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

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

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

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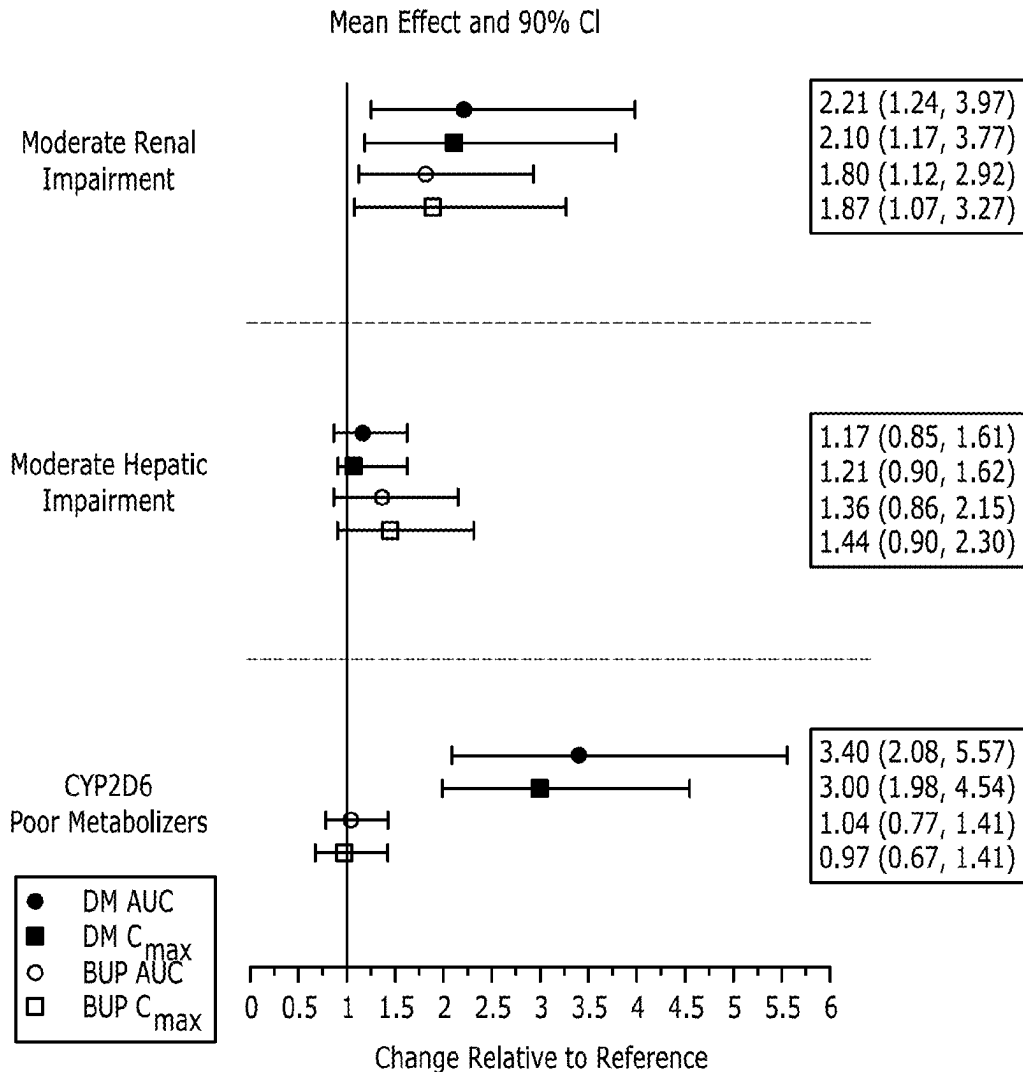
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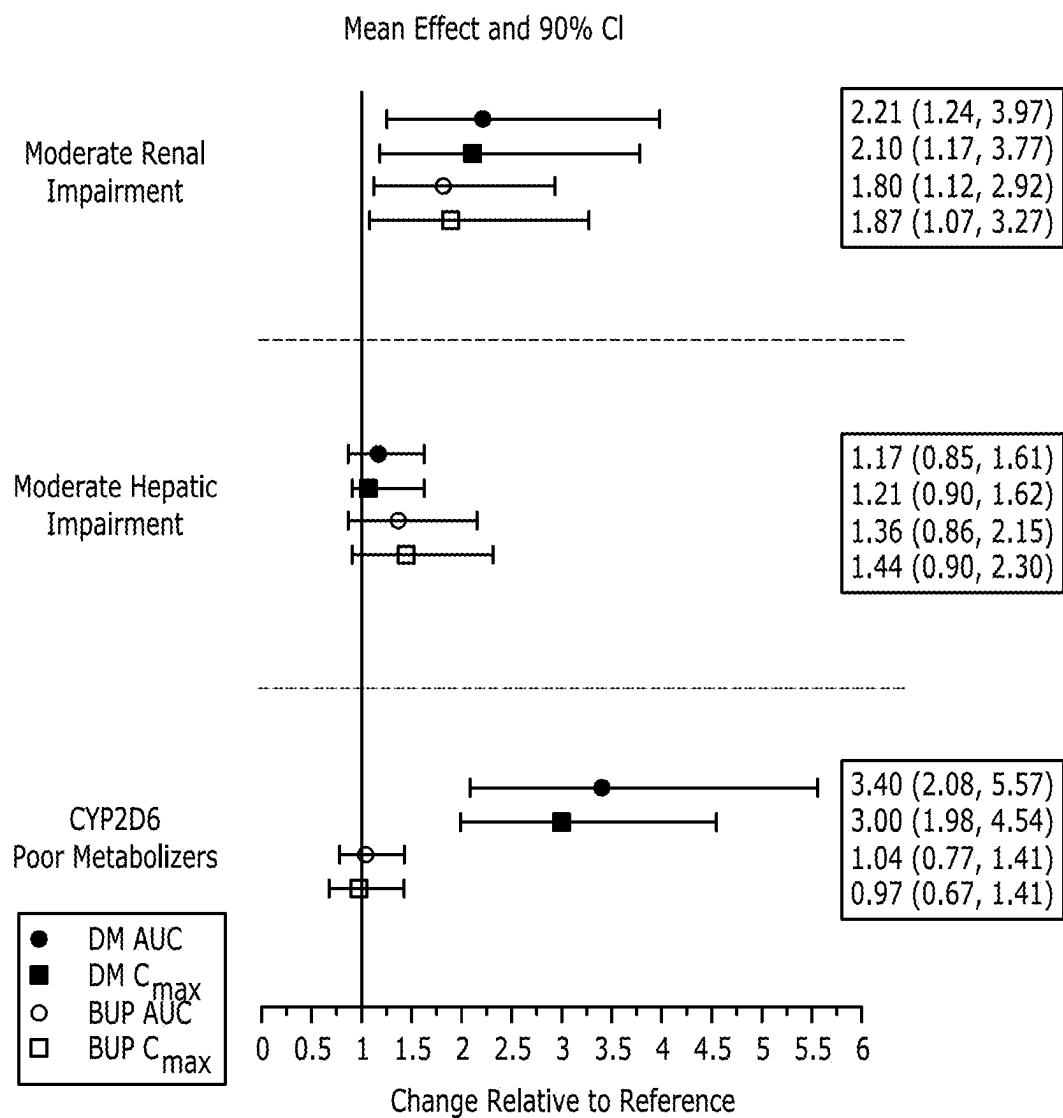
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ABSTRACT

Disclosed herein is a method of 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 are CYP2D6 poor metabo-
lizers.



*FIG. 1*

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

**CROSS-REFERENCE TO RELATED
APPLICATIONS**

[0001] This application is a continuation of International Pat. App. No. PCT/US2023/069286, filed Jun. 28, 2023; which claims the 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 herein in their entireties.

FIELD

[0002] 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

[0003] 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.

[0004] Disclosed herein is a method of 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.

[0005] 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.

[0006] 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.

[0007] Some embodiments include a method of treating a patient having a nervous system condition by administering a combination of dextromethorphan and bupropion, the method comprising:

[0008] orally administering to the patient, once a day, a dosage form comprising: 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan in the dosage form is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

[0009] wherein the patient is selected for: 1) having the nervous system condition and 2) being a CYP2D6 poor metabolizer, wherein the patient is determined to be a CYP2D6 poor metabolizer by an assay on a biological sample from the patient; and

[0010] wherein a risk of somnolence or dizziness for the patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

[0011] Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

[0012] determining whether the patient is a CYP2D6 poor metabolizer by:

[0013] obtaining or having obtained a biological sample from the patient; and

[0014] performing or having performed an assay on the biological sample to determine if the patient is a CYP2D6 poor metabolizer; and

[0015] if the patient is a CYP2D6 poor metabolizer, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the

molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

- [0016] if the patient is not a CYP2D6 poor metabolizer, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan;
- [0017] wherein a risk of somnolence or dizziness for a patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.
- [0018] Some embodiments include a method of treating a patient who is experiencing a nervous system condition, the method comprising the steps of:
- [0019] a) determining whether the patient is at risk of an adverse event associated with overexposure to dextromethorphan by:
- [0020] obtaining or having obtained a biological sample from the patient; and performing or having performed an assay on the biological sample to determine if the patient is a CYP2D6 poor metabolizer, wherein a result that the patient is a CYP2D6 poor metabolizer indicates that the patient is at risk of an adverse event associated with overexposure to dextromethorphan; and
- [0021] b) if the patient is at risk of an adverse event associated with overexposure to dextromethorphan, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide; and
- [0022] c) if the patient is not at risk of an adverse event associated with overexposure to dextromethorphan, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.
- [0023] Some embodiments include a method of treating a nervous system condition with a combination of dextromethorphan and bupropion, comprising:
- [0024] orally administering to a patient, once a day, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent

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

- [0025] wherein the patient is selected for: 1) having the nervous system condition and 2) being a CYP2D6 poor metabolizer, wherein the patient is determined to be a CYP2D6 poor metabolizer by an assay on a biological sample from the patient; and
- [0026] wherein the patient has a reduced risk of an adverse event as compared with the risk of the adverse event that the patient would have if the dosage form were administered twice daily to the patient.
- [0027] Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:
- [0028] determining whether the patient is a CYP2D6 poor metabolizer by:
- [0029] obtaining or having obtained a biological sample from the patient; and performing or having performed an assay on the biological sample to determine if the patient is a CYP2D6 poor metabolizer; and
- [0030] if the patient is a CYP2D6 poor metabolizer, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of bupropion to dextromethorphan in the dosage form is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide; and
- [0031] if the patient is not a CYP2D6 poor metabolizer, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan.
- [0032] Some embodiments include a method of treating a patient having a nervous system condition by administering a combination of dextromethorphan and bupropion, the method comprising:
- [0033] orally administering to the patient, once a day, a dosage form comprising: 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan in the dosage form is about the ratio of the molar amount bupropion in 105

mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

[0034] wherein the patient is selected for: 1) having the nervous system condition and 2) being a CYP2D6 poor metabolizer, wherein the patient is determined to be a CYP2D6 poor metabolizer by an assay on a biological sample from the patient; and

[0035] wherein a risk of somnolence and dizziness for the patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

[0036] Some embodiments include a method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

[0037] determining whether the patient is a CYP2D6 poor metabolizer by:

[0038] obtaining or having obtained a biological sample from the patient; and

[0039] performing or having performed an assay on the biological sample to determine if the patient is a CYP2D6 poor metabolizer; and

[0040] if the patient is a CYP2D6 poor metabolizer, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of bupropion in 105 mg of bupropion hydrochloride to the molar amount of dextromethorphan in 45 mg of dextromethorphan hydrobromide;

[0041] if the patient is not a CYP2D6 poor metabolizer, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan;

[0042] wherein a risk of somnolence and dizziness for a patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] 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

[0044] 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.

[0045] In some embodiments, the combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in a tablet.

[0046] 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.

[0047] 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.

[0048] In some embodiments, the tablet is orally administered in the morning.

[0049] In some embodiments, the dextromethorphan is in an immediate-release formulation.

[0050] In some embodiments, the bupropion is in an extended-release formulation.

[0051] In some embodiments, the tablet further contains a carbomer homopolymer.

[0052] In some embodiments, the tablet further contains colloidal silicon dioxide.

[0053] In some embodiments, the tablet further contains croscopolvidone.

[0054] In some embodiments, the tablet further contains glyceryl monocaprylocaprate.

[0055] In some embodiments, the tablet further contains L-cysteine hydrochloride monohydrate.

[0056] In some embodiments, the tablet further contains magnesium stearate.

[0057] In some embodiments, the tablet further contains microcrystalline cellulose.

[0058] In some embodiments, the tablet further contains polyvinyl alcohol.

[0059] In some embodiments, the tablet further contains red iron oxide.

[0060] In some embodiments, the tablet further contains sodium lauryl sulfate.

[0061] In some embodiments, the tablet further contains stearic acid.

[0062] In some embodiments, the tablet further contains talc.

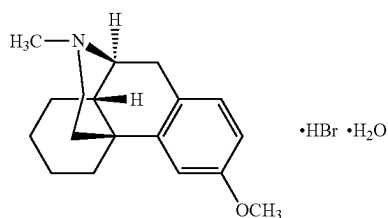
[0063] In some embodiments, the tablet further contains titanium dioxide.

[0064] In some embodiments, the tablet further contains yellow iron oxide.

[0065] 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.

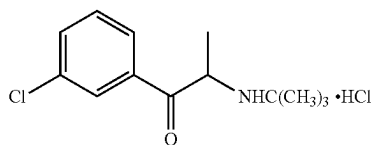
[0066] In some embodiments, the twice-daily administration of the tablet to the human patient for 8 days would result in the human patient having about same C_{max} of bupropion as compared to the C_{max} of bupropion that would result after 8 days of twice daily administration of the tablet to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

[0067] The chemical name of dextromethorphan hydrobromide is morphinan, 3-methoxy-17-methyl-, (9 α , 13 α , 14 α), 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.

[0068] The chemical name of bupropion hydrochloride is: (\pm)-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.

[0069] 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.

[0070] 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.

[0071] 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 Cucchiari, Ph.D., Mila Etropolis, 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, Kiiivet 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 Sep-

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[0072] 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.

[0073] 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.

[0074] 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.

[0075] For some patients, potential adverse events from increased dextromethorphan exposure may include dizzi-

ness, 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] In some embodiments, the dosage form provides sustained release of bupropion.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] In some embodiments, the dosage form provides immediate release of dextromethorphan.

[0084] 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.

[0085] 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).

[0086] 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.

[0087] The antidepressive efficacy of bupropion has been shown to be dose dependent. (See <https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a0fd621-165a-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).

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] 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.

[0095] The dosage form may be formulated for any suitable route of administration, such as oral administration.

[0096] 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.

[0097] An example of a bilayer dosage form is shown below:

| 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 |

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

[0098] 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.

[0099] 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 (GI:181303). The CYP2D6P34S/CYP2D6C100T polymorphism also corresponds to nucleotide 100 in GenBank mRNA sequence M20403.1 (GI:181349).

[0100] 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 P45011D6 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).

[0101] 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).

[0102] 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)

[0103] 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)

[0104] 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.

[0105] 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.

[0106] 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 (ADHD), 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.

[0107] 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.

[0108] 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.

[0109] 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.

[0110] 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.

[0111] 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.

[0112] 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.

[0113] 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 be treated include intermittent explosive disorder.

[0114] 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/amnesic 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.

[0115] 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.

[0116] 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.

[0117] 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.

[0118] 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.

[0119] 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 paraplegia.

[0120] 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.

[0121] Types of headaches that may be treated by the subject combination include, but are not limited to, migraine, tension, and cluster headaches.

[0122] 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 to, stress urinary incontinence, urge urinary incontinence, and fecal incontinence; and erectile dysfunction.

[0123] 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.

[0124] 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.

[0125] In some embodiments, the subject combination may be administered to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

[0126] 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.

[0127] In some embodiments, the subject combination is used to treat chronic musculoskeletal pain.

[0128] 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.

[0129] In some embodiments, the subject composition may be administered orally to relieve neuropathic pain.

[0130] 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 chemo-therapy associated neuropathy, etc.

[0131] In some embodiments, the subject composition may be administered to relieve fibromyalgia.

[0132] In some embodiments, the subject composition may be co-administered with one or more strong Inhibitors of CYP2D6. It has been found that the concomitant use of the subject combination with one or more strong CYP2D6 inhibitors increases plasma concentrations of dextromethorphan. It is, thus, recommended to monitor patients for adverse effects or adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

[0133] The dosage adjustment may be necessary when the subject composition is co-administered with one or more strong inhibitors of CYP2D6. Adjusting to a lower dose amount of the bupropion and/or the dextromethorphan in the subject combination or less frequent dosing of the subject combination may reduce adverse effects or adverse reactions, such as, but not limited to, somnolence, dizziness, or a combination thereof in a patient. For example, a recommended dosage of the subject combination when co-administered with one or more strong CYP2D6 inhibitors, is one tablet containing 45 mg or less of dextromethorphan hydrobromide and 105 mg or less of bupropion hydrochloride once daily, such as once daily in the morning.

[0134] In some embodiments, the subject composition may be administered to a patient who is a CYP2D6 poor metabolizer. It has been found that administering the subject composition to CYP2D6 inhibitors increases plasma concentrations of dextromethorphan as compared to patients who are not CYP2D6 poor metabolizers. It is, thus, recommended to monitor patients for adverse effects or adverse reactions potentially attributable to dextromethorphan, such as somnolence and dizziness.

[0135] The dosage adjustment may be necessary when the patient is a CYP2D6 poor metabolizer. Adjusting to a lower dose amount of the bupropion and/or the dextromethorphan in the subject combination or less frequent dosing of the subject combination may reduce adverse effects or adverse reactions, such as, but not limited to, somnolence, dizziness, or a combination thereof in a patient. For example, a recommended dosage of the subject combination when co-administered to a patient who is a CYP2D6 poor metabolizer, is one tablet containing 45 mg or less of dextromethorphan hydrobromide and 105 mg or less of bupropion hydrochloride once daily, such as once daily in the morning.

[0136] Administration of the subject combination once a day to patients who are receiving a concomitant strong CYP2D6 or to patients who are CYP2D6 poor metabolizers may reduce the adverse effects, such as, but not limited to, somnolence, dizziness, or a combination thereof, as compared to administration of the subject combination twice a day for same number of days. In some embodiments, reducing the dose amount or dose frequency of the subject combination may reduce somnolence. In some embodiments, reducing dose amount or dose frequency may reduce dizziness. As dizziness may link to falls, adjusting the dosage to lower amount or lower dose frequency of the subject combination may reduce the risk of falls for a patient taking the subject combination. For example, taking the subject combination once a day may reduce the risk of falls for a patient as compared to taking the subject combination twice a day for same number of days. This may be important, for example, to elderly patients or patients suffering from a dementia, such as Alzheimer's disease.

[0137] 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.

[0138] 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

[0139] 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.

[0140] 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 being increased only about 1.43-fold and 1.46-fold, respectively, compared to extensive metabolizers.

Example 2

[0141] 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

[0142] The properties of a tablet containing a combination of dextromethorphan hydrobromide, which is a non-competitive NMDA receptor antagonist and sigma-1 receptor agonist, and bupropion hydrochloride, which is an aminoketone and CYP450 2D6 inhibitor, were studied.

[0143] 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.

[0144] 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.

[0145] 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.

[0146] 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} .

[0147] 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.

[0148] 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.

[0149] 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.

[0150] Affirmative recitation of an element anywhere herein should be understood to contemplate both including and excluding that element.

[0151] 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 embodi-

ments 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.

[0152] 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.

[0153] 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.

[0154] 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.

1. A method of treating a patient having a nervous system condition by administering a combination of dextromethorphan and bupropion, the method comprising:

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

wherein the patient is selected for: 1) having the nervous system condition and 2) being a CYP2D6 poor metabolizer, wherein the patient is determined to be a CYP2D6 poor metabolizer by an assay on a biological sample from the patient; and

wherein a risk of somnolence and dizziness for the patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride

and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

2. A method of treating a patient with a combination of dextromethorphan and bupropion, wherein the patient is experiencing a nervous system condition, the method comprising the steps of:

determining whether the patient is a CYP2D6 poor metabolizer by:

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

performing or having performed an assay on the biological sample to determine if the patient is a CYP2D6 poor metabolizer; and

if the patient is a CYP2D6 poor metabolizer, then orally administering once a day to the patient, a dosage form containing a combination of 105 mg or less of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg or less of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan, wherein the molar ratio of the bupropion to the dextromethorphan is about the ratio of the molar amount of 105 mg of bupropion hydrochloride to the molar amount of 45 mg of dextromethorphan hydrobromide;

if the patient is not a CYP2D6 poor metabolizer, then orally administering twice a day to the patient, a dosage form containing a combination of 105 mg of bupropion hydrochloride, or a molar equivalent amount of the free base or another salt form of bupropion, and 45 mg of dextromethorphan hydrobromide, or a molar equivalent amount of the free base or another salt form of dextromethorphan; and

wherein a risk of somnolence and dizziness for a patient who is a CYP2D6 poor metabolizer is lower following orally administering the dosage form containing the combination once a day to the patient than it would be if a combination of 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide were administered twice a day to the patient for the same number of days.

3. A method of treating a nervous system condition in a CYP2D6 poor metabolizer comprising administering 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, once daily to a patient in need thereof, wherein the patient is known to be a poor CYP2D6 metabolizer, and wherein the molar ratio of the bupropion to the dextromethorphan in the dosage form is about the ratio of the molar amount of 105 mg of bupropion hydrochloride to the molar amount of 45 mg of dextromethorphan hydrobromide.

4. The method of claim 3, wherein 105 mg of bupropion hydrochloride and 45 mg of dextromethorphan hydrobromide is present in the dosage form.

5. The method of claim 3, wherein the dosage form provides immediate release of dextromethorphan.

6. The method of claim 3, wherein the dosage form provides sustained release of bupropion.

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

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

9. The method of claim 3, wherein the dosage form is orally administered in the morning.

10. The method of claim 3, wherein the dosage form further contains L-cysteine hydrochloride monohydrate.

11. The method of claim 3, wherein the dosage form further contains a carbomer homopolymer, colloidal silicon dioxide, crospovidone, glyceryl monocaprylocaprate, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol, red iron oxide, sodium lauryl sulfate, stearic acid, talc, titanium dioxide, yellow iron oxide, or a combination thereof.

12. The method of claim 3, wherein the dosage form is a solid dosage form.

13. The method of claim 3, 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 solid dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

14. The method of claim 3, 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 solid dosage form to a human patient who is an extensive or ultra-extensive CYP2D6 metabolizer.

15. The method of claim 3, wherein the nervous system condition is major depressive disorder.

16. The method of claim 3, wherein the nervous system condition is agitation associated with Alzheimer's disease.

17. The method of claim 3, wherein the nervous system condition is agitation associated with dementia.

18. The method of claim 3, wherein the nervous system condition is neuropathic pain.

19. The method of claim 3, wherein the nervous system condition is generalized anxiety disorder.

20. The method of claim 1, wherein the patient has a risk of fall.

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