 (61.2%)	52 (32.9%)
Somnolence	13 (8.2%)	2 (4.1%)	5 (3.2%)
Dizziness	10 (6.3%)	5 (10.2%)	5 (3.2%)
Diarrhea	7 (4.4%)	3 (6.1%)	7 (4.4%)
Headache	6 (3.8%)	3 (6.1%)	5 (2.5%)
Falls	4 (2.5%)	7 (14.3%)	3 (1.9%)
Fatigue	3 (1.9%)	5 (10.2%)	2 (1.3%)
Insomnia	1 (0.6%)	3 (6.1%)	3 (1.9%)
Serious AEs	5 (3.1%)	4 (8.2%)	9 (5.7%)
Discontinuation due to AEs	2 (1.3%)	1 (2.0%)	2 (1.3%)
Deaths	0	1 (2.0%	1 (0.6%)

Abbreviations: AE = adverse event; TEAE = Treatment-emergent adverse event.

Safety Population, data presented as number of subjects (% of subjects).

Treatment -emergent AEs occurring in ≥5% of subjects in any treatment group are presented.

Example 9

An open label study was started with 47 patients having major depressive disorder who had received two or more treatments in the current major depressive episode prior to

being treated with a combination of 45 mg of dextromethorphan hydrobromide and 105 mg of bupropion hydrochloride, given twice a day. Preliminary results for the ongoing study are depicted in Table 11 below.

TABLE 11

	Baseline	Week 1	Week 2	Week 4	Week 6	Week 8	Week 12
MADRS	33.28	23.11	18.28	14.58	9.20	9.11	11.15
MADRS Change from BL		−10.2	−15.2	−18.7	−24.1	−24.0	−22.2

Example 10

The open label study of Example 9 was continued. A total of 70 patients were enrolled who had ongoing symptoms of depression despite receiving treatment with two or more prior antidepressants during the current major depressive episode. Patients were treated with a 45 mg dextromethorphan-105 mg bupropion modulated delivery tablet twice daily for up to 12 months. The results are summarized in Table 12.

TABLE 12

Timepoint	MADRS Reduction
Baseline	0
1 week	−10.4
2 weeks	−14.7
6 weeks	−20.6
6 months	−22.9
1 year	−26.3

MADRS Reduction: mean reduction of MADRS score from baseline.

FIG. **25** depicts the reduction in MADRS Score from baseline from this trial DM/BU as compared to the combination of dextromethorphan and quinidine (DM/Q) as reported in Murrough (Journal of Affective Disorders 218 (2017) 277-283, FIG. 3A).

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as amounts, percentage, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

The terms "a," "an," "the" and similar referents used in the context of describing the embodiments (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the claims.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or to expedite prosecution. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups if used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the claimed embodiments. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the claimed embodiments to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

What is claimed is:

1. A method of treating major depressive disorder, comprising administering a dosage form by mouth once daily or twice daily to a human patient in need thereof, wherein the dosage form comprises about 105 mg of bupropion hydrochloride and about 45 mg of a dextromethorphan salt as the only therapeutically active compounds in the dosage form, wherein the human patient does not experience an adverse event as a result of receiving the dosage form, and wherein the adverse event is decreased appetite.

2. The method of claim **1**, wherein the dosage form is a tablet.

3. The method of claim **1**, wherein bupropion hydrochloride is in a sustained release formulation.

4. The method of claim **3**, wherein the dextromethorphan salt is in an immediate release formulation.

5. The method of claim **1**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the C_{max} of bupropion in the human patient is about 9×10^{1} ng/mL.

6. The method of claim **1**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days,

and wherein on the eighth day that the dosage form is administered, the AUC_{0-12} of bupropion in the human patient is about 7×10^2 ng·hr/mL.

7. The method of claim **1**, wherein the dextromethorphan salt is dextromethorphan hydrobromide.

8. The method of claim **7**, wherein the dosage form is a tablet.

9. The method of claim **7**, wherein bupropion hydrochloride is in a sustained release formulation.

10. The method of claim **9**, wherein dextromethorphan hydrobromide is in an immediate release formulation.

11. The method of claim **7**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the C_{max} of bupropion in the human patient is about 9×10^1 ng/mL.

12. The method of claim **7**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the AUC_{0-12} of bupropion in the human patient is about 7×10^2 ng·hr/mL.

13. The method of claim **7**, wherein the human patient is an extensive CYP2D6 metabolizer.

14. The method of claim **13**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter.

15. The method of claim **1**, wherein the human patient is an extensive CYP2D6 metabolizer.

16. The method of claim **15**, wherein the dosage form is a tablet.

17. The method of claim **15**, wherein bupropion hydrochloride is in a sustained release formulation.

18. The method of claim **17**, wherein the dextromethorphan salt is in an immediate release formulation.

19. The method of claim **15**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the C_{max} of bupropion in the human patient is about 9×10^1 ng/mL.

20. The method of claim **15**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the AUC_{0-12} of bupropion in the human patient is about 7×10^2 ng·hr/mL.

21. The method of claim **1**, wherein the dosage form is administered once daily by mouth for three days followed by twice daily by mouth thereafter.

22. The method of claim **21**, wherein the human patient is an extensive CYP2D6 metabolizer.

23. The method of claim **21**, wherein the dosage form is a tablet.

24. The method of claim **21**, wherein bupropion hydrochloride is in a sustained release formulation.

25. The method of claim **24**, wherein the dextromethorphan salt is in an immediate release formulation.

26. The method of claim **23** wherein the dosage form is administered for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the C_{max} of bupropion in the human patient is about 9×10^1 ng/mL.

27. The method of claim **23** wherein the dosage form is administered for a total of at least 8 days, and wherein on the eighth day that the dosage form is administered, the AUC_{0-12} of bupropion in the human patient is about 7×10^2 ng·hr/mL.

28. A method of treating major depressive disorder, comprising administering a dosage form by mouth once daily or twice daily to a human patient in need thereof, wherein the dosage form consists essentially of about 105 mg of bupropion hydrochloride and about 45 mg of a dextromethorphan salt, wherein the human patient does not experience an adverse event as a result of receiving the dosage form, and wherein the adverse event is decreased appetite.

29. A method of treating major depressive disorder, comprising orally administering a dosage form no more than twice daily to a human patient in need thereof, wherein the therapeutically active compounds in the dosage form consist of (i) about 105 mg of bupropion hydrochloride and (ii) about 45 mg of a dextromethorphan salt, wherein the human patient does not experience an adverse event as a result of receiving the dosage form, and wherein the adverse event is decreased appetite.

* * * * *