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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. 11,986,444 (the "'444 patent"), 12,036,191 (the "'191 patent"), and 12,042,473 (the "'473 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 May 21, 2024, the United States Patent and Trademark Office ("USPTO") duly and lawfully issued the '444 patent, entitled, "Treatment of Poor Metabolizers of Dextromethorphan with a Combination of Bupropion and Dextromethorphan." The face of the '444 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '444 patent; the assignment is recorded with the USPTO at Reel: 066116, Frame: 0656. Axsome is the exclusive licensee of the '444 patent. A copy of the '444 patent is attached hereto as Exhibit A.

7. On July 16, 2024, the USPTO duly and lawfully issued the '191 patent, entitled, "Treatment of Poor Metabolizers of Dextromethorphan with a Combination of Bupropion and Dextromethorphan." The face of the '191 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '191 patent; the assignment is recorded with the USPTO at Reel: 063524, Frame: 0142. Axsome is the exclusive licensee of the '191 patent. A copy of the '191 patent is attached hereto as Exhibit B.

8. On July 23, 2024, the USPTO duly and lawfully issued the '473 patent, entitled, "Compounds and Combinations Thereof for Treating Neurological and Psychiatric Conditions." The face of the '473 patent identifies Dr. Herriot Tabuteau as the inventor. Antecip is the present assignee of the '473 patent; the assignment is recorded with the USPTO at Reel: 064894, Frame: 0543. Axsome is the exclusive licensee of the '473 patent. A copy of the '473 patent is attached hereto as Exhibit C.

The Auvelity® Drug Product

9. 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.

10. 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

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

12. As set forth in Paragraphs 13-17 below, the Court has personal jurisdiction over Teva by virtue of, *inter alia*, its systematic and continuous contacts with the State of New Jersey.

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

14. 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.

15. 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").

16. 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, Sept. 11, 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).

17. 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.

18. For at least the foregoing reasons set forth above in Paragraphs 13-17 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-III

19. 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.

20. 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.

[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).

21. 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 "'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.

22. 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 United States Patent Nos. 11,839,612 (the "'612 patent") and 11,883,373 (the "'373 patent").[3] 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.

23. 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 United States Patent Nos. 11,844,797 (the "'797 patent"), 11,896,563 (the "'563 patent"), and

[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).

[3] The '612 and '373 patents are subject to an existing lawsuit, *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 24-6489 (MEF)(LDW) (D.N.J.).

11,925,636 (the "'636 patent").[4] 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.

24. No earlier than August 30, 2024, Teva sent written notice of its fifth Paragraph IV Certification ("Teva's Fifth Notice Letter") to Axsome. According to Teva's Fifth 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 '444, '191, and '473 patents. Teva's Fifth Notice Letter alleged that the claims of the '444, '191, and '473 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Teva's ANDA.

25. 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, '636, '444, '191, and '473 patents are invalid, unenforceable, and/or will not be infringed by the activities described in Teva's ANDA.

26. 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.

[4] The '797, '563, and '636 patents are subject to an existing lawsuit, *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 24-6489 (MEF)(LDW) (D.N.J.).

Count I: Infringement of the '444 Patent by Teva

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

28. 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 '444 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 18.

29. A justiciable controversy exists between the parties hereto as to the infringement of the '444 patent.

30. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '444 patent under 35 U.S.C. § 271(a), including at least claims 1 and 18, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

31. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '444 patent under 35 U.S.C. § 271(b), including at least claims 1 and 18, 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 '444 patent and knowledge that its acts are encouraging infringement.

32. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '444 patent under 35 U.S.C. § 271(c), including at least claims 1 and 18, 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 '444 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

33. Failure to enjoin Teva's infringement of the '444 patent will substantially and irreparably damage Plaintiffs.

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

35. 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 '191 Patent by Teva

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

37. 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 '191 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 26.

38. A justiciable controversy exists between the parties hereto as to the infringement of the '191 patent.

39. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '191 patent under 35 U.S.C. § 271(a), including at least claims 1 and 26, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

40. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '191 patent under 35 U.S.C. § 271(b), including at least claims 1 and 26, 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 '191 patent and knowledge that its acts are encouraging infringement.

41. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '191 patent under 35 U.S.C. § 271(c), including at least claims 1 and 26, 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 '191 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

42. Failure to enjoin Teva's infringement of the '191 patent will substantially and irreparably damage Plaintiffs.

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

44. 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 '473 Patent by Teva

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

46. 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 '473 patent, constitutes infringement of one or more of the claims of that patent under 35 U.S.C. § 271(e)(2)(A), including claims 1-9.

47. A justiciable controversy exists between the parties hereto as to the infringement of the '473 patent.

48. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will infringe one or more claims of the '473 patent under 35 U.S.C. § 271(a), including claims 1-9, by making, using, offering to sell, selling, and/or importing Teva's Proposed Product in the United States.

49. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will induce infringement of one or more claims of the '473 patent under 35 U.S.C. § 271(b), including claims 1-9, 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 '473 patent and knowledge that its acts are encouraging infringement.

50. Unless enjoined by this Court, upon FDA approval of Teva's ANDA, Teva will contributorily infringe one or more claims of the '473 patent under 35 U.S.C. § 271(c), including claims 1-9, 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 '473 patent, and Teva's Proposed Product lacks a substantial non-infringing use.

51. Failure to enjoin Teva's infringement of the '473 patent will substantially and irreparably damage Plaintiffs.

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

53. 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: September 30, 2024

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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 matters captioned *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 23-1695 (MEF)(LDW) (D.N.J.) (consolidated) and *Axsome Therapeutics, Inc., et al. v. Teva Pharmaceuticals, Inc.*, Civil Action No. 24-6489 (MEF)(LDW) (D.N.J.) are 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: September 30, 2024

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EXHIBIT A

US011986444B2

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 11,986,444 B2**
(45) **Date of Patent: *May 21, 2024**

(54) **TREATMENT OF POOR METABOLIZERS OF DEXTROMETHORPHAN WITH A COMBINATION OF BUPROPION AND DEXTROMETHORPHAN**

(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.: **18/488,366**

(22) Filed: **Oct. 17, 2023**

(65) **Prior Publication Data**

US 2024/0050383 A1 Feb. 15, 2024

Related U.S. Application Data

(63) Continuation of application No. 18/169,571, filed on Feb. 15, 2023.

(60) Provisional application No. 63/357,471, filed on Jun. 30, 2022, provisional application No. 63/370,577, filed on Aug. 5, 2022, provisional application No. 63/370,769, filed on Aug. 8, 2022.

(51) **Int. Cl.**

A61K 31/137	(2006.01)
A61K 9/20	(2006.01)
A61K 31/485	(2006.01)

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

CPC ***A61K 31/137*** (2013.01); ***A61K 9/2009*** (2013.01); ***A61K 9/2013*** (2013.01); ***A61K 9/2027*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/2086*** (2013.01); ***A61K 31/485*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(Continued)

Primary Examiner — Melissa S Mercier

(74) *Attorney, Agent, or Firm* — Procopio, Cory, Hargreaves & Savitch LLP; Brent A. Johnson; Yuefen Zhou

(57) **ABSTRACT**

Disclosed herein is a method of safely treating a nervous system condition with a combination of dextromethorphan and bupropion. This method is intended for patients having a neurological condition or a psychiatric condition, such as major depressive disorder, and a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

28 Claims, 1 Drawing Sheet

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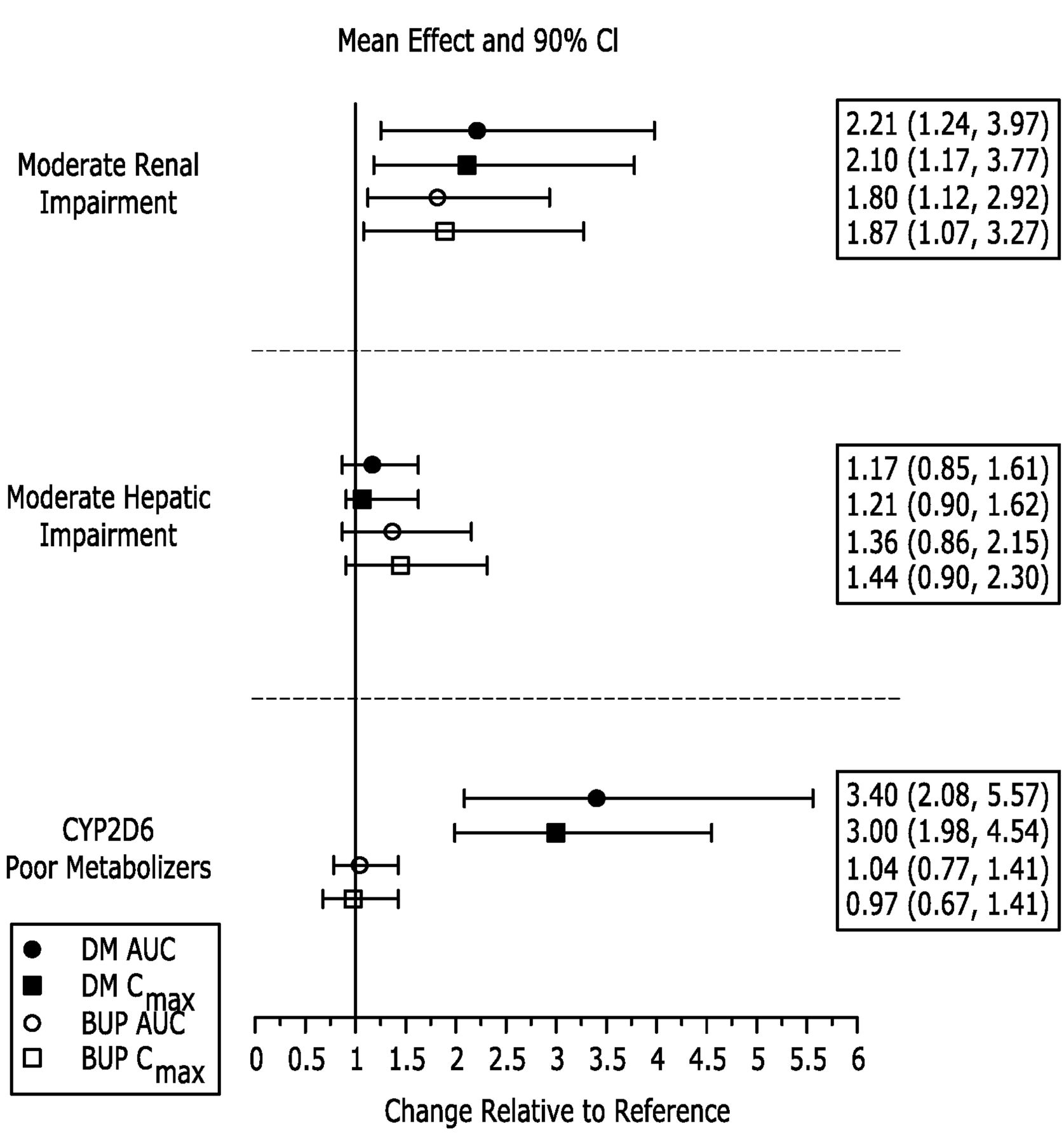

Mean Effect and 90% CI
Moderate Renal Impairment
2.21 (1.24, 3.97)
2.10 (1.17, 3.77)
1.80 (1.12, 2.92)
1.87 (1.07, 3.27)
Moderate Hepatic Impairment
1.17 (0.85, 1.61)
1.21 (0.90, 1.62)
1.36 (0.86, 2.15)
1.44 (0.90, 2.30)
CYP2D6 Poor Metabolizers
3.40 (2.08, 5.57)
3.00 (1.98, 4.54)
1.04 (0.77, 1.41)
0.97 (0.67, 1.41)
DM AUC
DM Cmax
BUP AUC
BUP Cmax
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6
Change Relative to Reference

TREATMENT OF POOR METABOLIZERS OF DEXTROMETHORPHAN WITH A COMBINATION OF BUPROPION AND DEXTROMETHORPHAN

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 18/169,571, filed Feb. 15, 2023; which claims benefit of U.S. Provisional App. Nos. 63/357,471, filed Jun. 30, 2022, 63/370,577, filed Aug. 5, 2022; 63/370,769, filed Aug. 8, 2022; all of which are incorporated by reference in their entireties.

FIELD

This disclosure relates to treatment of various neurological and psychiatric disorders or conditions with a combination of bupropion and dextromethorphan in patients who have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

SUMMARY

Disclosed herein is 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 CYP2D6 poor metabolizer comprising administering a daily dose of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide, such as in a once daily dose, to a human patient in need thereof, wherein the human patient is known to be a poor CYP2D6 metabolizer.

Disclosed herein is a method of safely treating a patient having major depressive disorder by administering a combination of dextromethorphan and bupropion. This method is intended for patients having a neurological disorder or condition or a psychiatric disorder or condition, such as major depressive disorder, and a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype. Typically, the CYP2D6 genotype or phenotype is determined by performing an assay on a biological sample from the patient. In this method a dosage form is orally administered, for example, once a day to a patient. The dosage form comprises 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. Alternatively, a dose of about 52.5 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base form or another salt form of bupropion, and 22.5 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base form or another salt form of dextromethorphan may be orally administered twice a day. As a result, a risk of dizziness, a potential side effect of dextromethorphan exposure, for a patient having a CYP2D6 poor metabolizer genotype 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 or of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

In some embodiments, if the patient does not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype, then a dosage form is orally administering twice a day to the patient, Wherein the dosage form contains a combination of 105 mg or more of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or more of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.

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

Disclosed herein is 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 CYP2D6 poor metabolizer comprising administering a daily dose of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide, such as in a once daily dose, to a human patient in need thereof, wherein the human patient is known to be a poor CYP2D6 metabolizer.

In some embodiments, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in a tablet.

In some embodiments, the once-daily administration avoids the human patient having an about 3.4-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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

In some embodiments, the once-daily administration avoids the patient having about 3-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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

In some embodiments, the tablet is orally administered in the morning.

In some embodiments, the dextromethorphan is in an immediate-release formulation.

In some embodiments, the bupropion is in an extended-release formulation.

In some embodiments, the tablet further contains a carbomer homopolymer.

In some embodiments, the tablet further contains colloidal silicon dioxide.

In some embodiments, the tablet further contains crospovidone.

In some embodiments, the tablet further contains glyceryl monocaprylocaprate.

In some embodiments, the tablet further contains L-cysteine hydrochloride monohydrate.

In some embodiments, the tablet further contains magnesium stearate.

In some embodiments, the tablet further contains microcrystalline cellulose.

In some embodiments, the tablet further contains polyvinyl alcohol.

In some embodiments, the tablet further contains red iron oxide.

In some embodiments, the tablet further contains sodium lauryl sulfate.

In some embodiments, the tablet further contains stearic acid.

In some embodiments, the tablet further contains talc.

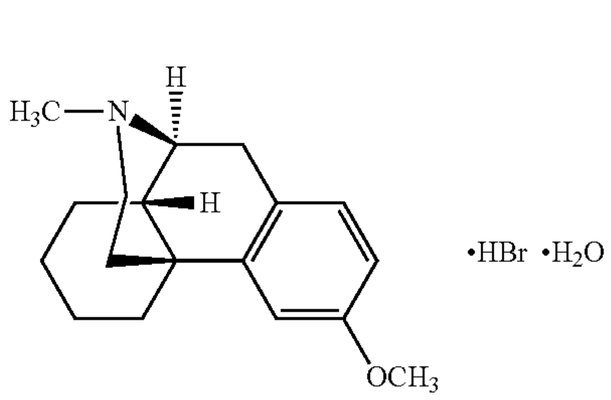
In some embodiments, the tablet further contains titanium dioxide.

In some embodiments, the tablet further contains yellow iron oxide.

In some embodiments, the twice-daily administration of the tablet to the human patient for 8 days would result in the human patient having about 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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

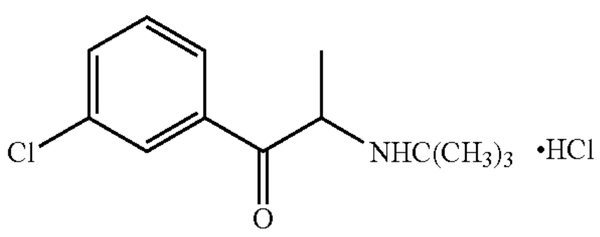
In some embodiments, the twice-daily administration of the tablet to the human patient for 8 days would result in the human patient having about same C_{max} of bupropion as compared to the C_{max} of bupropion that would result after 8 days of twice daily administration of the tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

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.

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 (239.74 bupropion base). The structural formula is:



Bupropion hydrochloride powder is white and highly soluble in water.

Cytochrome P450 2D6 (CYP2D6) is an enzyme that in humans is encoded by the CYP2D6 gene. The CYP2D6 function in any particular subject may be described as one of the following: 1) a poor metabolizer, who has little or no CYP2D6 function; 2) an extensive metabolizer, who has normal CYP2D6 function; 3) an intermediate metabolizer, who metabolizes drugs at a rate somewhere between the poor and extensive metabolizers; and 4) an ultrarapid metabolizer, who has multiple copies of the CYP2D6 gene that are expressed, so that greater-than-normal CYP2D6 function occurs. See, e.g., Bertilsson et al. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs, British Journal of Clinical Pharmacology, 53(2): 111-22, February 2002. Patients who do not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype, include intermediate metabolizers, extensive metabolizers, or ultrarapid metabolizers.

This disclosure relates to treating patients with a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype. Individuals with a CYP2D6 poor metabolizer genotype may be identified by obtaining a biological sample, such as a blood sample, a saliva sample, or any other sample containing the individual's DNA, and performing a genotyping assay. A CYP2D6 poor metabolizer phenotype may be obtained by comparing the plasma levels of dextromethorphan of a patient from administering dextromethorphan alone to those that would be expected based upon the dose of a combination of bupropion and dextromethorphan administered to the patient. It may also be determined by administering dextromethorphan alone and comparing the dextromethorphan/dextrorphan metabolic ratio in a patient, e.g., as described in Jurica et al. Journal of Clinical Pharmacology and Therapeutics, 2012, 37, 486-490. Typically, a metabolic ratio of dextromethorphan/dextrorphan of 0.3 or greater indicates a poor metabolizer phenotype.

There are many other genotyping tests that may be used to determine whether a person is a poor CYP2D6 metabolizer. See, e.g. Schaeffeler et al. CYP2D6 Genotyping Strategy Based on Gene Copy Number Determination by TaqMan Real-Time PCR. Human Mutation 22, 476-485 (2003); Bradford L D. CYP2D6 allele frequency in European Caucasians, Asians, Africans, and their descendants. Pharmacogenomics 2002 March; 3(2):229-43; Bertilsson L, Dahl M L, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 2002 February; 53(2): 111-22; Bryan Campbell, Pharm. D., Jane Xu, Ph.D., Josephine Cucchiaro, Ph.D., Mila Etropolski, M. D., Mark Schmidt, M. D. Protocol No. CILO522A2328. 22 Oct. 2001. Chainvuati S, Nafziger A N, Leeder J S, Gaedigk A, Kearns G L, Sellers E, Zhang Y, Kashuba A D, Rowland E, Bertino J S Jr. Combined phenotypic assessment of cytochrome p450 1A2, 2C9, 2C19, 2D6, and 3A, N-acetyltransferase-2, and xanthine oxidase activities with the "Cooperstown 5+1 cocktail." Clin. Pharmacol. Ther. 2003 November; 74(5): 437-47; Dahl M L, Yue Q Y, Roh H K, Johansson I, Sawe J, Sjoqvist F, Bertilsson L. Genetic analysis of the CYP2D locus in relation to debrisoquine hydroxylation capacity in Korean, Japanese and Chinese subjects. Pharmacogenetics 1995 June; 5(3):159-64; Gough A C, Miles J S, Spurr N K, Moss J E, Gaedigk A, Eichelbaum M, Wolf C R. Identification of the primary gene defect at the cytochrome P450 CYP2D locus. Nature 1990 Oct. 5; 47(6295):773-6; Hanioka N, Kimura S, Meyer U A, Gonzalez F J. The human CYP2D locus associated with a common genetic defect in

drug oxidation: a G1934—A base change in intron 3 of a mutant CYP2D6 allele results in an aberrant 3' splice recognition site. Am J Hum Genet. 1990 December; 47(6): 994-1001; Jaanson P, Marandi T, Kiivet R A, Vasar V, Vaan S, Svensson J O, Dahl M L. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology (Berl) 2002 June; 162(1):67-73; Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation: Mol Pharmacol 1994 September; 46(3):452-9; Juif Jen, Sujata Vaidyanathan, Michael Hayes. Clinical Pharmacology Report: Protocol No CILO522A 2328: 12 Jul. 2002; Kagimoto M, Heim M, Kagimoto K, Zeugin T, Meyer U A. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. J Biol Chem 1990 Oct. 5; 265(28):17209-14; Lyamichev V, Mast A L, Hall J G, Prudent J R, Kaiser M W, Takova T, Kwiatkowski R W, Sander T J, de Arruda M, Arco D A, Neri B P, Brow M A. Polymorphism identification and quantitative detection of genomic DNA by invasive cleavage of oligonucleotide probes. Nat Biotechnol 1999 March; 17(3):292-6; McElroy S, Richmond J, Lira M, Friedman D, Silber B M, Milos P M, Sachse C, Brochmoller, Roots I. CYP2D6 genotyping as an alternative to phenotyping for determination of metabolic status in a clinical trial setting. AAPS Pharmsci 2000; 2(4):article 33; Nevilie M, Selzer R, Aizenstein B, Maguire M, Hogan K, Walton R, Welsh K, Neri B, de Arruda M. Characterization of cytochrome P450 2D6 alleles using the Invader system. Biotechniques 2002 June; Suppl:34-8, 40-3; and Yokota H, Tamura S, Furuya H, Kimura S, Watanabe M, Kanazawa I, Kondo I, Gonzalez F J. Evidence for a new variant CYP2D6 allele CYP2D6) in a Japanese population associated with lower in vivo rates of sparteine metabolism: Pharmacogenetics 1993 October; 3(5):256-63.

In some embodiments, the patient has a CYP2D6G1846 (AA) genotype. In some embodiments, the patient has a CYP2D6G1846 (AG) genotype. In some embodiments, the patient has a CYP2D6C100T (TT) genotype. In some embodiments, the patient has a CYP2D6C100T (CT) genotype.

Patients having a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be treated for a neurological disorder or condition or a psychiatric disorder or condition by 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 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. Alternatively, a dose of about 52.5 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base form or another salt form of bupropion, and 22.5 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base form or another salt form of dextromethorphan may be administered twice a day.

Administering bupropion in combination with dextromethorphan to a human being having a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype has been found to result in higher blood plasma levels of dextromethorphan as compared to a patient who does not have a poor metabolizer genotype or phenotype. This raises safety concerns for the poor metabolizers because of the increased risk of adverse events associated with high blood plasma levels of dextromethorphan.

For some patients, potential adverse events from increased dextromethorphan exposure may include dizziness, nausea, dry mouth, somnolence, headache, agitation, hypomania, confusion, including mental confusion, hallucinations, coma, drowsiness shivering, hyperthermia, vasoconstriction, tachycardia, diarrhea, myoclonus (muscle twitching), hyperreflexia (manifested by clonus), tremor, restlessness, insomnia, dissociation, vomiting, delusions of grandeur, blurred vision, double vision, bloodshot eyes, dilated pupils, sweating, fever, bruxia (teeth grinding), hypotension, hypertension, shallow respiration, slowed breathing, difficulty in urination, urinary retention, muscle spasms, shakiness, sedation, paresthesia, hypomania, slurred speech, unsteady walk, blackouts, inability to focus eyes, skin rash, severe itchiness, spontaneous memory recall, acute psychosis, unusual excitement, nervousness, irritability, constipation, stomach pain, etc. Administering a lower dose, such as half the dose or less, may decrease the risk of any of these adverse events. For example, the dosage form may be administered once a day instead of twice a day. Alternatively, or additionally, the amount of bupropion and dextromethorphan may be reduced. For example, the amount of bupropion and dextromethorphan may be reduced by 50%, 75%, 90%, or more. Administering the reduced and/or less frequent dose of bupropion and dextromethorphan (for example administering a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide once a day) may have a reduced risk of the adverse event as compared to administering a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day to the patient.

A dosage form described herein may include, or be prepared from, any suitable form of bupropion, such as a salt form, e.g., bupropion hydrochloride, other salt forms, 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 other than a bupropion and/or a dextromethorphan.

The dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may include any suitable amount of bupropion for once daily administration, i.e. less than 105 mg, such as about 1-105 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 100-105 mg, about 103-107 mg, about 105 mg, about 53 mg, about 26 mg, about 13 mg, or about 12 mg of bupropion hydrochloride, a molar equivalent amount of another salt form of bupropion, or the free base form of bupropion.

Alternatively, the dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be administered twice a day, and that daily dose may be less than 105 mg, such as about 1-105 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 100-105 mg, about 103-107

mg, about 105 mg, about 53 mg, about 26 mg, about 13 mg, or about 12 mg of bupropion hydrochloride, a molar equivalent amount of another salt form of bupropion, or the free base form of bupropion.

In some embodiments, the dosage form provides sustained release of bupropion.

A dosage form described herein may include, or be prepared from, any suitable form of dextromethorphan, such as a salt form, e.g., dextromethorphan bromide, other salt forms, the free base form, hydrates, solvates, polymorphs, other solid forms, etc.

The dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may include any suitable amount of dextromethorphan for once daily administration, i.e. less than 45 mg, such as about 1-45 mg, about 1-5 mg, about 5-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-45 mg, about 45 mg, about 34 mg, about 23 mg, about 11 mg, about 6 mg, or about 5 mg of the dextromethorphan, such as dextromethorphan bromide, a molar equivalent amount of another salt form of dextromethorphan, or the free base form of dextromethorphan.

Alternatively, the dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be administered twice a day, and that daily dose may be, for example, about 1-45 mg, about 1-5 mg, about 5-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-45 mg, about 45 mg, about 34 mg, about 23 mg, about 11 mg, about 6 mg, or about 5 mg of the dextromethorphan, such as dextromethorphan bromide, a molar equivalent amount of another salt form of dextromethorphan, or the free base form of dextromethorphan.

In some embodiments, the dosage form provides immediate release of dextromethorphan.

The pharmaceutical dosage form has a molar ratio of bupropion to dextromethorphan in the dosage form that 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. There are 0.38 moles of bupropion in 105 mg of bupropion hydrochloride (Molecular weight: 276.2 g/mol); and there are 0.122 moles of dextromethorphan in 45 mg of dextromethorphan hydrobromide (Molecular weight: 370.3 g/mol). So, this ratio is about 0.38 moles of bupropion to about 0.12 mole of dextromethorphan. In some embodiments, the ratio is about 0.37-0.39 moles of bupropion to about 0.11-0.13 moles of dextromethorphan, about 2.5-3.1 to 1, about 2.6-3.3 to 1, or about 2.5-3.3 to 1.

Pope reported that when CYP2D6 was inhibited by administering quinidine, the C_{max} of dextromethorphan was about 40% higher for poor metabolizers and the AUC_{0-12} of dextromethorphan was about 46% higher for CYP2D6 poor metabolizers, as compared to other patients who were not CYP2D6 poor metabolizers. (Pope, et al., J. Clin Pharmacol 2004; 44:1132-1142.) Bupropion also is a CYP2D6 inhibitor. The inventor has found that, like quinidine, administration of the combination of bupropion and dextromethorphan results in poor metabolizers having a significantly higher C_{max} and AUC of dextromethorphan than other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers).

When the combination of bupropion and dextromethorphan is administered to CYP2D6 poor metabolizers, there would be no particular reason to believe that the C_{max} and AUC of bupropion would be different than that of other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers). Thus, a person of ordinary skill in the art would expect that, when the combination of bupropion and dextromethorphan is administered to CYP2D6 poor metabolizers, the CYP2D6 poor metabolizers would have blood plasma levels of bupropion that are similar to other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers), but would have significantly higher blood plasma levels of dextromethorphan. The inventor has found this to be the case in clinical trials. This increase in dextromethorphan exposure for CYP2D6 poor metabolizers increases the risk of adverse events caused by dextromethorphan as compared to patients who do not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

The antidepressive efficacy of bupropion has been shown to be dose dependent. (See https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a0fdfc21-165a-43fa-9 b3c-e4813 b892250&version=3.) Thus, reducing the dose of bupropion would be expected to result in a loss in the antidepressive effect of bupropion, especially when the dose (e.g., 210 mg/day) is already below the target dose of bupropion for treating depression. To avoid losing efficacy of bupropion, a person of ordinary skill in the art would likely decrease the dose of dextromethorphan while keeping the same dose of bupropion. For example, a person of ordinary skill in the art might reduce the dextromethorphan dose from 90 mg/day to 45 mg/day while maintaining a 210 mg/day dose of bupropion. This would be expected to result in CYP2D6 poor metabolizer having similar plasma levels of both bupropion and dextromethorphan as the plasma levels of bupropion and dextromethorphan in other patients who are not CYP2D6 poor metabolizer (e.g., extensive, intermediate, or ultra-rapid metabolizers).

However, the inventor believes that the dose of both bupropion and dextromethorphan can be reduced by the same proportion (e.g. by giving a dosage form containing 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan once a day instead of giving a dosage form with 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan twice a day or giving a dosage form with 210 mg of bupropion hydrochloride and 90 mg of dextromethorphan once a day) without reducing the therapeutic effect of the combination in the treatment of depression.

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 comprise a sustained release or controlled release polymer, e.g., a polymer for providing sustained release of bupropion, such as a crosslinked or uncross linked 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 20-30%, 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 bilayer dosage form is shown below:

Layer 1

Ingredient	Amount (mg)
Bupropion Hydrochloride	105
Cysteine	10-100
Carbopol 971P	20-60
Microcrystalline Cellulose	200-300
Colloidal Silicon Dioxide	1-10
Magnesium Stearate	1-10

Layer 2

Ingredient	Amount (mg)
Dextromethorphan hydrobromide	45
Microcrystalline Cellulose	100-150
Croscarmellose sodium	1-20
Magnesium Stearate	1-10

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., in genotypically poor metabolizers of dextromethorphan. For example, the pharmaceutical composition or dosage form may be administered once 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 2 weeks, 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.

The CYP2D6 gene is highly polymorphic, with more than 70 allelic variants described so far. See, e.g., http://www.imm.ki.se/CYPalleles/cyp2d6.htm. Two common polymorphisms within the CYP2D6 gene in Caucasian populations are CYP2D6G1846A and CYP2D6P34S (also referred to as CYP2D6C100T). These polymorphisms correspond to nucleotides 3465 and 1719, respectively, in GenBank sequence M33388.1 (G1:181303). The CYP2D6P34S/CYP2D6C100T polymorphism also corresponds to nucleotide 100 in GenBank mRNA sequence M20403.1 (GI:181349).

The CYP2D6G1846A polymorphism (known as the CYP2D6*4 alleles, encompassing *4A, *4B, *4C, *4D, *4E, *4F, *4G, *4H, *4J, *4K, and *4L) represents a G to A transition at the junction between intron 3 and exon 4, shifting the splice junction by one base pair, resulting in frameshift and premature termination of the protein (Kagimoto M, Heim M, Kagimoto K, Zeugin T, Meyer U A. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. J Biol Chem 1990 Oct. 5; 265(28):17209-14; Gough A C, Miles J S, Spurr N K, Moss J E, Gaedigk A, Eichelbaum M, Wolf C R. Identification of the primary gene defect at the cytochrome P450 CYP2D locus. Nature 1990 Oct. 5; 47(6295):773-6; Hanioka N, Kimura S, Meyer U A, Gonzalez F J. The human CYP2D locus associated with a common genetic defect in drug oxidation: a G1934—A base change in intron 3 of a mutant CYP2D6 allele results in an aberrant 3' splice recognition site. Am J Hum Genet. 1990 December; 47(6):994-1001). The CYP2D6P34S/CYP2D6C100T polymorphism (known as the CYP2D6*10 and CYP2D6*14 alleles) represents a C to T change that results in the substitution of a Proline at position 34 by Serine (Yokota H, Tamura S, Furuya H, Kimura S, Watanabe M, Kanazawa I, Kondo I, Gonzalez F J. Evidence for a new variant CYP2D6 allele CYP2D6) in a Japanese population associated with lower in vivo rates of sparteine metabolism: Pharmacogenetics 1993 October; 3(5):256-63; Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation: Mol Pharmacol 1994 September; 46(3):452-9). Both of these polymorphisms have been associated with reduced enzymatic activity for different substrates (Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation: Mol

Pharmacol 1994 September; 46(3):452-9; Dahl M L, Yue Q Y, Roh H K, Johansson I, Sawe J, Sjoqvist F, Bertilsson L. Genetic analysis of the CYP2D locus in relation to debrisoquine hydroxylation capacity in Korean, Japanese and Chinese subjects. Pharmacogenetics 1995 June; 5(3):159-64; Jaanson P, Marandi T, Kiivet R A, Vasar V, Vaan S, Svensson J O, Dahl M L. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology (Berl) 2002 June; 162(1):67-73; Bertilsson L, Dahl M L, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 2002 February; 53(2): 111-22).

In one study, blood samples were collected from 128 individuals according to the pharmacogenetics protocol and after the consent of patients. The DNA was extracted from whole blood by Covance using the PUREGENE DNA isolation kit (D-50K). (U.S. Pat. No. 8,586,610)

In this study, genotypes for the CYP2D6G1846A polymorphism were ascertained for 123 of the 128 consenting individuals, while genotypes for the CYP2D6C100T polymorphism were identified for all 128 participants. Genotyping was performed on amplified DNA fragments. The CYP2D6 genomic region was amplified using a triplex PCR strategy (Neville 2002).

In this study, amplification was performed on 40-100 ng of genomic DNA using a GC-rich PCR kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. Thermocycling conditions were as follows: initial denaturation (3 min 95° C.), 10 cycles of 30 s of denaturation (30 s at 95° C.), annealing (30 s at 66° C.), and extension, (60 s at 72° C.) followed by 22 cycles: 30 s at 95° C., 30 s at 66° C., 60 s+5 s/cycle at 72° C. A final extension followed (7 min at 72° C.). (U.S. Pat. No. 8,586,610)

In this study, third Wave Technologies, Inc (Madison, Wis.) developed the probe sets for genotyping. Genotyping was performed on PCR products using the Invader® assay (Lyamichev 1999) (Third Wave Technologies, Inc) according to the manufacturer's recommendations. (U.S. Pat. No. 8,586,610)

The study reported the genotyping results of 74 of the study participants. Of these participants, 57 were the CC genotype, 14 were the CT genotype, and 3 were the TT genotype of the CYP2D6C100T polymorphism. The TT and CT genotypes of the CYP2D6C100T polymorphism were determined to include poor CYP2D6 metabolizers. For the CYP2D6G1846A polymorphism, 2 participants were of the AA genotype, 14 participants were of the AG genotype, and 55 participants were of the GG phenotype. The AA and AG genotypes were determined to represent poor CYP2D6 metabolizers. (U.S. Pat. No. 8,586,610)

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, 10,080,727, 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.

Example 1

In 3 poor metabolizers, administration of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day resulted in an approximate 3-fold and 3.4-fold increase in dextromethorphan C_{max} and AUC_{0-12}, respectively, compared to extensive metabolizers.

By way of comparison, Flesher (WO 2009/006194, p. 86, Table IV) reported that 7 days of twice-daily dosing of 30 mg of dextromethorphan and 30 mg of quinidine resulted in the C_{max} and AUC_{0-12} of poor metabolizers to be increased only about 1.43-fold and 1.46-fold, respectively, compared to extensive metabolizers.

Example 2

An analysis of steady state pharmacokinetic data in 12 poor metabolizers treated with 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day in efficacy clinical trials showed plasma concentrations of dextromethorphan that were generally higher than exposures for non-poor metabolizer.

Example 3

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 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 CYP2D6 poor metabolizers, a 3.40-fold increase in dextromethorphan AUC_{0-12} and a 3.00-fold increase in dextromethorphan C_{max} were observed. No significant change was observed in bupropion AUC_{0-12} or bupropion C_{max}.

Based upon these results, dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metaboliz-

ers. The recommended dosage for patients known to be poor CYP2D6 metabolizers is one tablet once daily, such as in the morning.

The invention claimed is:

1. A method of treating major depressive disorder in a CYP2D6 poor metabolizer comprising, selecting a human patient known to be a poor CYP2D6 metabolizer who is experiencing major depressive disorder, and administering, once daily in the morning for at least two weeks to the human patient, a dosage form containing 1 mg to 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion and 1 mg to 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the dextromethorphan AUC_{0-12} of the human patient is increased 208% to 557% compared to extensive or ultra-extensive CYP2D6 metabolizers.

2. The method of claim **1**, wherein the dextromethorphan AUC_{0-12} of the human patient is increased 340% compared to extensive or ultra-extensive CYP2D6 metabolizers.

3. The method of claim **1**, wherein approximately 26% of the dextromethorphan is excreted unchanged in the urine of the human patient.

4. The method of claim **1**, wherein a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in a solid dosage form.

5. The method of claim **1**, wherein once-daily administration for 8 days avoids the human patient having an about 3.4-fold increase in the 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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

6. The method of claim **1**, wherein once-daily administration for 8 days avoids the human patient having an about 3-fold increase in the C_{max} of dextromethorphan as compared to the C_{max} of dextromethorphan that would result after 8 days of twice daily administration of the dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

7. The method of claim **1**, wherein the dextromethorphan is in an immediate-release formulation.

8. The method of claim **7**, wherein the bupropion is in an extended-release formulation.

9. The method of claim **1**, wherein the dosage form further contains a carbomer homopolymer and colloidal silicon dioxide.

10. The method of claim **1**, wherein the dosage form further contains crospovidone and glyceryl monocaprylocaprate.

11. The method of claim **1**, wherein the dosage form further contains L-cysteine hydrochloride monohydrate.

12. The method of claim **1**, wherein the dosage form further contains magnesium stearate and microcrystalline cellulose.

13. The method of claim **1**, wherein the dosage form further contains polyvinyl alcohol and sodium lauryl sulfate.

14. The method of claim **1**, wherein the dosage form further contains red iron oxide and stearic acid.

15. The method of claim **1**, wherein the dosage form further contains talc, titanium dioxide, or yellow iron oxide.

16. The method of claim **1**, wherein twice-daily administration of the dosage form to the human patient for 8 days would result in the human patient having about 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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

17. The method of claim **1**, wherein twice-daily administration of the dosage form to the human patient for 8 days would result in the human patient having about 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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

18. A method of treating major depressive disorder in a CYP2D6 poor metabolizer comprising, selecting a human patient known to be a poor CYP2D6 metabolizer who is experiencing major depressive disorder, and administering, once daily in the morning for at least four weeks to the human patient, a dosage form containing 1 mg to 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion and 1 mg to 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the dextromethorphan AUC_{0-12} of the human patient is increased 208% to 557% compared to extensive or ultra-extensive CYP2D6 metabolizers.

19. The method of claim **18**, wherein the dextromethorphan AUC_{0-12} of the human patient is increased 340% compared to extensive or ultra-extensive CYP2D6 metabolizers.

20. The method of claim **18**, wherein approximately 26% of the dextromethorphan is excreted unchanged in the urine of the human patient.

21. The method of claim **18**, wherein the dextromethorphan is in an immediate-release formulation.

22. The method of claim **21**, wherein the bupropion is in an extended-release formulation.

23. The method of claim **18**, wherein the dosage form further contains a carbomer homopolymer and colloidal silicon dioxide.

24. The method of claim **18**, wherein the dosage form further contains crospovidone and glyceryl monocaprylocaprate.

25. The method of claim **18**, wherein the dosage form further contains L-cysteine hydrochloride monohydrate.

26. The method of claim **18**, wherein the dosage form further contains magnesium stearate and microcrystalline cellulose.

27. The method of claim **18**, wherein the dosage form further contains polyvinyl alcohol and sodium lauryl sulfate.

28. The method of claim **18**, wherein the dosage form further contains red iron oxide and stearic acid.

* * * * *

EXHIBIT B

US012036191B1

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 12,036,191 B1**
(45) **Date of Patent: Jul. 16, 2024**

(54) **TREATMENT OF POOR METABOLIZERS OF DEXTROMETHORPHAN WITH A COMBINATION OF BUPROPION AND DEXTROMETHORPHAN**

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

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(57) **ABSTRACT**

Disclosed herein is a method of safely treating a nervous system condition with a combination of dextromethorphan and bupropion. This method is intended for patients having a neurological condition or a psychiatric condition, such as major depressive disorder, and a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

30 Claims, 1 Drawing Sheet

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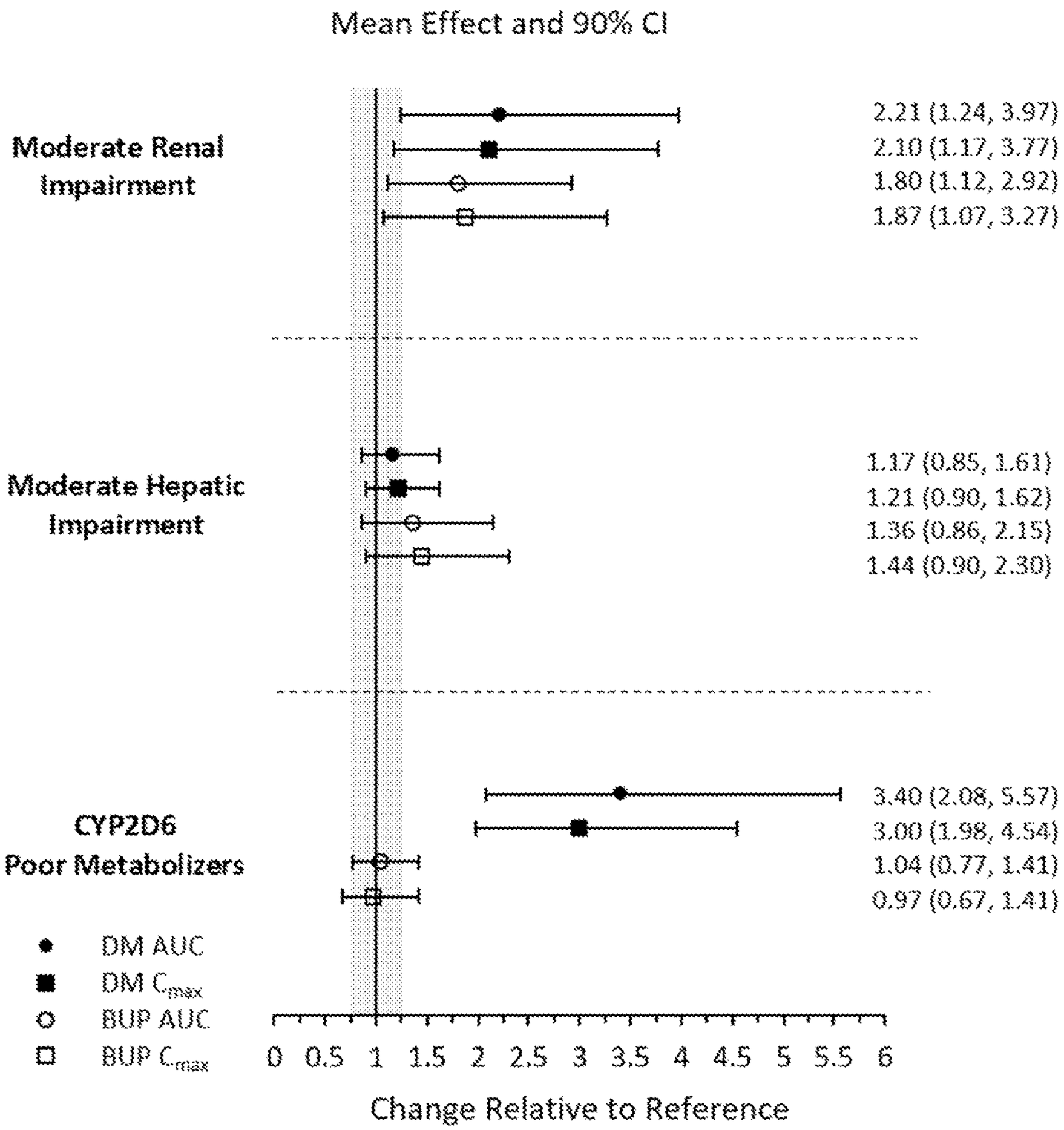


Effects of Renal Impairment, Hepatic Impairment, and CYP2D6 Poor Metabolizer Status on Dextromethorphan/Bupropion PK

TREATMENT OF POOR METABOLIZERS OF DEXTROMETHORPHAN WITH A COMBINATION OF BUPROPION AND DEXTROMETHORPHAN

FIELD

This disclosure relates to treatment of various neurological and psychiatric disorders or conditions with a combination of bupropion and dextromethorphan in patients who have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

SUMMARY

Disclosed herein is 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 CYP2D6 poor metabolizer comprising administering a daily dose of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide, such as in a once daily dose, to a human patient in need thereof, wherein the human patient is known to be a poor CYP2D6 metabolizer.

Disclosed herein is a method of safely treating a patient having major depressive disorder by administering a combination of dextromethorphan and bupropion. This method is intended for patients having a neurological disorder or condition or a psychiatric disorder or condition, such as major depressive disorder, and a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype. Typically, the CYP2D6 genotype or phenotype is determined by performing an assay on a biological sample from the patient. In this method a dosage form is orally administered, for example, once a day to a patient. The dosage form comprises 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. Alternatively, a dose of about 52.5 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base form or another salt form of bupropion, and 22.5 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base form or another salt form of dextromethorphan may be orally administered twice a day. As a result, a risk of dizziness, a potential side effect of dextromethorphan exposure, for a patient having a CYP2D6 poor metabolizer genotype 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 or of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

In some embodiments, if the patient does not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype, then a dosage form is orally administering twice a day to the patient, Wherein the dosage form contains a combination of 105 mg or more of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or more of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.

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

Disclosed herein is 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 CYP2D6 poor metabolizer comprising administering a daily dose of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide, such as in a once daily dose, to a human patient in need thereof, wherein the human patient is known to be a poor CYP2D6 metabolizer.

In some embodiments, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in a tablet.

In some embodiments, the once-daily administration avoids the human patient having an about 3.4-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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

In some embodiments, the once-daily administration avoids the patient having about 3-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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

In some embodiments, the tablet is orally administered in the morning.

In some embodiments, the dextromethorphan is in an immediate-release formulation.

In some embodiments, the bupropion is in an extended-release formulation.

In some embodiments, the tablet further contains a carbomer homopolymer.

In some embodiments, the tablet further contains colloidal silicon dioxide.

In some embodiments, the tablet further contains crospovidone.

In some embodiments, the tablet further contains glyceryl monocaprylocaprate.

In some embodiments, the tablet further contains I-cysteine hydrochloride monohydrate.

In some embodiments, the tablet further contains magnesium stearate.

In some embodiments, the tablet further contains microcrystalline cellulose.

In some embodiments, the tablet further contains polyvinyl alcohol.

In some embodiments, the tablet further contains red iron oxide.

In some embodiments, the tablet further contains sodium lauryl sulfate.

In some embodiments, the tablet further contains stearic acid.

In some embodiments, the tablet further contains talc.

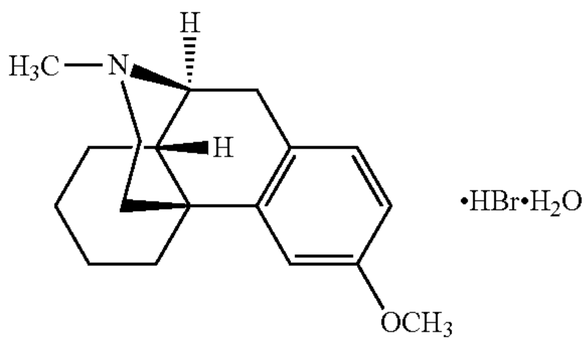
In some embodiments, the tablet further contains titanium dioxide.

In some embodiments, the tablet further contains yellow iron oxide.

In some embodiments, the twice-daily administration of the tablet to the human patient for 8 days would result in the human patient having about 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 tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

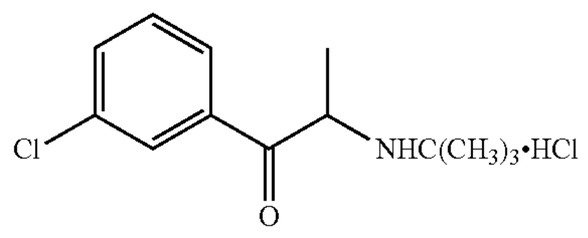
In some embodiments, the twice-daily administration of the tablet to the human patient for 8 days would result in the human patient having about same C_{max} of bupropion as compared to the C_{max} of bupropion that would result after 8 days of twice daily administration of the tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

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.

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 (239.74 bupropion base). The structural formula is:



Bupropion hydrochloride powder is white and highly soluble in water.

Cytochrome P450 2D6 (CYP2D6) is an enzyme that in humans is encoded by the CYP2D6 gene. The CYP2D6 function in any particular subject may be described as one of the following: 1) a poor metabolizer, who has little or no CYP2D6 function; 2) an extensive metabolizer, who has normal CYP2D6 function; 3) an intermediate metabolizer, who metabolizes drugs at a rate somewhere between the poor and extensive metabolizers; and 4) an ultrarapid metabolizer, who has multiple copies of the CYP2D6 gene that are expressed, so that greater-than-normal CYP2D6 function occurs. See, e.g., Bertilsson et al. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs, British Journal of Clinical Pharmacology, 53(2): 111-22, February 2002. Patients who do not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype, include intermediate metabolizers, extensive metabolizers, or ultrarapid metabolizers.

This disclosure relates to treating patients with a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype. Individuals with a CYP2D6 poor metabolizer genotype may be identified by obtaining a biological sample, such as a blood sample, a saliva sample, or any other sample containing the individual's DNA, and performing a genotyping assay. A CYP2D6 poor metabolizer phenotype may be obtained by comparing the plasma levels of dextromethorphan of a patient from administering dextromethorphan alone to those that would be expected based upon the dose of a combination of bupropion and dextromethorphan administered to the patient. It may also be determined by administering dextromethorphan alone and comparing the dextromethorphan/dextrorphan metabolic ratio in a patient, e.g., as described in Jurica et al. Journal of Clinical Pharmacology and Therapeutics, 2012, 37, 486-490. Typically, a metabolic ratio of dextromethorphan/dextrorphan of 0.3 or greater indicates a poor metabolizer phenotype.

There are many other genotyping tests that may be used to determine whether a person is a poor CYP2D6 metabolizer. See, e.g. Schaeffeler et al. CYP2D6 Genotyping Strategy Based on Gene Copy Number Determination by TaqMan Real-Time PCR. Human Mutation 22, 476-485 (2003); Bradford L D. CYP2D6 allele frequency in European Caucasians, Asians, Africans, and their descendants. Pharmacogenomics 2002 March; 3(2):229-43; Bertilsson L, Dahl M L, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 2002 February; 53(2): 111-22; Bryan Campbell, Pharm. D., Jane Xu, Ph.D., Josephine Cucchiaro, Ph.D., Mila Etropolski, M. D., Mark Schmidt, M. D. Protocol No. CILO522A2328. 22 Oct. 2001. Chainvuati S, Nafziger A N, Leeder J S, Gaedigk A, Kearns G L, Sellers E, Zhang Y, Kashuba A D, Rowland E, Bertino J S Jr. Combined phenotypic assessment of cytochrome p450 1A2, 2C9, 2C19, 2D6, and 3A, N-acetyltransferase-2, and xanthine oxidase activities with the "Cooperstown 5+1 cocktail." Clin. Pharmacol. Ther. 2003 November; 74(5): 437-47; Dahl M L, Yue Q Y, Roh H K, Johansson I, Sawe J, Sjoqvist F, Bertilsson L. Genetic analysis of the CYP2D locus in relation to debrisoquine hydroxylation capacity in Korean, Japanese and Chinese subjects. Pharmacogenetics 1995 June; 5(3):159-64; Gough A C, Miles J S, Spurr N K, Moss J E, Gaedigk A, Eichelbaum M, Wolf C R. Identification of the primary gene defect at the cytochrome P450 CYP2D locus. Nature 1990 Oct. 5; 47(6295):773-6; Hanioka N, Kimura S, Meyer U A, Gonzalez F J. The human CYP2D locus associated with a common genetic defect in drug oxidation: a G1934—A base change in intron 3 of a mutant CYP2D6 allele results in an aberrant 3' splice recognition site. Am J Hum Genet. 1990 December; 47(6): 994-1001; Jaanson P, Marandi T, Kiivet R A, Vasar V, Vaan S, Svensson J O, Dahl M L. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology (Berl) 2002 June; 162(1):67-73; Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese

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In some embodiments, the patient has a CYP2D6G1846 (AA) genotype. In some embodiments, the patient has a CYP2D6G1846 (AG) genotype. In some embodiments, the patient has a CYP2D6C100T (TT) genotype. In some embodiments, the patient has a CYP2D6C100T (CT) genotype.

Patients having a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be treated for a neurological disorder or condition or a psychiatric disorder or condition by orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, ora 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 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. Alternatively, a dose of about 52.5 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base form or another salt form of bupropion, and 22.5 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base form or another salt form of dextromethorphan may be administered twice a day.

Administering bupropion in combination with dextromethorphan to a human being having a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype has been found to result in higher blood plasma levels of dextromethorphan as compared to a patient who does not have a poor metabolizer genotype or phenotype. This raises safety concerns for the poor metabolizers because of the increased risk of adverse events associated with high blood plasma levels of dextromethorphan.

For some patients, potential adverse events from increased dextromethorphan exposure may include dizziness, nausea, dry mouth, somnolence, headache, agitation, hypomania, confusion, including mental confusion, hallucinations, coma, drowsiness shivering, hyperthermia, vasoconstriction, tachycardia, diarrhea, myoclonus (muscle twitching), hyperreflexia (manifested by clonus), tremor, restlessness, insomnia, dissociation, vomiting, delusions of grandeur, blurred vision, double vision, bloodshot eyes, dilated pupils, sweating, fever, bruxia (teeth grinding), hypotension, hypertension, shallow respiration, slowed breathing, difficulty in urination, urinary retention, muscle spasms, shakiness, sedation, paresthesia, hypomania, slurred speech, unsteady walk, blackouts, inability to focus eyes, skin rash, severe itchiness, spontaneous memory recall, acute psychosis, unusual excitement, nervousness, irritability, constipation, stomach pain, etc. Administering a lower dose, such as half the dose or less, may decrease the risk of any of these adverse events. For example, the dosage form may be administered once a day instead of twice a day. Alternatively, or additionally, the amount of bupropion and dextromethorphan may be reduced. For example, the amount of bupropion and dextromethorphan may be reduced by 50%, 75%, 90%, or more. Administering the reduced and/or less frequent dose of bupropion and dextromethorphan (for example administering a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide once a day) may have a reduced risk of the adverse event as compared to administering a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day to the patient.

A dosage form described herein may include, or be prepared from, any suitable form of bupropion, such as a salt form, e.g., bupropion hydrochloride, other salt forms, 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 other than a bupropion and/or a dextromethorphan.

The dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may include any suitable amount of bupropion for once daily administration, i.e. less than 105 mg, such as about 1-105 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 100-105 mg, about 103-107 mg, about 105 mg, about 53 mg, about 26 mg, about 13 mg, or about 12 mg of bupropion hydrochloride, a molar equivalent amount of another salt form of bupropion, or the free base form of bupropion.

Alternatively, the dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be administered twice a day, and that daily dose may be less than 105 mg, such as about 1-105 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 100-105 mg, about 103-107 mg, about 105 mg, about 53 mg, about 26 mg, about 13 mg, or about 12 mg of bupropion hydrochloride, a molar equivalent amount of another salt form of bupropion, or the free base form of bupropion.

In some embodiments, the dosage form provides sustained release of bupropion.

A dosage form described herein may include, or be prepared from, any suitable form of dextromethorphan, such as a salt form, e.g., dextromethorphan bromide, other salt forms, the free base form, hydrates, solvates, polymorphs, other solid forms, etc.

The dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may include any suitable amount of dextromethorphan for once daily administration, i.e. less than 45 mg, such as about 1-45 mg, about 1-5 mg, about 5-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-45 mg, about 45 mg, about 34 mg, about 23 mg, about 11 mg, about 6 mg, or about 5 mg of the dextromethorphan, such as dextromethorphan bromide, a molar equivalent amount of another salt form of dextromethorphan, or the free base form of dextromethorphan.

Alternatively, the dosage form for administering to a patient who has a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype may be administered twice a day, and that daily dose may be, for example, about 1-45 mg, about 1-5 mg, about 5-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-45 mg, about 45 mg, about 34 mg, about 23 mg, about 11 mg, about 6 mg, or about 5 mg of the dextromethorphan, such as dextromethorphan bromide, a molar equivalent amount of another salt form of dextromethorphan, or the free base form of dextromethorphan.

In some embodiments, the dosage form provides immediate release of dextromethorphan.

The pharmaceutical dosage form has a molar ratio of bupropion to dextromethorphan in the dosage form that 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. There are 0.38 moles of bupropion in 105 mg of bupropion hydrochloride (Molecular weight: 276.2 g/mol); and there are 0.122 moles of dextromethorphan in 45 mg of dextromethorphan hydrobromide (Molecular weight: 370.3 g/mol). So, this ratio is about 0.38 moles of bupropion to about 0.12 mole of dextromethorphan. In some embodiments, the ratio is about 0.37-0.39 moles of bupropion to about 0.11-0.13 moles of dextromethorphan, about 2.5-3.1 to 1, about 2.6-3.3 to 1, or about 2.5-3.3 to 1.

Pope reported that when CYP2D6 was inhibited by administering quinidine, the C_{max} of dextromethorphan was about 40% higher for poor metabolizers and the AUC_{0-12} of dextromethorphan was about 46% higher for CYP2D6 poor metabolizers, as compared to other patients who were not CYP2D6 poor metabolizers. (Pope, et al., J. Clin Pharmacol 2004; 44:1132-1142.) Bupropion also is a CYP2D6 inhibitor. The inventor has found that, like quinidine, administration of the combination of bupropion and dextromethorphan results in poor metabolizers having a significantly higher C_{max} and AUC of dextromethorphan than other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers).

When the combination of bupropion and dextromethorphan is administered to CYP2D6 poor metabolizers, there would be no particular reason to believe that the C_{max} and AUC of bupropion would be different than that of other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers). Thus, a person of ordinary skill in the art would expect that, when the combination of bupropion and dextromethorphan is administered to CYP2D6 poor metabolizers, the CYP2D6 poor metabolizers would have blood plasma levels of bupropion that are similar to other patients who are not poor metabolizers (e.g., extensive, intermediate, or ultra-rapid metabolizers), but would have significantly higher blood plasma levels of dextromethorphan. The inventor has found this to be the case in clinical trials. This increase in dextromethorphan exposure for CYP2D6 poor metabolizers increases the risk of adverse events caused by dextromethorphan as compared to patients who do not have a CYP2D6 poor metabolizer genotype or a CYP2D6 poor metabolizer phenotype.

The antidepressive efficacy of bupropion has been shown to be dose dependent. (See https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a0fdfc21-165a-43fa-9b3c-e48f3b892250&version=3.) Thus, reducing the dose of bupropion would be expected to result in a loss in the antidepressive effect of bupropion, especially when the dose (e.g., 210 mg/day) is already below the target dose of bupropion for treating depression. To avoid losing efficacy of bupropion, a person of ordinary skill in the art would likely decrease the dose of dextromethorphan while keeping the same dose of bupropion. For example, a person of ordinary skill in the art might reduce the dextromethorphan dose from 90 mg/day to 45 mg/day while maintaining a 210 mg/day dose of bupropion. This would be expected to result in CYP2D6 poor metabolizer having similar plasma levels of both bupropion and dextromethorphan as the plasma levels of bupropion and dextromethorphan in other patients who are not CYP2D6 poor metabolizer (e.g., extensive, intermediate, or ultra-rapid metabolizers).

However, the inventor believes that the dose of both bupropion and dextromethorphan can be reduced by the same proportion (e.g. by giving a dosage form containing 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan once a day instead of giving a dosage form with 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan twice a day or giving a dosage form with 210 mg of bupropion hydrochloride and 90 mg of dextromethorphan once a day) without reducing the therapeutic effect of the combination in the treatment of depression.

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 comprise a sustained release or controlled release polymer, e.g., a polymer for providing sustained release of bupropion, such as a crosslinked or uncross linked 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 20-30%, 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 bilayer dosage form is shown below:

Layer 1

Ingredient	Amount (mg)
Bupropion Hydrochloride	105
Cysteine	10-100
Carbopol 971P	20-60
Microcrystalline Cellulose	200-300
Colloidal Silicon Dioxide	1-10
Magnesium Stearate	1-10

Layer 2

Ingredient	Amount (mg)
Dextromethorphan hydrobromide	45
Microcrystalline Cellulose	100-150
Croscarmellose sodium	1-20
Magnesium Stearate	1-10

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., in genotypically poor metabolizers of dextromethorphan. For example, the pharmaceutical composition or dosage form may be administered once 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 2 weeks, 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.

The CYP2D6 gene is highly polymorphic, with more than 70 allelic variants described so far. See, e.g., imm.ki.se/CYPalleles/cyp2d6.htm. Two common polymorphisms within the CYP2D6 gene in Caucasian populations are CYP2D6G1846A and CYP2D6P34S (also referred to as CYP2D6C100T). These polymorphisms correspond to nucleotides 3465 and 1719, respectively, in GenBank sequence M33388.1 (GI:181303). The CYP2D6P34S/CYP2D6C100T polymorphism also corresponds to nucleotide 100 in GenBank mRNA sequence M20403.1 (GI:181349).

The CYP2D6G1846A polymorphism (known as the CYP2D6*4 alleles, encompassing *4A, *4B, *4C, *4D, *4E, *4F, *4G, *4H, *4J, *4K, and *4L) represents a G to A transition at the junction between intron 3 and exon 4, shifting the splice junction by one base pair, resulting in frameshift and premature termination of the protein (Kagimoto M, Heim M, Kagimoto K, Zeugin T, Meyer U A. Multiple mutations of the human cytochrome P450IID6 gene (CYP2D6) in poor metabolizers of debrisoquine. Study of the functional significance of individual mutations by expression of chimeric genes. J Biol Chem 1990 Oct. 5; 265(28):17209-14; Gough A C, Miles J S, Spurr N K, Moss J E, Gaedigk A, Eichelbaum M, Wolf C R. Identification of the primary gene defect at the cytochrome P450 CYP2D locus. Nature 1990 Oct. 5; 47(6295):773-6; Hanioka N, Kimura S, Meyer U A, Gonzalez F J. The human CYP2D locus associated with a common genetic defect in drug oxidation: a G1934—A base change in intron 3 of a mutant CYP2D6 allele results in an aberrant 3' splice recognition site. Am J Hum Genet. 1990 December; 47(6):994-1001). The CYP2D6P34S/CYP2D6C100T polymorphism (known as the CYP2D6*10 and CYP2D6*14 alleles) represents a C to T change that results in the substitution of a Proline at position 34 by Serine (Yokota H, Tamura S, Furuya H, Kimura S, Watanabe M, Kanazawa I, Kondo I, Gonzalez F J. Evidence for a new variant CYP2D6 allele CYP2D6J in a Japanese population associated with lower in vivo rates of sparteine metabolism: Pharmacogenetics 1993 October; 3(5):256-63; Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation: Mol Pharmacol 1994 September; 46(3):452-9). Both of these polymorphisms have been associated with reduced enzymatic activity for different substrates (Johansson I, Oscarson M, Yue Q Y, Bertilsson L, Sjoqvist F, Ingelman-Sundberg M. Genetic analysis of the Chinese cytochrome P4502D locus: characterization of variant CYP2D6 genes present in subjects with diminished capacity for debrisoquine hydroxylation: Mol Pharmacol 1994 September; 46(3):452-9; Dahl M L, Yue Q Y, Roh H K, Johansson I, Sawe J, Sjoqvist F, Bertilsson L. Genetic analysis of the CYP2D locus in relation to debrisoquine hydroxylation capacity in Korean, Japanese and Chinese subjects. Pharmacogenetics 1995 June; 5(3):159-64; Jaanson P, Marandi T, Kiivet R A, Vasar V, Vaan S, Svensson J O, Dahl M L. Maintenance therapy with zuclopenthixol decanoate: associations between plasma concentrations, neurological side effects and CYP2D6 genotype. Psychopharmacology (Berl) 2002 June; 162(1):67-73; Bertilsson L, Dahl M L, Dalen P, Al-Shurbaji A. Molecular genetics of

CYP2D6: clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 2002 February; 53(2): 111-22).

In one study, blood samples were collected from 128 individuals according to the pharmacogenetics protocol and after the consent of patients. The DNA was extracted from whole blood by Covance using the PUREGENE DNA isolation kit (D-50K). (U.S. Pat. No. 8,586,610)

In this study, genotypes for the CYP2D6G1846A polymorphism were ascertained for 123 of the 128 consenting individuals, while genotypes for the CYP2D6C100T polymorphism were identified for all 128 participants. Genotyping was performed on amplified DNA fragments. The CYP2D6 genomic region was amplified using a triplex PCR strategy (Neville 2002).

In this study, amplification was performed on 40-100 ng of genomic DNA using a GC-rich PCR kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's recommendations. Thermocycling conditions were as follows: initial denaturation (3 min 95° C.), 10 cycles of 30 s of denaturation (30 s at 95° C.), annealing (30 s at 66° C.), and extension, (60 s at 72° C.) followed by 22 cycles: 30 s at 95° C., 30 s at 66° C., 60 s+5 s/cycle at 72° C. A final extension followed (7 min at 72° C.). (U.S. Pat. No. 8,586,610)

In this study, third Wave Technologies, Inc (Madison, Wis.) developed the probe sets for genotyping. Genotyping was performed on PCR products using the Invader® assay (Lyamichev 1999) (Third Wave Technologies, Inc) according to the manufacturer's recommendations. (U.S. Pat. No. 8,586,610)

The study reported the genotyping results of 74 of the study participants. Of these participants, 57 were the CC genotype, 14 were the CT genotype, and 3 were the TT genotype of the CYP2D6C100T polymorphism. The TT and CT genotypes of the CYP2D6C100T polymorphism were determined to include poor CYP2D6 metabolizers. For the CYP2D6G1846A polymorphism, 2 participants were of the AA genotype, 14 participants were of the AG genotype, and 55 participants were of the GG phenotype. The AA and AG genotypes were determined to represent poor CYP2D6 metabolizers. (U.S. Pat. No. 8,586,610)

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, 10,080,727, 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.

Example 1

In 3 poor metabolizers, administration of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day resulted in an approximate 3-fold

and 3.4-fold increase in dextromethorphan C_{max} and AUC_{0-12}, respectively, compared to extensive metabolizers.

By way of comparison, Flesher (WO 2009/006194, p. 86, Table IV) reported that 7 days of twice-daily dosing of 30 mg of dextromethorphan and 30 mg of quinidine resulted in the C_{max} and AUC_{0-12} of poor metabolizers to be increased only about 1.43-fold and 1.46-fold, respectively, compared to extensive metabolizers.

Example 2

An analysis of steady state pharmacokinetic data in 12 poor metabolizers treated with 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide twice a day in efficacy clinical trials showed plasma concentrations of dextromethorphan that were generally higher than exposures for non-poor metabolizer.

Example 3

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, I-cysteine hydrochloride monohydrate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, and 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 CYP2D6 poor metabolizers, a 3.40-fold increase in dextromethorphan AUC_{0-12} and a 3.00-fold increase in dextromethorphan C_{max} were observed. No significant change was observed in bupropion AUC_{0-12} or bupropion C_{max}.

Based upon these results, dosage adjustment is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher dextromethorphan concentrations than extensive/intermediate CYP2D6 metabolizers. The recommended dosage for patients known to be poor CYP2D6 metabolizers is one tablet once daily, such as in the morning.

The invention claimed is:

1. A method of treating major depressive disorder in a CYP2D6 poor metabolizer comprising, selecting a human patient known to be a poor CYP2D6 metabolizer who is experiencing major depressive disorder, and administering, once daily for at least two weeks to the human patient, a dosage form containing 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.

2. The method of claim **1**, wherein 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in the dosage form.

3. The method of claim **2**, wherein the once-daily administration for 8 days avoids the human patient having an about 3.4-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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

4. The method of claim **2**, wherein the once-daily administration for 8 days avoids the human patient having an about 3-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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

5. The method of claim **2**, wherein the dosage form is orally administered in the morning.

6. The method of claim **5**, wherein the dextromethorphan is in an immediate-release formulation.

7. The method of claim **6**, wherein the bupropion is in an extended-release formulation.

8. The method of claim **7**, wherein the once-daily administration for 8 days avoids the human patient having an about 3.4-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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

9. The method of claim **7**, wherein the once-daily administration for 8 days avoids the human patient having an about 3-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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

10. The method of claim **7**, wherein the dosage form further contains a carbomer homopolymer.

11. The method of claim **7**, wherein the dosage form further contains colloidal silicon dioxide.

12. The method of claim **7**, wherein the dosage form further contains crospovidone.

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

14. The method of claim **7**, wherein the dosage form further contains L-cysteine hydrochloride monohydrate.

15. The method of claim **7**, wherein the dosage form further contains magnesium stearate.

16. The method of claim **7**, wherein the dosage form further contains microcrystalline cellulose.

17. The method of claim **7**, wherein the dosage form further contains polyvinyl alcohol.

18. The method of claim **7**, wherein the dosage form further contains red iron oxide.

19. The method of claim **7**, wherein the dosage form further contains sodium lauryl sulfate.

20. The method of claim **7**, wherein the dosage form further contains stearic acid.

21. The method of claim **7**, wherein the dosage form further contains talc.

22. The method of claim **7**, wherein the dosage form further contains titanium dioxide.

23. The method of claim **7**, wherein the dosage form further contains yellow iron oxide.

24. The method of claim **8**, wherein twice-daily administration of the solid dosage form to the human patient for 8 days would result in the human patient having about 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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

25. The method of claim **9**, wherein twice-daily administration of the solid dosage form to the human patient for 8 days would result in the human patient having about 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 dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

26. A method of treating major depressive disorder in a CYP2D6 poor metabolizer comprising, selecting a human patient known to be a poor CYP2D6 metabolizer who is experiencing major depressive disorder, and administering, once daily for at least four weeks to the human patient, a dosage form containing 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.

27. The method of claim **26**, wherein the dextromethorphan is in an immediate-release formulation.

28. The method of claim **26**, wherein the bupropion is in an extended-release formulation.

29. The method of claim **26**, wherein the dosage form further contains a carbomer homopolymer.

30. The method of claim **26**, wherein the dosage form further contains colloidal silicon dioxide.

* * * * *

EXHIBIT C


US012042473B2

(12) **United States Patent**
Tabuteau

(10) **Patent No.: US 12,042,473 B2**
(45) **Date of Patent: *Jul. 23, 2024**

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

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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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(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.

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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.

9 Claims, No Drawings

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COMPOUNDS AND COMBINATIONS THEREOF FOR TREATING NEUROLOGICAL AND PSYCHIATRIC CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 18/173,291, filed Feb. 23, 2023; Which claims the benefit of U.S. Provisional Application No. 63/359,143, filed Jul. 7, 2022, U.S. Provisional Application No. 63/370,592, filed Aug. 5, 2022, U.S. Provisional Application No. 63/396,182, filed Aug. 8, 2022, U.S. Provisional Application No. 63/373,040, filed Aug. 19, 2022, and U.S. Provisional Application No. 63/401,541, filed Aug. 26, 2022; all of which are incorporated by reference 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 a non-competitive 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 a non-competitive antagonist of the NMDA receptor and a sigma-1 receptor agonist, and the human patient does not experience dissociation.

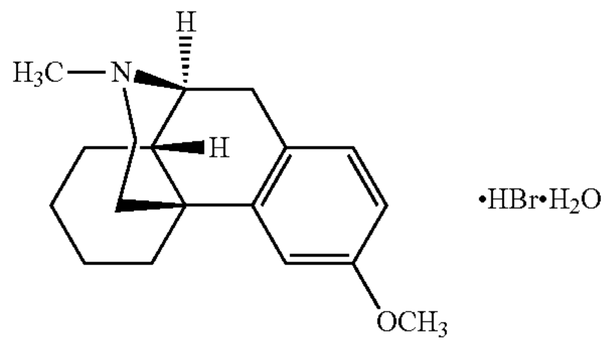
Some embodiments include a method of treating major depressive disorder in a human patient at risk of QT prolongation, comprising administering, no more than twice daily, a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide to a human patient who is experiencing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

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.

Dextromethorphan hydrobromide is a non-competitive NMDA receptor antagonist and A sigma-1 receptor agonist.

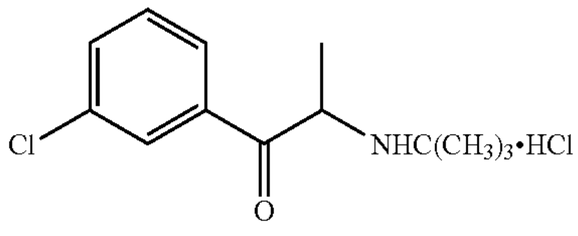
The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9α, 13α, 14α), hydrobromide monohydrate. Dextromethorphan hydrobromide has the empirical formula $C_{18}H_{25}NO \cdot HBr \cdot H_2O$ and a molecular weight of 370.33. The structural formula is:



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 con-

tains 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 (eGFR 30 to 59 mL/minute/1.73 m^2) 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.

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, a non-competitive 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.

The following information includes the kinds of dissociative and other effects that may be avoided with the combination of dextromethorphan and bupropion.

In clinical trials, 48% to 61% of esketamine-treated patients developed sedation based on the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S), and 0.3% to 0.4% of esketamine-treated patients experienced loss of consciousness (MOAA/S score of 0). For a combination of dextromethorphan and bupropion, NMDA receptor antagonism may be achieved without a significant risk of sedation.

Because of the possibility of delayed or prolonged sedation, patients receiving esketamine must be monitored by a healthcare provider 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. No such monitoring is required for the treatment of the combination of dextromethorphan and bupropion.

Esketamine-treated patients must be closely monitored for sedation with concomitant use of ESKETAMINE with CNS depressants. No such monitoring is required for the treatment of the combination of dextromethorphan and bupropion.

Esketamine is available only through a restricted program under a REMS. No such restrictions are required for the combination of dextromethorphan and bupropion.

The most common psychological effects of esketamine were dissociative or perceptual changes (including distortion of time, space and illusions), derealization and depersonalization (61% to 84% of esketamine-treated patients developed dissociative or perceptual changes based on the Clinician-Administered Dissociative States Scale). Given its potential to induce dissociative effects, patients with psychosis must be carefully assessed before administering esketamine. No such assessment is required for the treatment of the combination of dextromethorphan. Treatment with esketamine should be initiated only if the benefit outweighs the risk. No such restriction is required with the treatment of the combination of dextromethorphan and bupropion.

Because of the risks of dissociation, patients receiving esketamine must be monitored by a healthcare provider 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. No

such monitoring, assessment, or restriction is required for the treatment of the combination of dextromethorphan and bupropion. Esketamine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). No such restrictions are required for the combination of dextromethorphan and bupropion.

Dissociation includes: delusional perception (including distortion of space and time, and illusions); depersonalization/derealization disorder; derealization; diplopia; dissociation; dysesthesia; feeling cold; feeling hot; feeling of body temperature change; hallucination; hallucination, auditory; hallucination, visual; hallucinations, mixed; hyperacusis; illusion; ocular discomfort; oral dysesthesia; paresthesia; paresthesia oral; pharyngeal paresthesia; photophobia; time perception altered; tinnitus; vision blurred; and visual impairment.

Esketamine is a Schedule Ill controlled substance (CIII), and may be subject to abuse and diversion. The combination of dextromethorphan and bupropion is not a controlled substance. Each patient's risk for abuse or misuse must be assessed prior to prescribing and all patients receiving esketamine must be monitored for the development of these behaviors or conditions, including drug-seeking behavior, while on therapy. No such monitoring or assessment is required for the treatment of the combination of dextromethorphan and bupropion.

Esketamine is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) and is called the esketamine REMS because of the risks of serious adverse outcomes from sedation, dissociation, and abuse and misuse. No such restrictions are required for the combination of dextromethorphan and bupropion.

Important requirements of the esketamine REMS include the following:

- Healthcare settings must be certified in the program and ensure that esketamine is:
  - Only dispensed and administered in healthcare settings.
  - Patients treated in outpatient settings (e.g., medical offices and clinics) must be enrolled in the program.
  - Administered by patients under the direct observation of a healthcare provider and that patients are monitored by a healthcare provider for at least 2 hours after administration of esketamine.

None of these requirements apply to the combination of dextromethorphan and bupropion.

Esketamine was evaluated for safety in 262 adults for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior from two Phase 3 studies (Study 3 and Study 4) and one Phase 2 study.

Sedation was evaluated by adverse event reports and the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). In the MOAA/S, a score of 5 means "responds readily to name spoken in normal tone;" a score of 0 means "no response after painful trapezius squeeze;" a score of 4 means "lethargic response to name spoken in normal tone;" a score of 3 means "responds only after name is spoken loudly and/or repeatedly;" a score of 2 means "responds only after mild prodding or shaking;" and a score of 1 means "does not respond to mild prodding or shaking." Any decrease in MOAA/S score from pre-dose is considered to indicate the presence of sedation, and such a decrease occurred in a higher number of patients on esketamine than placebo during the short-term Treatment Resistant Depression (TRD) studies. Dose-related increases in the incidence of sedation (MOAA/S score<5) were observed in a fixed-dose TRD study. Table 1 presents the incidence of sedation

(MOAA/S score<5) in a fixed-dose study with adult patients<65 years of age with TRD and a flexible-dose study with patients>65 years of age with TRD.

TABLE 1

Incidence of Sedation (MOAA/S Score <5) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with treatment-resistant depression and Flexible-Dose Study with Patients ≥65 Years of Age with treatment-resistant depression)

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	SPRAVATO + Oral AD 56 mg	SPRAVATO + Oral AD 84 mg	Placebo + Oral AD	SPRAVATO + Oral AD 28 to 84 mg
Number of patients*	N = 112	N = 114	N = 114	N = 63	N = 72
Sedation (MOAA/S score <5)	11%	50%	61%	19%	49%

*Patients who were evaluated with MOAA/S

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, there was a higher incidence of sedation (MOAA/S score<5) in patients treated with esketamine plus oral antidepressant compared to patients treated with placebo plus oral antidepressant (AD), similar to the treatment-resistant depression study results in Table 1.

Dissociation/Perceptual Changes

Esketamine can cause dissociative symptoms (including derealization and depersonalization) and perceptual changes (including distortion of time and space, and illusions). In clinical trials, dissociation was transient and occurred on the day of dosing. Dissociation was evaluated by adverse event reports and the Clinician-Administered Dissociative States Scale (CADSS). A CADSS total score of more than 4 indicates the presence of dissociative symptoms, and such an increase to a score of 4 or more occurred in a higher number of patients on esketamine compared to placebo during the short-term treatment-resistant depression studies. Dose-related increases in the incidence of dissociative symptoms (CADSS total score>4 and change>0) were observed in a fixed-dose treatment-resistant depression study. Table 2 presents the incidence of dissociation (CADSS total score>4 and change>0) in a fixed-dose study with adult patients<65 years of age with treatment-resistant depression and a flexible-dose study with patients>65 years of age with treatment-resistant depression.

In studies for the treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior, patients treated with esketamine plus oral AD also demonstrated a higher number (84%) with dissociation (CADSS total score>4 and change>0) compared to patients treated with placebo plus oral AD (16%).

Because the subject combination can be administered without dissociation or dissociative events, its risk of abuse is reduced as compared to esketamine. Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Clinical studies with the combination of dextromethorphan and bupropion did not reveal drug-seeking behavior, although these observations were not systematic. Therefore, patients with a history of drug abuse may be observed closely for signs of the subject combination of dextromethorphan and bupropion misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior). 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 pointes, 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.

TABLE 2

Incidence of Dissociation (CADSS Total Score >4 and Change >0) in Double-Blind, Randomized, Placebo-Controlled Studies (Fixed-Dose Study with Adult Patients <65 Years of Age with treatment-resistant depression and Flexible-Dose Study with Patients ≥65 Years of Age with treatment-resistant depression)

	Patients <65 years			Patients ≥65 years	
	Placebo + Oral AD	ESKETAMINE + Oral AD 56 mg	ESKETAMINE + Oral AD 84 mg	Placebo + Oral AD	ESKETAMINE + Oral AD 28 to 84 mg
Number of patients*	N = 113	N = 113	N = 116	N = 65	N = 72
CADSS total score >4 and change >0	5%	61%	69%	12%	75%

*Number of patients who were evaluated with CADSS

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 be 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-Barre 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, 9,198,905, 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.

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 depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33

mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience depersonalization or derealization disorder, and wherein the combination of the dextromethorphan and the bupropion are administered in a dosage form that further comprises an L-cysteine.

2. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience depersonalization or derealization disorder, and wherein the human patient is monitored for any indication of clinical worsening.

3. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience sedation, and wherein the human patient is monitored for any emergence of suicidal thoughts or behaviors.

4. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience sedation, and wherein the combination of the dextromethorphan and the bupropion are administered in a dosage form that further comprises an L-cysteine.

5. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience sedation, and wherein the human patient is monitored for any indication of clinical worsening.

6. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience sedation, and wherein the human patient is monitored for any emergence of suicidal thoughts or behaviors.

7. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience a clinically significant prolongation of the QT interval, and wherein the combination of the dextromethorphan and the bupropion are administered in a dosage form that further comprises an L-cysteine.

8. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what

would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience a clinically significant prolongation of the QT interval, and wherein the human patient is monitored for any indication of clinical worsening.

9. A method of treating depression in a human patient using an N-methyl D-aspartate (NMDA) receptor antagonist, comprising administering a combination of the NMDA receptor antagonist and a second agent that increases the plasma levels of the NMDA receptor antagonist to the human patient, wherein the NMDA receptor antagonist is dextromethorphan in the free base form at a dose of about 33 mg twice daily, or a molar equivalent amount of a salt form of dextromethorphan, and the second agent is bupropion in the free base form at a dose of 91 mg twice daily, or a molar equivalent amount of a salt form of bupropion, wherein the human patient experiences a reduction in depression symptoms after one week of treatment that is greater than what would be achieved with a placebo, wherein the human patient has a history of drug abuse, wherein the human patient does not experience a clinically significant prolongation of the QT interval, and wherein the human patient is monitored for any emergence of suicidal thoughts or behaviors.

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