(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2015 (14.05.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/070253 A1

(51) International Patent Classification:
A01N 57/00 (2006.01) *A61K 31/67* (2006.01)

(21) International Application Number:
PCT/US2014/065095

(22) International Filing Date:
11 November 2014 (11.11.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/902,762 11 November 2013 (11.11.2013) US
62/077,107 7 November 2014 (07.11.2014) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2015/070253 A1

(54) Title: NOVEL METHODS

(57) Abstract: Provided is a method of treating female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, to a female in need thereof.

NOVEL METHODS

[0001] This application claims priority to U.S. Provisional Application No. 62/077,107, filed November 7, 2014, and U.S. Provisional Application No. 61/902,762, filed November 11, 2013, the contents of each of which are incorporated herein by reference.

BACKGROUND

[0002] Females can suffer from female sexual dysfunction (FSD). It has been reported that approximately 40 million American women are affected by FSD and that sexual dysfunction is more prevalent in women (43%) than in men (31%) and increases as women age.

[0003] There is thus a need for methods to treat female sexual dysfunction.

BRIEF SUMMARY

[0004] Provided is a method of treating female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a female in need thereof.

[0005] Further provided is a method of treating female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, to a female in need thereof.

[0006] Further areas of applicability of the present disclosure will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating the preferred embodiment of this disclosure, are intended for purposes of illustration only and are not intended to limit the scope of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The present disclosure will become more fully understood from the detailed description and the accompanying drawings, wherein:

[0008] Figure 1 shows SFI Score for Item 1: Amitifadine 100 mg vs. Paroxetine.

[0009] Figure 2 shows SFI Score for Item 2: Amitifadine 100 mg vs. Paroxetine.

[0010] Figure 3 shows SFI Score for Item 3: Amitifadine 100 mg vs. Paroxetine.

[0011] Figure 4 shows SFI Score for Item 4: Amitifadine 100 mg vs. Paroxetine.

[0012] Figure 5 shows SFI Score for Item 5: Amitifadine 100 mg vs. Paroxetine.

[0013] Figure 6 shows SFI Total Score: Amitifadine 100 mg vs. Paroxetine.

[0014] Figure 7 shows SFI Score for Item 1 by Gender: Amitifadine 100 mg vs. Placebo.

[0015] Figure 8 shows SFI Score for Item 2 by Gender: Amitifadine 100 mg vs. Placebo.

[0016] Figure 9 shows SFI Score for Item 3 by Gender: Amitifadine 100 mg vs. Placebo.

[0017] Figure 10 shows SFI Score for Item 4 by Gender: Amitifadine 100 mg vs. Placebo.

[0018] Figure 11 shows SFI Score for Item 5 by Gender: Amitifadine 100 mg vs. Placebo.

[0019] Figure 12 shows SFI Total Score by Gender: Amitifadine 100 mg vs. Placebo

DETAILED DESCRIPTION

[0020] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit this disclosure, its application, or uses.

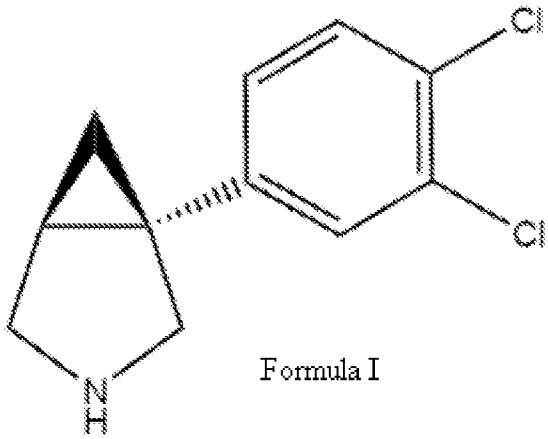
[0021] As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by referenced in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0022] There are both excitatory and inhibitory factors that may influence sexual desire. Excitatory factors include testosterone, melanocortin, oxytocin, dopamine, and norepinephrine. Inhibitory factors include serotonin (5-hydroxytryptamine (5-HT)), prolactin, and endogenous opioids.

[0023] It has been reported that in both *in vitro* and *in vivo* studies dopamine inhibits prolactin (PRL) release. Dopamine binds to the D2 receptor subclass expressed on lactotroph cell membranes. Activation of that receptor results in suppression of PRL gene expression and inhibition of PRL exocytosis.

[0024] Serotonin has a stimulatory role in prolactin secretion. Changes in sexual desire, sexual performance, and sexual satisfaction may occur as a side effect of treatment with a selective serotonin reuptake inhibitor (SSRI).

[0025] (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, also known as (1R,5S)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, also known amitifadine, is shown as Formula I below.



Formula I

[0026] "(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane," "(1R,5S)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane," and "amitifadine" are used interchangeably herein. (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is an unbalanced triple reuptake inhibitor with the greatest potency towards serotonin reuptake (5-HT), half as much towards norepinephrine reuptake (NE), and one eighth towards dopamine reuptake (DA). (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride is reported to inhibit the reuptake of [^{3}H]serotonin, [^{3}H]norepinephrine, and [^{3}H]dopamine in human embryonic kidney (HEK) 293 cells expressing the corresponding human recombinant transporters at IC_{50} values of 12, 23, and 96 nm, respectively.

[0027] In a recent clinical trial for use of amitifadine in the treatment of major depressive disorder, individuals receiving amitifadine 100 mg had significantly less overall worsening of sexual function than those receiving paroxetine as assessed with the Sexual Functioning Inventory (SFI). In addition, women experienced significant improvement in SFI on 100 mg amitifadine from baseline compared with placebo, which is unexpected considering that amitifadine more strongly inhibits serotonin reuptake than dopamine reuptake.

[0028] Without being bound by theory, amitifadine, by inhibiting dopamine reuptake, may enhance the synaptic availability of dopamine enough to inhibit prolactin (PRL) release. As prolactin is an inhibitory factor on sexual desire, inhibiting its release may enhance sexual desire.

[0029] (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane may be synthesized as described in U.S. Patent Publication No. 2008/0045725, incorporated herein by reference in its entirety.

[0030] As used herein, "(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer" means containing no more than 5% w/w (weight/weight) of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 2% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 1% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form.

[0031] As used herein, "(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane" embraces the compound in any form, for example, free or pharmaceutically acceptable salt form, e.g., as a pharmaceutically acceptable acid addition salt. Pharmaceutically acceptable salts are known in the art and include salts that are physiologically acceptable at the dosage amount and form to be administered, for example, hydrochloride salts.

[0032] As used herein, "(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane" is also to be understood as embracing the compound in crystalline and amorphous form including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" may be used interchangeably herein, and are meant to include all crystalline forms of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrates), and conformational polymorphs, as well as mixtures thereof, unless a particular crystalline form is referred to.

[0033] (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane exists in at least three polymorphic forms, labeled polymorphs A, B, and C, as disclosed in U.S. Patent Publication Nos. 2007/0043100 and 2009/0326245, incorporated herein by reference in their entirety.

[0034] Crystalline and amorphous forms of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane may be used in any combination or in forms that are substantially free of one or more of the other crystalline forms or free of the amorphous form.

[0035] As used herein, "substantially free of other polymorphic forms" means that the crystalline material contains no more than 5% w/w of any other crystalline form, e.g., no more than 2% w/w of any other crystalline form, e.g., no more than 1% w/w of any other crystalline form.

[0036] (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane may in some cases also exist in prodrug form. Prodrugs are considered to be any covalently bonded carriers that release the active parent drug *in vivo*.

[0037] As used herein, "therapeutically effective amount" refers to an amount effective, when administered to a human or non-human patient, to provide a therapeutic benefit such as amelioration of symptoms. The specific dose of substance administered to obtain a therapeutic benefit will, of course, be determined by the particular circumstances surrounding the case, including, for example, the specific substance administered, the route of administration, the condition being treated, and the individual being treated.

[0038] As used herein, "concurrently" means the compounds are administered simultaneously or within the same composition. In some embodiments, the compounds are administered simultaneously. In some embodiments, the compounds are administered within the same composition.

[0039] As used herein, "female sexual dysfunction" generally refers to impairment of sexual function. For example, "female sexual dysfunction" includes, but is not limited to, hypoactive sexual desire, sexual aversion disorder, sexual arousal disorder, orgasmic disorder, sexual pain disorder (including, e.g., dyspareunia, vaginismus, and noncoital sexual pain disorder), and combinations thereof.

[0040] As used herein, "female" includes premenopausal and post-menopausal females.

[0041] As used herein, "treatment" and "treating" embrace enhancing or improving sexual response and/or sexual pleasure and/or sensation. "Enhancing" or "improving" sexual response and/or sexual pleasure and/or sensation means that administration of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane increases the female's satisfaction with the sexual activity as compared to the activity when in the absence of (+)-1-(3,4-dichlorophenyl)-3-

azabicyclo[3.1.0]hexane. This includes, e.g., enhancement of vaginal wetness, warmth, engorgement, sensitivity, sensation, tingling, arousal, orgasm, quicker to arousal, quicker to orgasm, and enhancement of any of the above-mentioned conditions (for example, clitoral and labial sensation or vaginal smooth muscle relaxation), etc.

[0042] Provided herein is a method (Method 1) of prophyalaxis or treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a female in need thereof.

[0043] Further provided is Method 1 as follows:

1.1 Method 1 wherein the method is for the treatment of female sexual dysfunction.

1.2 Method 1 or 1.1 wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 5% w/w of the corresponding (-) enantiomer.

1.3 Method 1, 1.1, or 1.2 wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 2% w/w of the corresponding (-) enantiomer.

1.4 Method 1 or 1.1-1.3 wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 1% w/w of the corresponding (-) enantiomer.

1.5 Method 1 or 1.1-1.4 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.

1.6 Method 1 or 1.1-1.5 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.

1.7 Method 1 or 1.1-1.6 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride.

1.8 Method 1 or 1.1-1.7 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is crystalline.

1.9 Method 1 or 1.1-1.8 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph A.

1.10 Method 1 or 1.1-1.8 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph B.

1.11 Method 1 or 1.1-1.8 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph C.

1.12 Method 1 or 1.1-1.11 comprising administering 10 mg to 1800 mg, e.g., 25 mg to 1800 mg, e.g., 10 mg to 1600 mg, e.g., 10 mg to 1200 mg, e.g., 50 mg to 1200 mg, e.g., 75 mg to 1000 mg, e.g., 75 mg to 800 mg, e.g., 75 mg to 500 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 10 mg to 100 mg, 200 mg, or 300 mg, e.g., 25 mg to 100 mg, 200 mg, or 300 mg, e.g., 50 mg to 100 mg, 200 mg, or 300 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.13 Method 1 or 1.1-1.12 comprising administering 75 mg to 1000 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.14 Method 1 or 1.1-1.13 comprising administering 25 mg to 600 mg, 50 mg to 600 mg, e.g., 25 mg to 200 mg, e.g., 50 mg to 200 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.15 Method 1 or 1.1-1.14 comprising administering 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100 mg, 200 mg, 300 mg, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.16 Method 1 or 1.1-1.15 comprising administering 100 mg to 200 mg, e.g., 100 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.17 Method 1 or 1.1-1.16 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.

1.18 Method 1 or 1.1-1.17 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least once daily.

1.19 Method 1 or 1.1-1.18 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least twice daily.

1.20 Method 1 or 1.1-1.19 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least three times daily.

1.21 Method 1 or 1.1-1.20 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.

1.22 Method 1 or 1.1-1.21 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, 24 hours or less, e.g., 12 hours, e.g., 10 hours, e.g., 8 hours, e.g., 6 hours, e.g., 4 hours, e.g., 3 hours, e.g., 2 hours, e.g., 1 hour or less, before sexual activity.

1.23 Method 1 or 1.1-1.22 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another treatment for female sexual dysfunction.

1.24 Method 1 or 1.1-1.23 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with a hormone or a derivative thereof (e.g., estrogen, testosterone (e.g., micronized oral testosterone), methyltestosterone, testosterone propionate, dehydroepiandrosterone, dehydroepiandrosterone sulfate), a prostaglandin (e.g., alprostadil), a melanocortin agonist (e.g., bremelanotide), a phosphodiesterase inhibitor (e.g., a PDE5 inhibitor, e.g., Viagra, or, e.g., a PDE1 inhibitor), a dopamine-norepinephrine reuptake inhibitor (e.g., bupropion), a 5-hydroxytryptamine$_{1a}$ receptor agonist, a dopamine agonist (e.g., apomorphine), a serotonin antagonist and reuptake inhibitor (e.g., trazodone), a lubricant, vitamin E, mineral oil, or a combination thereof.

1.25 Method 1 or 1.1-1.24 wherein the female has major depressive disorder.

1.26 Method 1 or 1.1-1.25 wherein the female is taking an anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a

serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the female is taking an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

1.27 Method 1 or 1.1-1.26 wherein the sexual dysfunction is a side effect of a drug, e.g., an anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the sexual dysfunction is a side effect of an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

1.28 Method 1.26 or 1.27 comprising administering a subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

1.29 Method 1.28 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment of depression.

1.30 Method 1.28 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment of female sexual dysfunction.

1.31 Any of Method 1.26-1.30 comprising administering 10 mg to 400 mg, e.g., 25 mg to 400 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 400 mg, e.g., 50 mg to 300 mg, e.g., 50 mg to

200 mg, e.g., 50 to 100 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100 mg, 200 mg, 300 mg, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

[0044] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0045] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0046] Also provided is a pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in combination with a pharmaceutically acceptable diluent or carrier for use in treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0047] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0048] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0049] Also provided is a pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in combination with a pharmaceutically acceptable diluent or carrier for use in treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

[0050] Provided herein is a method (Method 2) of prophyalaxis or treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, to a female in need thereof.

[0051] Further provided is Method 2 as follows:

2.1 Method 2 wherein the method is for the treatment of female sexual dysfunction.

2.2 Method 2 or 2.1 wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 2% w/w of the corresponding (-) enantiomer.

2.3 Method 2, 2.1, or 2.2 wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 1% w/w of the corresponding (-) enantiomer.

2.4 Method 2 or 2.1-2.3 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form substantially free of the corresponding (-) enantiomer.

2.5 Method 2 or 2.1-2.4 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt substantially free of the corresponding (-) enantiomer.

2.6 Method 2 or 2.1-2.5 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride substantially free of the corresponding (-) enantiomer.

2.7 Method 2 or 2.1-2.6 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is crystalline substantially free of the corresponding (-) enantiomer.

2.8 Method 2 or 2.1-2.7 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph A substantially free of other polymorphic forms and substantially free of the corresponding (-) enantiomer.

2.9 Method 2 or 2.1-2.7 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph B substantially free of other polymorphic forms and substantially free of the corresponding (-) enantiomer.

2.10 Method 2 or 2.1-2.7 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph C substantially free of other polymorphic forms and substantially free of the corresponding (-) enantiomer.

2.11 Method 2 or 2.1-2.10 comprising administering 10 mg to 1800 mg, e.g., 25 mg to 1800 mg, e.g., 10 mg to 1600 mg, e.g., 10 mg to 1200 mg, e.g., 50 mg to 1200 mg, e.g., 75 mg to 1000 mg, e.g., 75 mg to 800 mg, e.g., 75 mg to 500 mg, e.g., 100 mg to 500 mg, e.g.,

100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 10 mg to 100 mg, 200 mg, or 300 mg, e.g., 25 mg to 100 mg, 200 mg, or 300 mg, e.g., 50 mg to 100 mg, 200 mg, or 300 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.12 Method 2 or 2.1-2.11 comprising administering 75 mg to 1000 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.13 Method 2 or 2.1-2.12 comprising administering 25 mg to 600 mg, 50 mg to 600 mg, e.g., 25 mg to 200 mg, e.g., 50 mg to 200 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.14 Method 2 or 2.1-2.13 comprising administering 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100, 200, 300, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.15 Method 2 or 2.1-2.14 comprising administering 100 mg to 200 mg, e.g., 100 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.16 Method 2 or 2.1-2.15 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, once, twice, three, or four times daily.

2.17 Method 2 or 2.1-2.16 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, at least once daily.

2.18 Method 2 or 2.1-2.17 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, at least twice daily.

2.19 Method 2 or 2.1-2.18 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, at least three times daily.

2.20 Method 2 or 2.1-2.19 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, four times daily.

2.21 Method 2 or 2.1-2.20 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, 24 hours or less, e.g., 12 hours, e.g., 10 hours, e.g., 8 hours, e.g., 6 hours, e.g., 4 hours, e.g., 3 hours, e.g., 2 hours, e.g., 1 hour or less, before sexual activity.

2.22 Method 2 or 2.1-2.21 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, is administered concurrently or sequentially, in either order, with another treatment for female sexual dysfunction.

2.23 Method 2 or 2.1-2.22 wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, is administered concurrently or sequentially, in either order, with a hormone or a derivative thereof (e.g., estrogen, testosterone (e.g., micronized oral testosterone), methyltestosterone, testosterone propionate, dehydroepiandrosterone, dehydroepiandrosterone sulfate), a prostaglandin (e.g., alprostadil), a melanocortin agonist (e.g., bremelanotide), a phosphodiesterase inhibitor (e.g., a PDE5 inhibitor, e.g., Viagra, or, e.g., a PDE1 inhibitor), a dopamine-norepinephrine reuptake inhibitor (e.g., bupropion), a 5-hydroxytryptamine$_{1a}$ receptor agonist, a dopamine agonist (e.g., apomorphine), a serotonin antagonist and reuptake inhibitor (e.g., trazodone), a lubricant, vitamin E, mineral oil, or a combination thereof.

2.24 Method 2 or 2.1-2.23 wherein the female has major depressive disorder.

2.25 Method 2 or 2.1-2.24 wherein the female is taking an anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin

-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the female is taking an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

2.26 Method 2 or 2.1-2.25 wherein the sexual dysfunction is a side effect of a drug, e.g., an anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the sexual dysfunction is a side effect of an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

2.27 Method 2.25 or 2.26 comprising administering a subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

2.28 Method 2.27 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treatment of depression.

2.29 Method 2.27 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treatment of female sexual dysfunction.

2.30 Any of Method 2.25-2.29 comprising administering 10 mg to 400 mg, e.g., 25 mg to 400 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 400 mg, e.g., 50 mg to 300 mg, e.g., 50 mg to 200 mg, e.g., 50 to 100 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100 mg, 200 mg, 300 mg, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

[0052] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0053] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in the manufacture of a medicament for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0054] Also provided is a pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in combination with a pharmaceutically acceptable diluent or carrier for use in treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0055] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0056] Also provided herein is use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in the manufacture of a medicament for treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0057] Also provided is a pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in combination with a pharmaceutically

acceptable diluent or carrier for use in treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

[0058] A dose or method of administration of the dose of the present disclosure is not particularly limited. Dosages employed in practicing the present disclosure will of course vary depending, e.g. on the mode of administration and the therapy desired. In general, satisfactory results, e.g. for the treatment of female sexual dysfunction are indicated to be obtained on oral administration at dosages of the order from about 0.01 to 2.0 mg/kg. In larger females, for example human females, an indicated daily dosage for oral administration will accordingly be in the range of from about 0.75 mg to 150 mg, conveniently administered once, or in divided doses 2 to 4 times, daily or in sustained release form. Unit dosage forms for oral administration thus for example may comprise from about 0.2 mg to 75 mg or 150 mg, e.g. from about 0.2 mg or 2.0 mg or 50 mg or 75 mg or 100 mg to 200 mg or 500 mg of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier therefor. Unit dosage forms for oral administration thus for example may comprise from about 0.2 mg to 75 mg or 150 mg, e.g. from about 0.2 mg or 2.0 mg or 50 mg or 75 mg or 100 mg to 200 mg or 500 mg of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, together with a pharmaceutically acceptable diluent or carrier therefor.

[0059] (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, may be administered by any suitable route, including orally, parenterally, transdermally, inhalation, slow release, controlled release, although various other known delivery routes, devices and methods can likewise be employed. (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, may be administered by any suitable route, including orally, parenterally, transdermally, inhalation, slow release, controlled release, although various other known delivery routes, devices and methods can likewise be employed. In some embodiments, provided is a sustained release pharmaceutical composition, e.g., an oral sustained release pharmaceutical composition, comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, which provides therapeutically effective levels of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane over a sustained delivery period of

approximately 6 hours or longer, e.g., 8 hours or longer, e.g., 12 hours or longer, e.g., 18 hours or longer, e.g., 24 hours or longer. In some embodiments, provided is a sustained release pharmaceutical composition, e.g., an oral sustained release pharmaceutical composition, comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, which provides therapeutically effective levels of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane over a sustained delivery period of approximately 6 hours or longer, e.g., 8 hours or longer, e.g., 12 hours or longer, e.g., 18 hours or longer, e.g., 24 hours or longer. In some embodiments, provided is an immediate release pharmaceutical composition, e.g., an oral immediate release pharmaceutical composition, comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form. In some embodiments, provided is an immediate release pharmaceutical composition, e.g., an oral immediate release pharmaceutical composition, comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer.

[0060] Pharmaceutical compositions comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, may be prepared using conventional diluents or excipients and techniques known in the galenic art. Pharmaceutical compositions comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus, oral dosage forms may include tablets, capsules, solutions, suspensions, and the like.

[0061] Where two active agents are administered, the therapeutically effective amount of each agent may be below the amount needed for activity as monotherapy. Accordingly, a subthreshold amount (i.e., an amount below the level necessary for efficacy as monotherapy) may be considered therapeutically effective. Indeed, an advantage of administering different agents with different mechanisms of action and different side effect profiles may be to reduce the dosage and side effects of either or both agents, as well as to enhance or potentiate their activity as monotherapy.

[0062] Examples of sexual functioning questionnaires to detect sexual dysfunction are described in Labbate, L. et al., "Sexual Dysfunction in Male psychiatric Outpatients: Validity of

the Massachusetts General Hospital Sexual Functioning Questionnaire," Psychotherapy and Psychosomatics, 2001, 70, 221-225, which is incorporated by reference in its entirety.

EXAMPLE

Example 1

[0063] A multicenter, randomized, double blind, placebo- and paroxetine- controlled trial of amitifadine for major depressive disorder (MDD) non-responsive to an adequate trial of an antidepressant theraphy in the current depressive episode. A sequential parallel comparison design (SPCD) is utilized. All patients are initially randomized to receive either amitifadine 50 mg or 100 mg, paroxetine 40 mg, or placebo. The study is 12 weeks in duration, with two 6-week phases. The primary outcome measure is change on the Montgomery Asberg Depression Rating Scale (MADRS). Secondary outcomes include Hamilton Rating Scale for Depression (HAM-D), Clinical Global Impression of Improvement (CGI-I), Sexual Functioning Inventory (SFI), Clinical Global Impression (Improvement and Severity versions), and the Massachusetts General Hospital (MGH) Cognitive and Physical Functioning Questionnaire (MGH-CPFQ). Male and female patients, between the ages of 18-65, are eligible who had MDD, based on the Structured Clinical Interview for DSM Disorders (SCID) interview, and validated by remote raters, a history of non-response to an adequate trial of an antidepressant during the current episode of MDD (an adequate dose for $\geq$ 8 weeks), and a HAM-D-17 score of $\geq$ 18 at screening.

[0064] In addition to standard inclusion criteria the trial requires: 1) diagnosis of MDD, based on the Structured Clinical Interview for DSM Disorders Clinical Trials version (SCID-CT), validated by remote independent raters using the SAFER criteria interview, 2) one and only one antidepressant therapy (ADT) failure in the current episode of MDD, treated with an adequate dose of one of an allowed standard antidepressant (paroxetine or an monoamine oxidase inhibitor (MAOI) not allowed) during the current episode for > 6 weeks, with the same, adequate dose for > 4 weeks, 3) HAM-D17 $\geq$ 18 at the end of screening phase, 4) < 25% reduction in Quick Inventory of Depressive Symptoms Self-Rated (QIDS-SR) score between the screen and baseline visits. Inadequate response: defined as < 50% reduction in depressive symptom severity, assessed by the MGH Antidepressant Treatment Response Questionnaire (ATRQ) administered by remote, independent raters (Targum, S. et al., CNS Neuroscience & Therapeutics, 2010, 16 (5), 322-325). An adequate trial is defined as an ADT > 6 weeks at least

at the minimum dose specified in the MGH ATRQ. Patients do not have to be on the failed ADT medication at the time of screening visit.

[0065] *Additional criteria for defining non-response for patients in Phase 2: Among patients randomized to receive placebo in Phase 1 and to be re-randomized to receive placebo, amitifadine 50 mg/day or amitifadine 100 mg/day in Phase 2, only those meeting non-response criteria are added to the primary efficacy sample.* Placebo non-responders are defined as those patients who fail to achieve at least a 50% decrease from Phase 1 baseline in their MADRS score at visit 8 (Week 6), and had a MADRS score of $\geq$ 16 at visit 8 (Week 6) of Phase 1. The SCID-CT is administered by study clinicians at the screening visit to diagnose Axis I disorders. The remote, independent raters also administer the SAFER Criteria Inventory (SCI) during the screening phase to assess whether the MDD is a "valid" clinical entity.

[0066] **Efficacy and Safety Assessments**

[0067] The primary efficacy assessment is the MADRS, administered at every study visit and clinicians complete it by using a structured interview guide developed by Massachusetts General Hospital (MGH). The primary tolerability assessment is the change in the SFI, completed by the patient at every study visit. The MGH-CPFQ, a brief self-report inventory to assess rates of significant cognitive symptoms, sleepiness and fatigue, is filled out by patients at every visit. The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner K. et al., American Journal of Psychiatry, 2011, 168 (12)1266-77) is administered at every visit. Vital signs are recorded at each visit; physical exam is performed at screen and week 12 (or early termination). Laboratory tests are obtained at screen, baseline, and weeks 2, 4, 6, 8, 10, 12 (or early termination). Twelve-lead ECGs are obtained at screen, baseline, and weeks 3, 6, 9, 12 (or early termination). Consumptive habits (smoking, alcohol, and caffeinated beverages) are recorded at every visit. Adverse events and concomitant medications are collected at every visit.

[0068] Results: A total of 342 patients are randomized. In the primary analysis, there is no significant difference in MADRS change from baseline for amitifadine 50 mg or 100 mg compared to placebo. There is a significant difference between paroxetine and placebo, verifying the internal validity of the trial. There are no significant differences on the CGI-Improvement between amitifadine 50 mg or 100 mg and placebo; there is a significant difference on the CGI-I between paroxetine and placebo at both 6 and 12 weeks.

[0069] Despite lack of efficacy on the primary outcome, exploratory analyses does suggest potential signals for a dose related antidepressant effect of amitifadine. In exploratory analyses, paroxetine demonstrates significantly better improvement compared to both placebo and amitifadine 50 mg, although the difference between paroxetine and amitifadine 100 mg is non-significant.

[0070] However, the trial is not powered as a non-inferiority trial. For patients with confirmed adherence based on PK levels, the improvement in terms of change on the MADRS from baseline with amitifadine 100 mg is similar to that seen with paroxetine. Neither dose is associated with significant changes in heart rate or blood pressure.

[0071] Those receiving amitifadine 100 mg had significantly less overall worsening of sexual function than those receiving paroxetine. On most individual items of the SFI, amitifadine 100 mg is significantly less impairing than paroxetine, such as anorgasmia, arousal, and overall satisfaction. In post-hoc analyses of the SFI by gender, women experience significant improvement on 100 mg amitifadine from baseline compared with placebo. See Tables 1 and 2.

Table 1. LOCF Analysis of Mean Change from Baseline SFI

SFI Item	Compare vs. Paroxetine	Both Genders	p-Values
1	Amitifadine 100	-1.02	
	Paroxetine	-0.57	0.1054
2	Amitifadine 100	-1.00	
	Paroxetine	-0.45	0.0326
3	Amitifadine 100	-0.80	
	Paroxetine	-0.27	0.0391
4	Amitifadine 100	-0.79	
	Paroxetine	-0.13	0.0621
5	Amitifadine 100	-1.00	
	Paroxetine	-0.23	0.0032
SFI TOTAL	Amitifadine 100	-3.86	
	Paroxetine	-1.52	0.0134

Table 2. LOCF Analysis of Mean Change from Baseline SFI

SFI Item	Compare vs. Placebo		
1		Female	Male
	Amitifadine 100	-1.16	-0.83
	Placebo	-0.45	-0.92
	p-Value	0.0147	0.1018
2		Female	Male
	Amitifadine 100	-1.12	-0.83
	Placebo	-0.27	-0.83
	p-Value	0.0276	0.9847
3		Female	Male
	Amitifadine 100	-0.97	-0.58
	Placebo	-0.19	-0.85
	p-Value	0.0042	0.4317
4		Female	Male
	Amitifadine 100		-0.79
	Placebo		-0.56
	p-Value		0.4321
5		Female	Male
	Amitifadine 100	-1.09	-0.88
	Placebo	-0.41	-0.69
	p-Value	0.0131	0.5906
SFI Total		Female	Male
	Amitifadine 100	-4.41	-3.12
	Placebo	-1.25	-3.29
	p-Value	0.0016	0.8936

CLAIMS

WHAT IS CLAIMED IS:

1. A method of prophyalaxis or treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
2. A method of treating female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
3. A method of treating female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, to a female in need thereof.
4. The method of any one of claims 1-3, wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 2% w/w of the corresponding (-) enantiomer.
5. The method of any one of claims 1-4, wherein the therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 1% w/w of the corresponding (-) enantiomer.
6. The method of any one of claims 1-5, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form substantially free of the corresponding (-) enantiomer.
7. The method of any one of claims 1-6, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
8. The method of any one of claims 1-7, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride.

9. The method of any one of claims 1-8, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is crystalline.

10. The method of any one of claims 1-9, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph A.

11. The method of any one of claims 1-9, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph B.

12. The method of any one of claims 1-9, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is Polymorph C.

13. The method of any one of claims 1-12 comprising administering 10 mg to 1800 mg, e.g., 25 mg to 1800 mg, e.g., 10 mg to 1600 mg, e.g., 10 mg to 1200 mg, e.g., 50 mg to 1200 mg, e.g., 75 mg to 1000 mg, e.g., 75 mg to 800 mg, e.g., 75 mg to 500 mg, e.g., 100 mg to 500 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 10 mg to 100 mg, 200 mg, or 300 mg, e.g., 25 mg to 100 mg, 200 mg, or 300 mg, e.g., 50 mg to 100 mg, 200 mg, or 300 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

14. The method of any one of claims 1-13 comprising administering 75 mg to 1000 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

15. The method of any one of claims 1-14 comprising administering 25 mg to 600 mg, 50 mg to 600 mg, e.g., 25 mg to 200 mg, e.g., 50 mg to 200 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

16. The method of any one of claims 1-15 comprising administering 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100 mg, 200

mg, 300 mg, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

17. The method of any one of claims 1-16 comprising administering 100 mg to 200 mg, e.g., 100 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

18. The method of any one of claims 1-17 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.

19. The method of any one of claims 1-18 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least once daily.

20. The method of any one of claims 1-19 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least twice daily.

21. The method of any one of claims 1-20 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, at least three times daily.

22. The method of any one of claims 1-21 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.

23. The method of any one of claims 1-22 comprising administering (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, 24 hours or less, e.g., 12 hours, e.g., 10 hours, e.g., 8 hours, e.g., 6 hours, e.g., 4 hours, e.g., 3 hours, e.g., 2 hours, e.g., 1 hour or less, before sexual activity.

24. The method of any one of claims 1-23, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another treatment for female sexual dysfunction.

25. The method of any one of claims 1-24, wherein (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with a hormone or a derivative thereof (e.g., estrogen, testosterone (e.g., micronized oral testosterone), methyltestosterone, testosterone propionate, dehydroepiandrosterone, dehydroepiandrosterone sulfate), a prostaglandin (e.g., alprostadil), a melanocortin agonist (e.g., bremelanotide), a phosphodiesterase inhibitor (e.g., a PDE5 inhibitor, e.g., Viagra, or, e.g., a PDE1 inhibitor), a dopamine--norepinephrine reuptake inhibitor (e.g., bupropion), a 5-hydroxytryptamine$_{1a}$ receptor agonist, a dopamine agonist (e.g., apomorphine), a serotonin antagonist and reuptake inhibitor (e.g., trazodone), a lubricant, vitamin E, mineral oil, or a combination thereof.

26. The method of any one of claims 1-25, wherein the female has major depressive disorder.

27. The method of any one of claims 1-26, wherein the female is taking anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the female is taking an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

28. The method of any one of claims 1-27, wherein the female is taking an anti-depressant (e.g., a selective serotonin re-uptake inhibitor).

29. The method of any one of claims 1-28, wherein the sexual dysfunction is a side effect of a drug, e.g., an anti-hypertensive (e.g., a diuretic, a beta blocker, a calcium-channel blocker, an anti-adrenergic), an anticholinergic (e.g., propantheline, methantheline), a barbiturate, a benzodiazepine (e.g, diazepam, alprazolam), an anti-depressant (e.g., a

selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., selective serotonin re-uptake inhibitor, e.g., paroxetine), a chemotherapeutic (e.g., cyclophosphamide, an anti-estrogen), or an opiate (e.g., morphine, codeine, methadone), e.g., wherein the sexual dysfunction is a side effect of an anti-depressant (e.g., a selective serotonin re-uptake inhibitor, a serotonin-norepinephrine re-uptake inhibitor, a tricyclic antidepressant, a tetracyclic antidepressant, or a monoamine oxidase inhibitor, e.g., a selective serotonin re-uptake inhibitor, e.g., paroxetine).

30. The method of any one of claims 1-29, wherein the sexual dysfunction is a side effect of an anti-depressant (e.g., a selective serotonin re-uptake inhibitor).

31. The method of any one of claims 1-30 comprising administering a subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

32. The method of claim 31 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment of depression.

33. The method of claim 31 wherein the subthreshold amount is the subthreshold amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment of female sexual dysfunction.

34. The method of any one of claims 27-33 comprising administering 10 mg to 400 mg, e.g., 25 mg to 400 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 400 mg, e.g., 50 mg to 300 mg, e.g., 50 mg to 200 mg, e.g., 50 to 100 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 300 mg, e.g., 100 mg to 200 mg, e.g., 100 mg, 200 mg, 300 mg, or 400 mg, of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

35. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

36. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

37. A pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in combination with a pharmaceutically acceptable diluent or carrier for use in treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

38. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, for treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

39. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

40. A pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in combination with a pharmaceutically acceptable diluent or carrier for use in treating female sexual dysfunction, e.g., for use in any of Method 1 or 1.1-1.31.

41. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

42. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in the manufacture of a medicament for treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

43. A pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in combination with a pharmaceutically acceptable diluent or carrier for use in treatment or prophylaxis of female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

44. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, for treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

45. Use of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in the manufacture of a medicament for treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

46. A pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, substantially free of the corresponding (-) enantiomer, in combination with a pharmaceutically acceptable diluent or carrier for use in treating female sexual dysfunction, e.g., for use in any of Method 2 or 2.1-2.30.

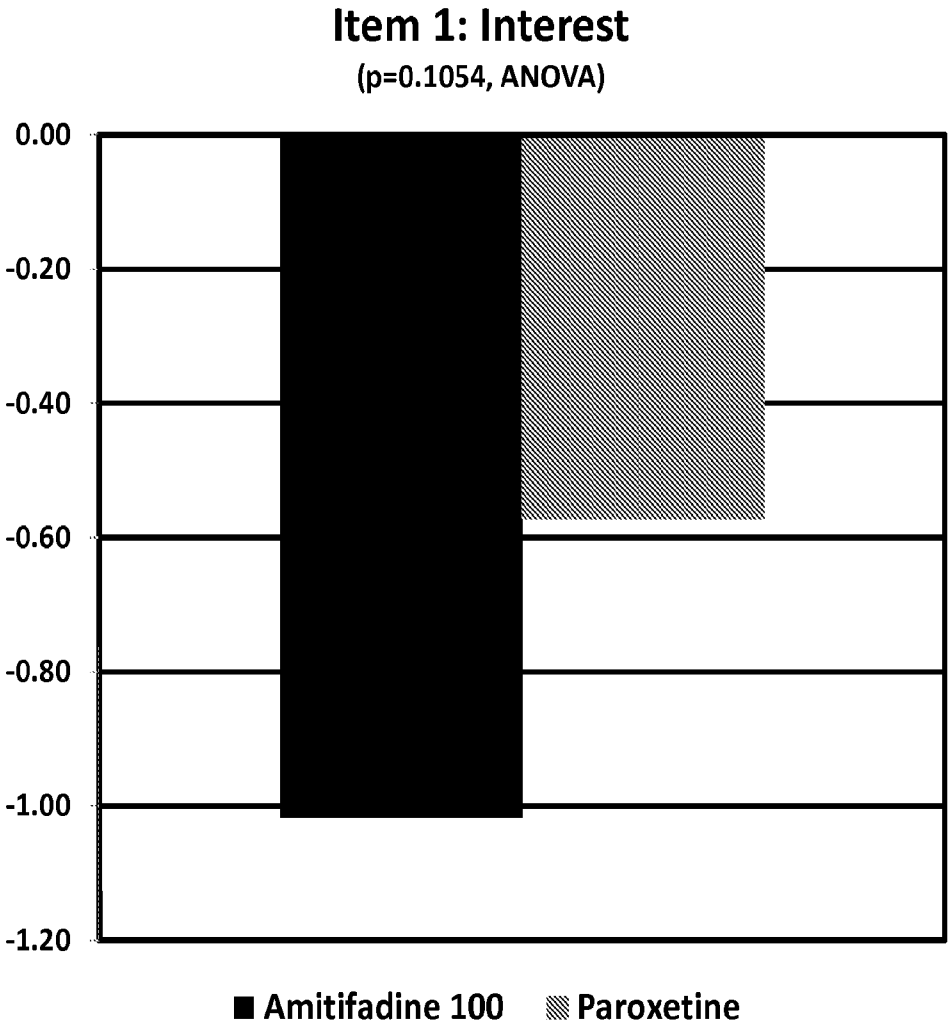

Item 1: Interest
(p=0.1054, ANOVA)
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
Amitifadine 100
Paroxetine

FIGURE 1

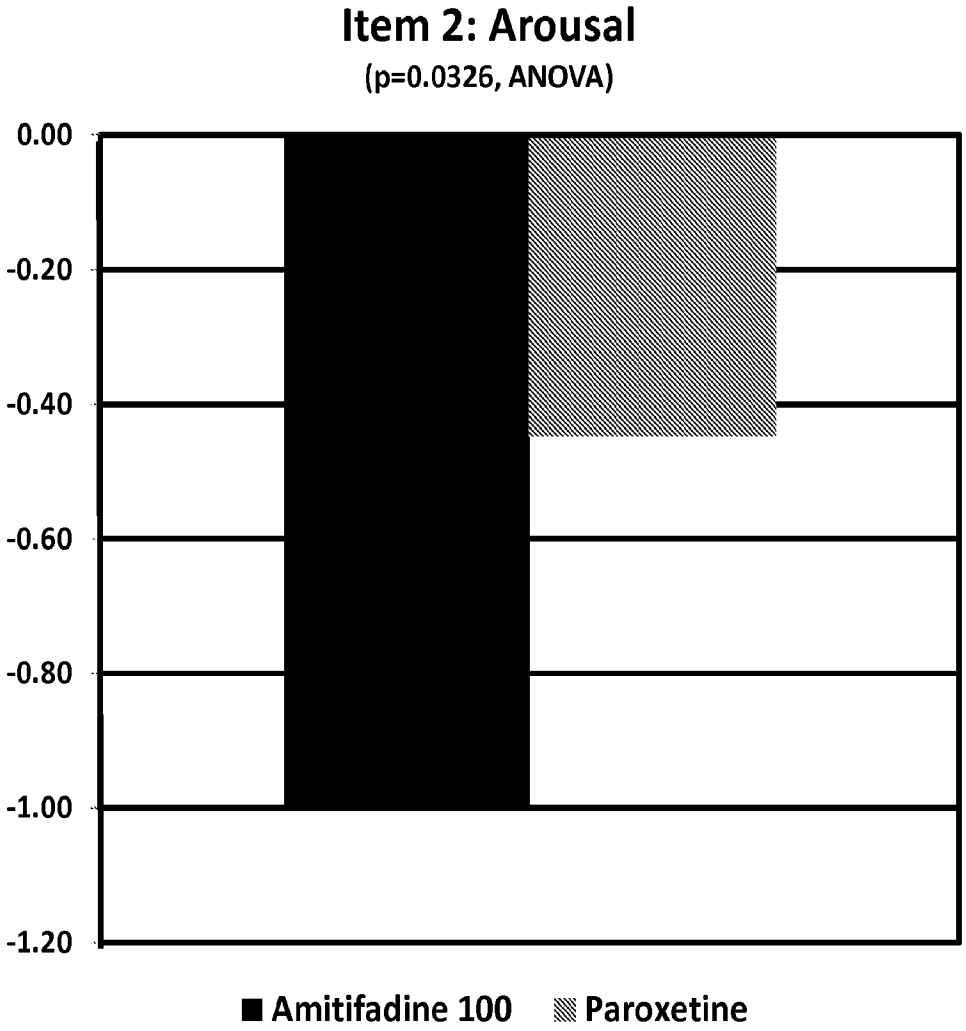

Item 2: Arousal
(p=0.0326, ANOVA)
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
Amitifadine 100
Paroxetine

FIGURE 2

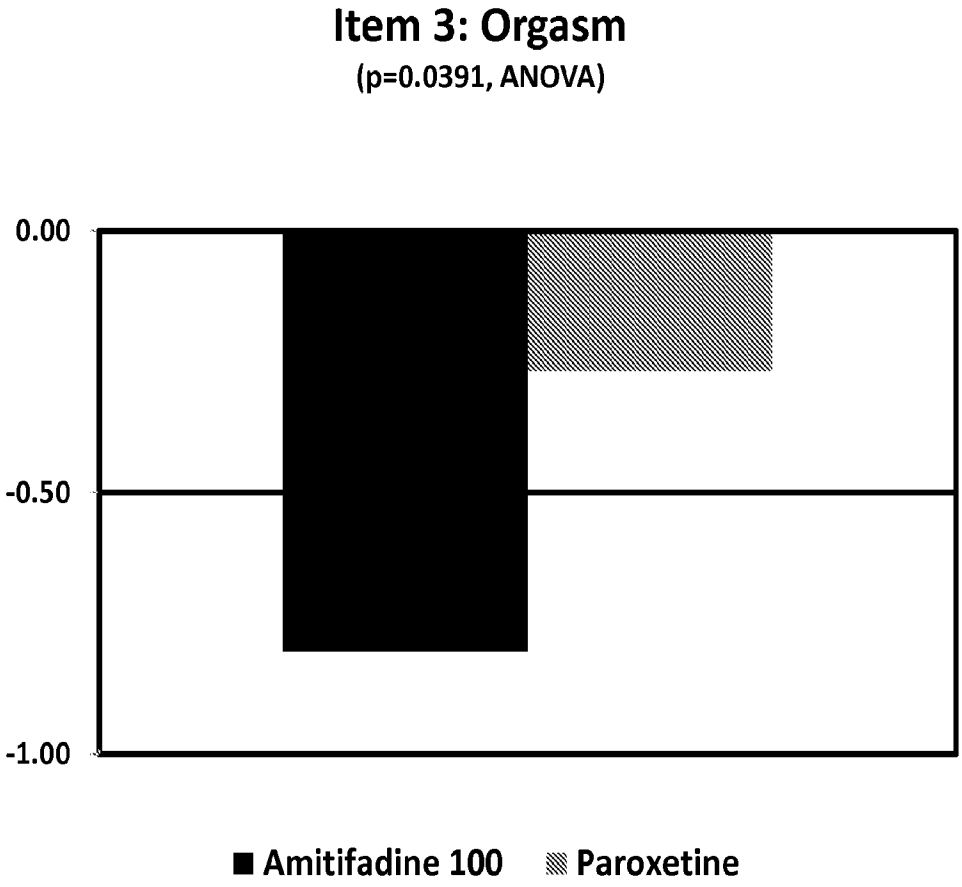

Item 3: Orgasm
(p=0.0391, ANOVA)
0.00
-0.50
-1.00
Amitifadine 100
Paroxetine

FIGURE 3

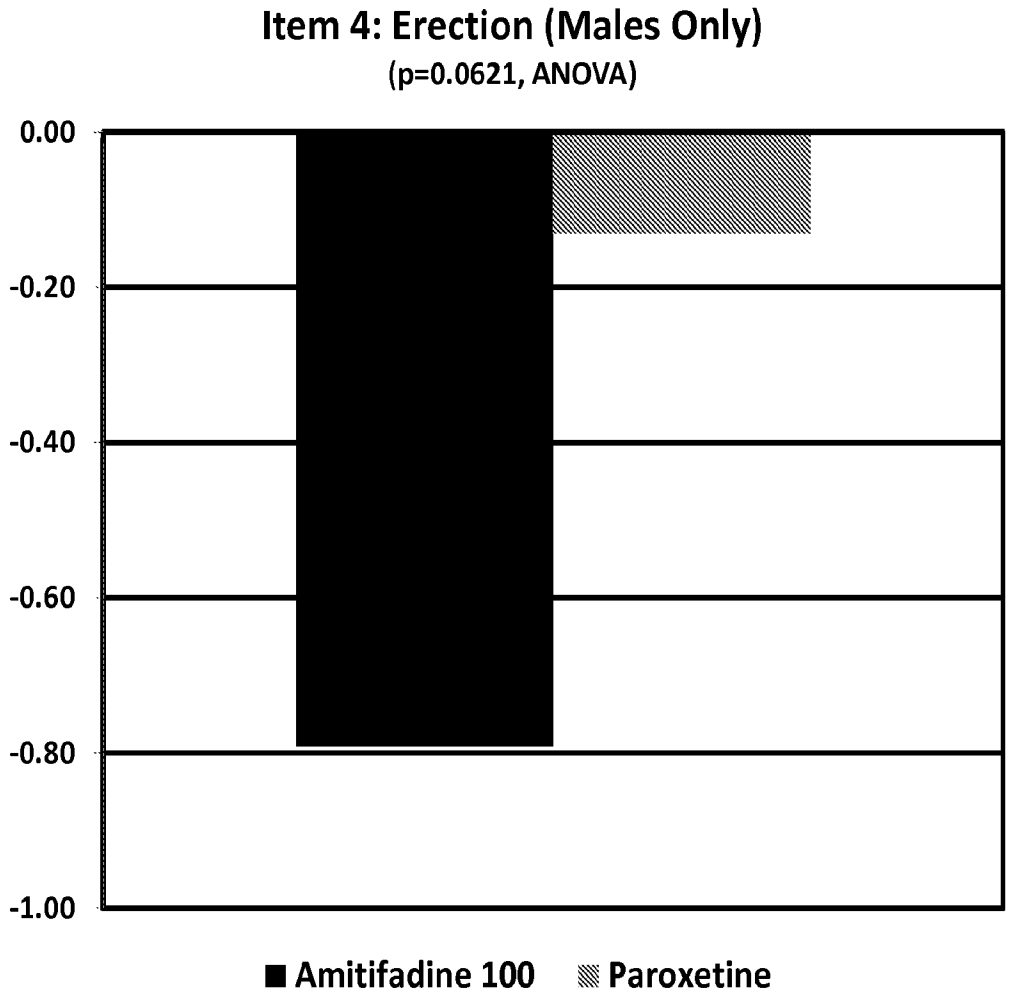

Item 4: Erection (Males Only)
(p=0.0621, ANOVA)
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
Amitifadine 100
Paroxetine

FIGURE 4

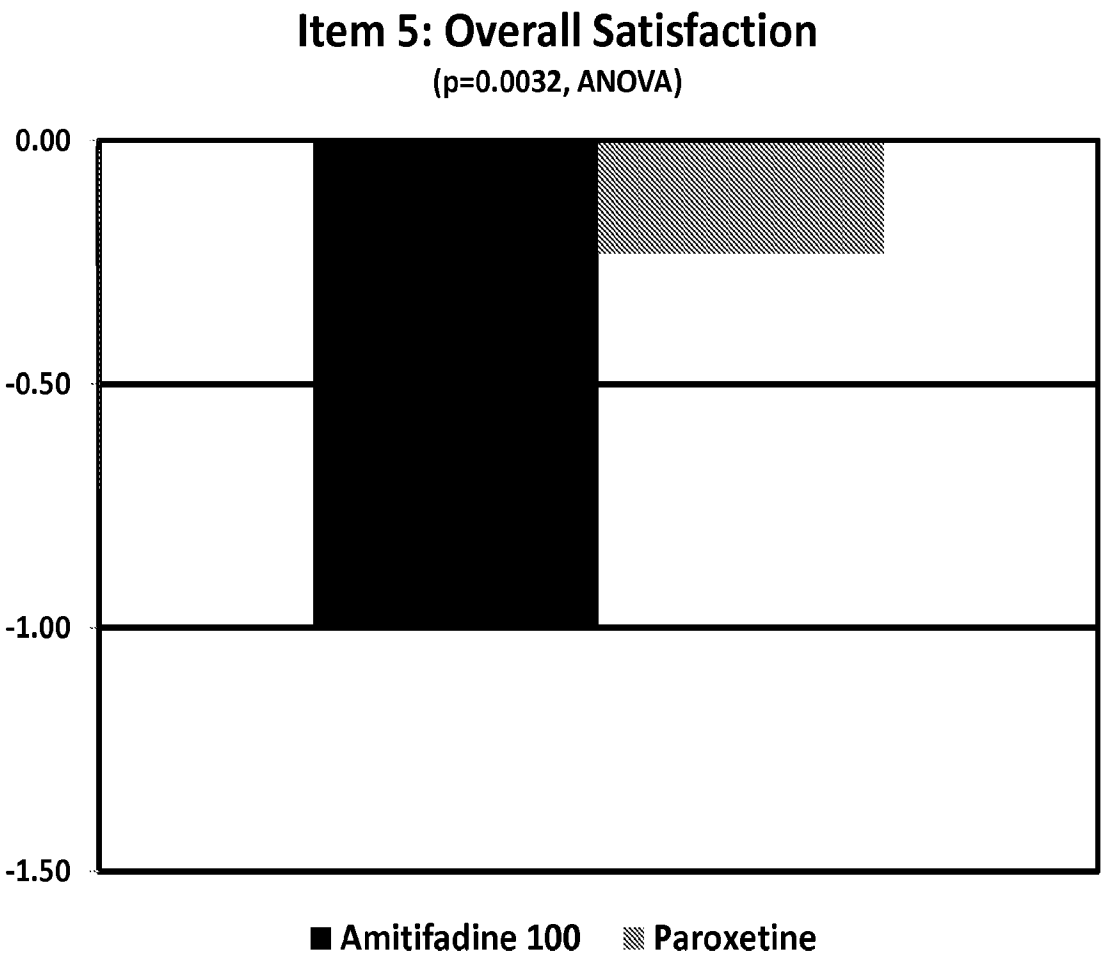

Item 5: Overall Satisfaction
(p=0.0032, ANOVA)
0.00
-0.50
-1.00
-1.50
Amitifadine 100
Paroxetine

FIGURE 5

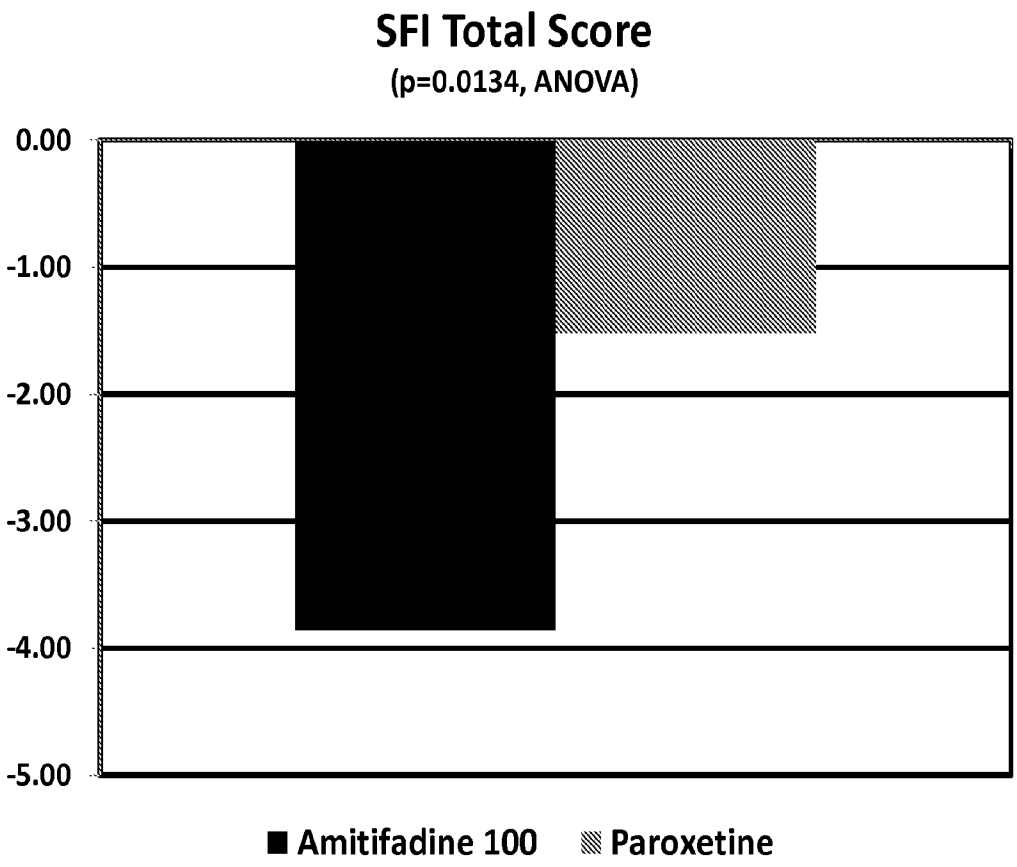

SFI Total Score
(p=0.0134, ANOVA)
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
Amitifadine 100
Paroxetine

FIGURE 6

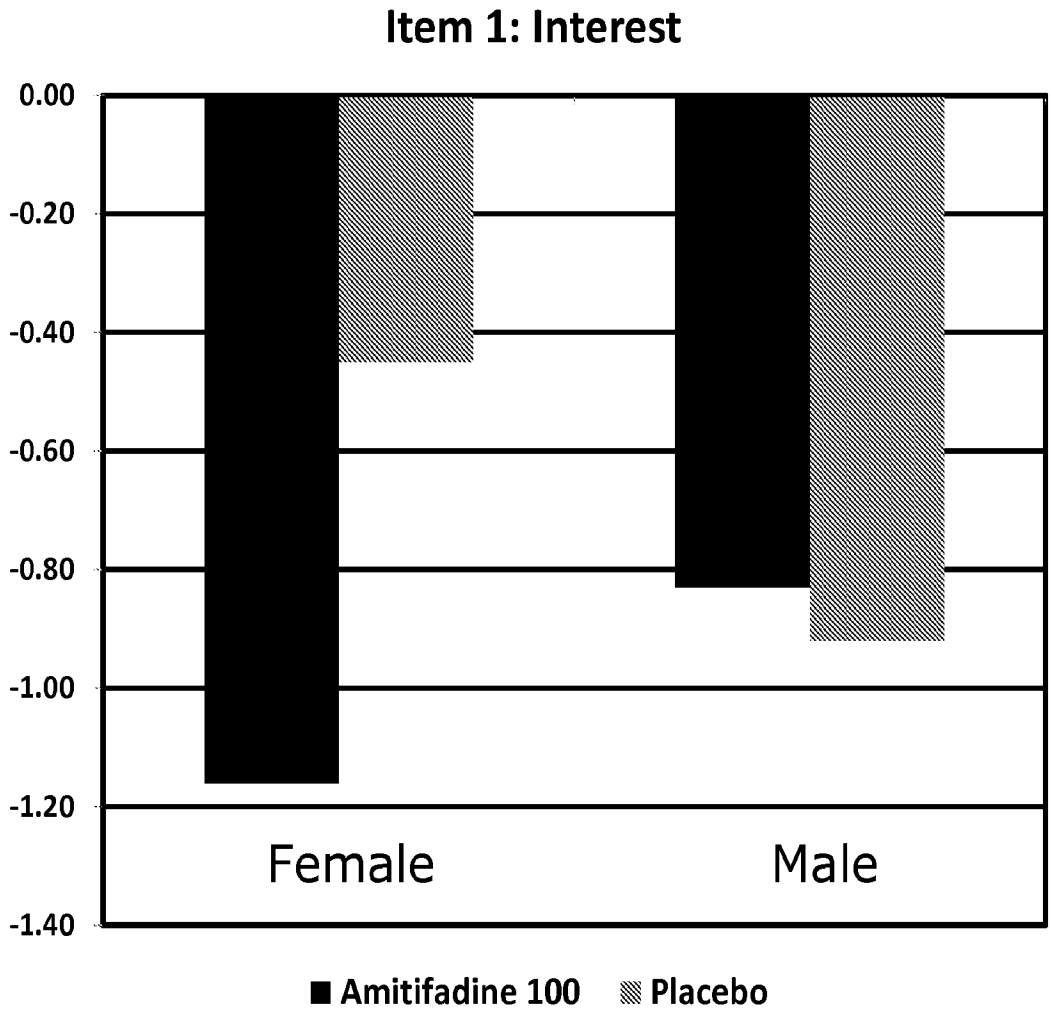

Item 1: Interest
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
-1.40
Female
Male
Amitifadine 100
Placebo

FIGURE 7

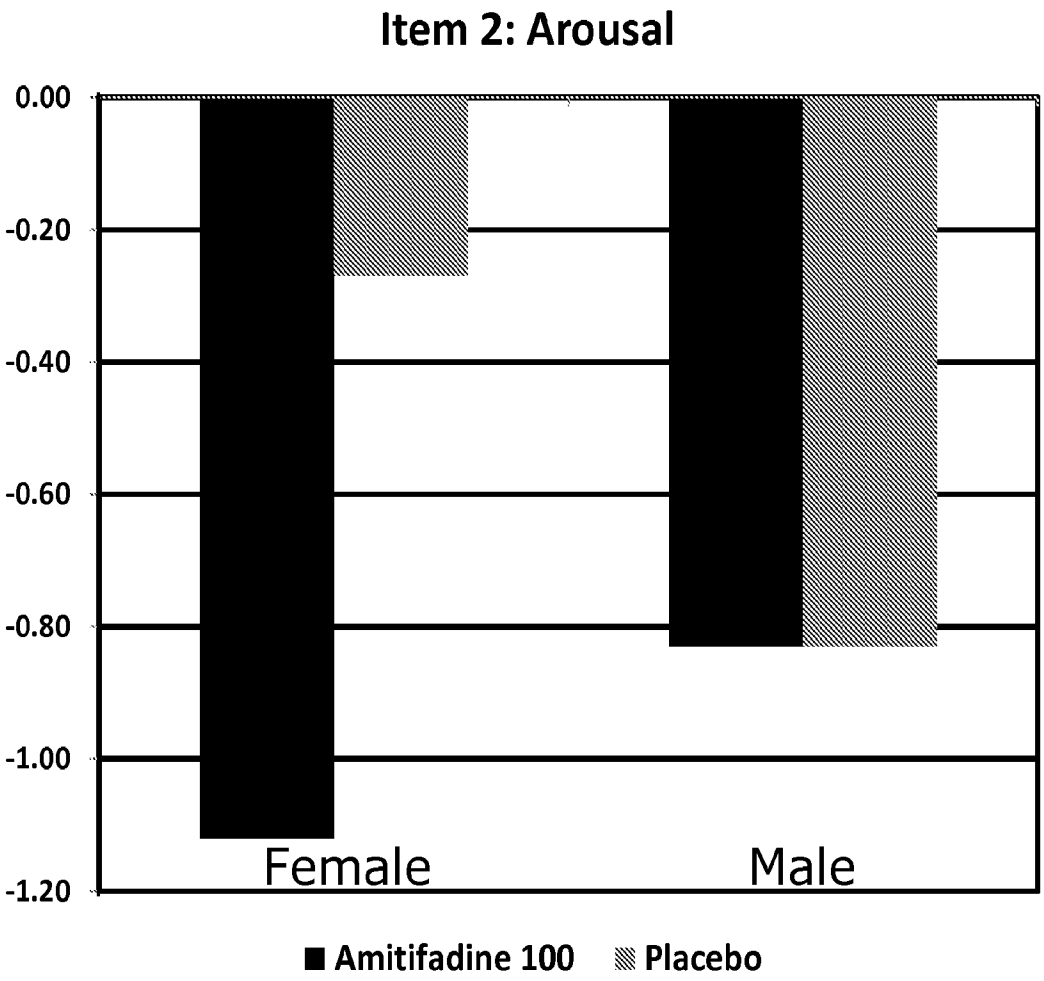

Item 2: Arousal
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
Female
Male
Amitifadine 100
Placebo

FIGURE 8

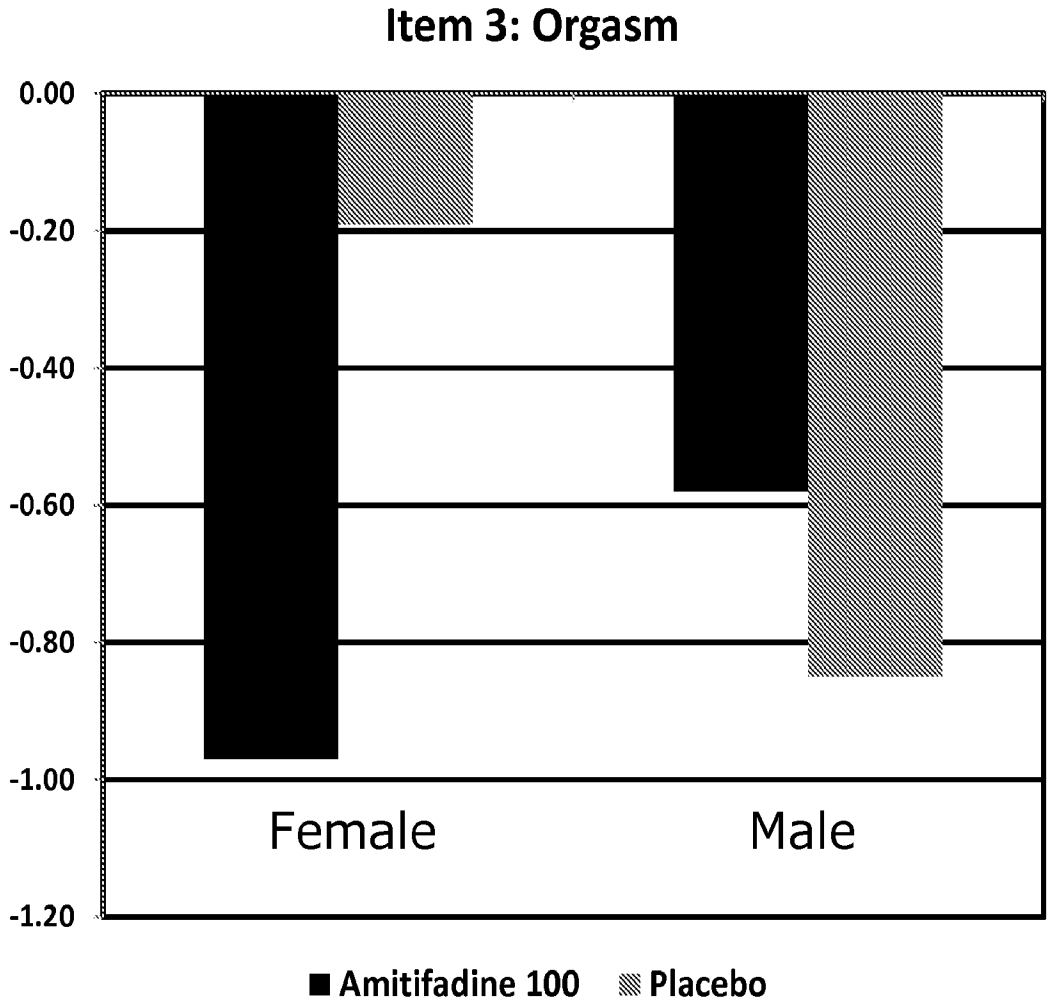

Item 3: Orgasm
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
Female
Male
Amitifadine 100
Placebo

FIGURE 9

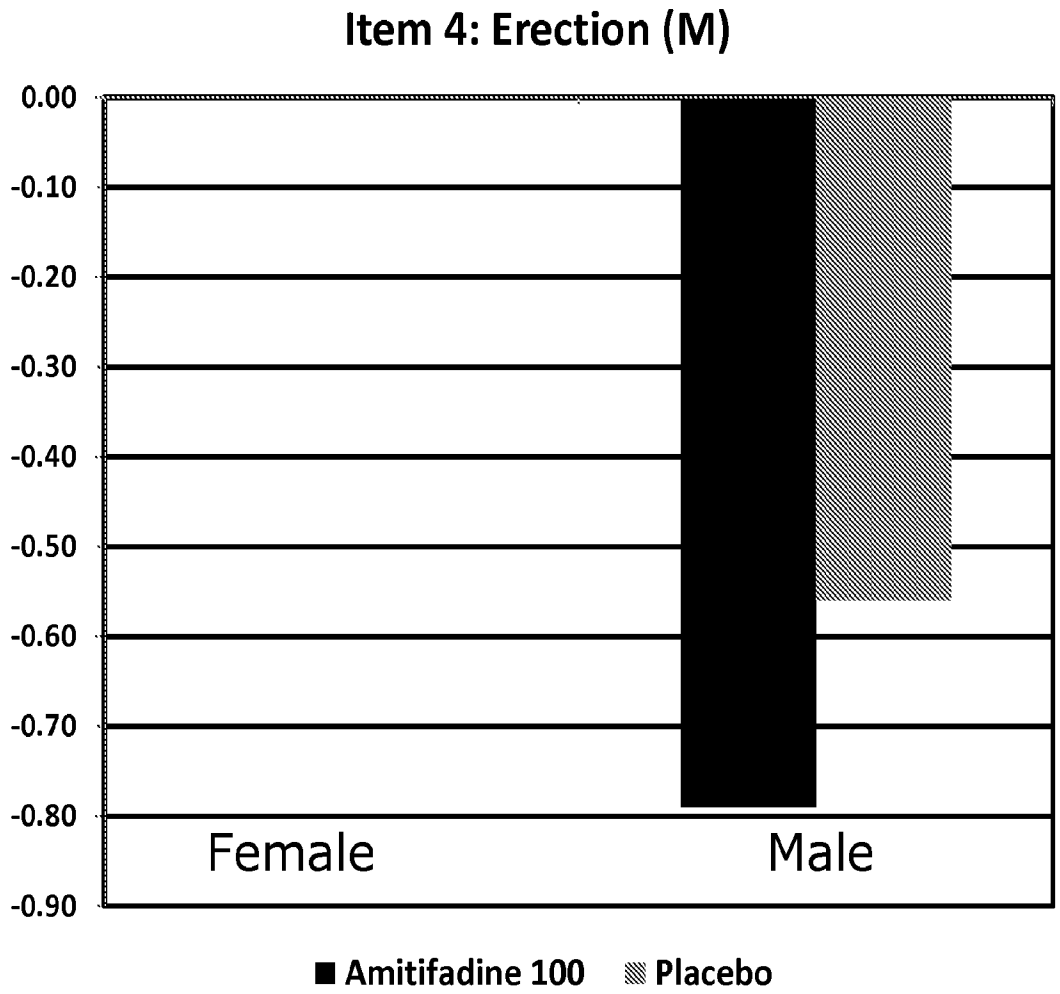

Item 4: Erection (M)
0.00
-0.10
-0.20
-0.30
-0.40
-0.50
-0.60
-0.70
-0.80
-0.90
Female
Male
Amitifadine 100
Placebo

FIGURE 10

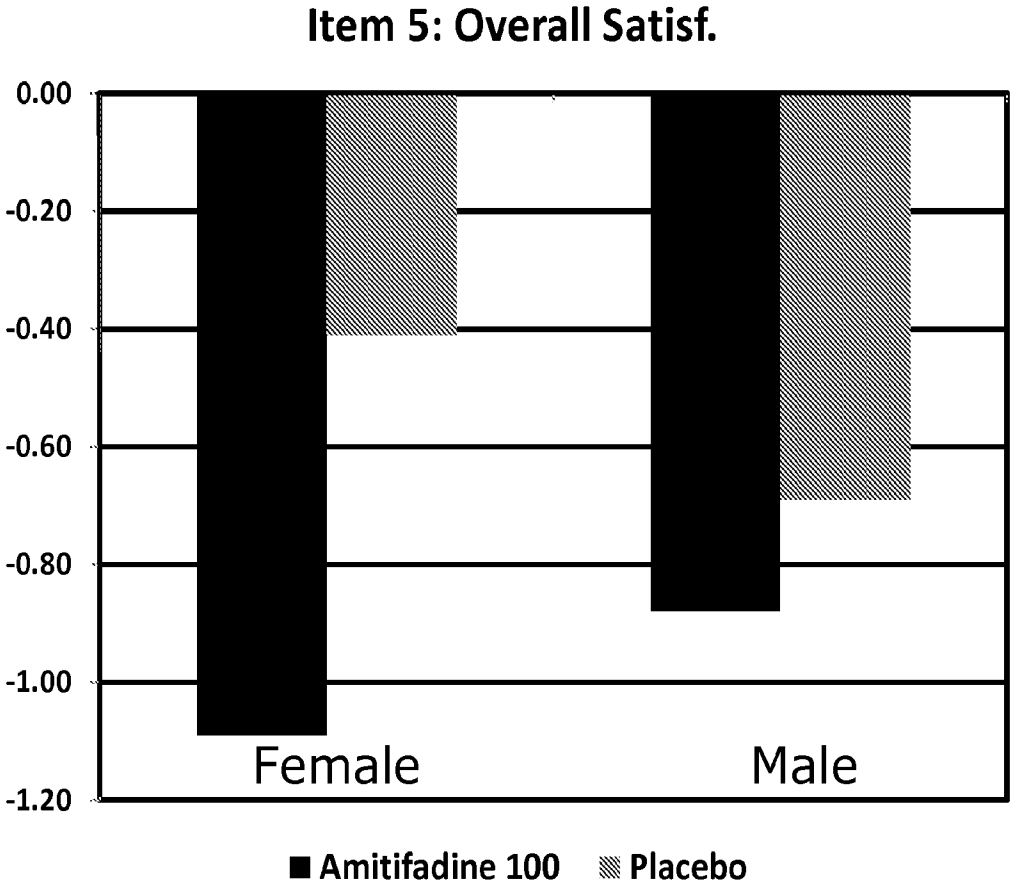

Item 5: Overall Satisf.
0.00
-0.20
-0.40
-0.60
-0.80
-1.00
-1.20
Female
Male
Amitifadine 100
Placebo

FIGURE 11

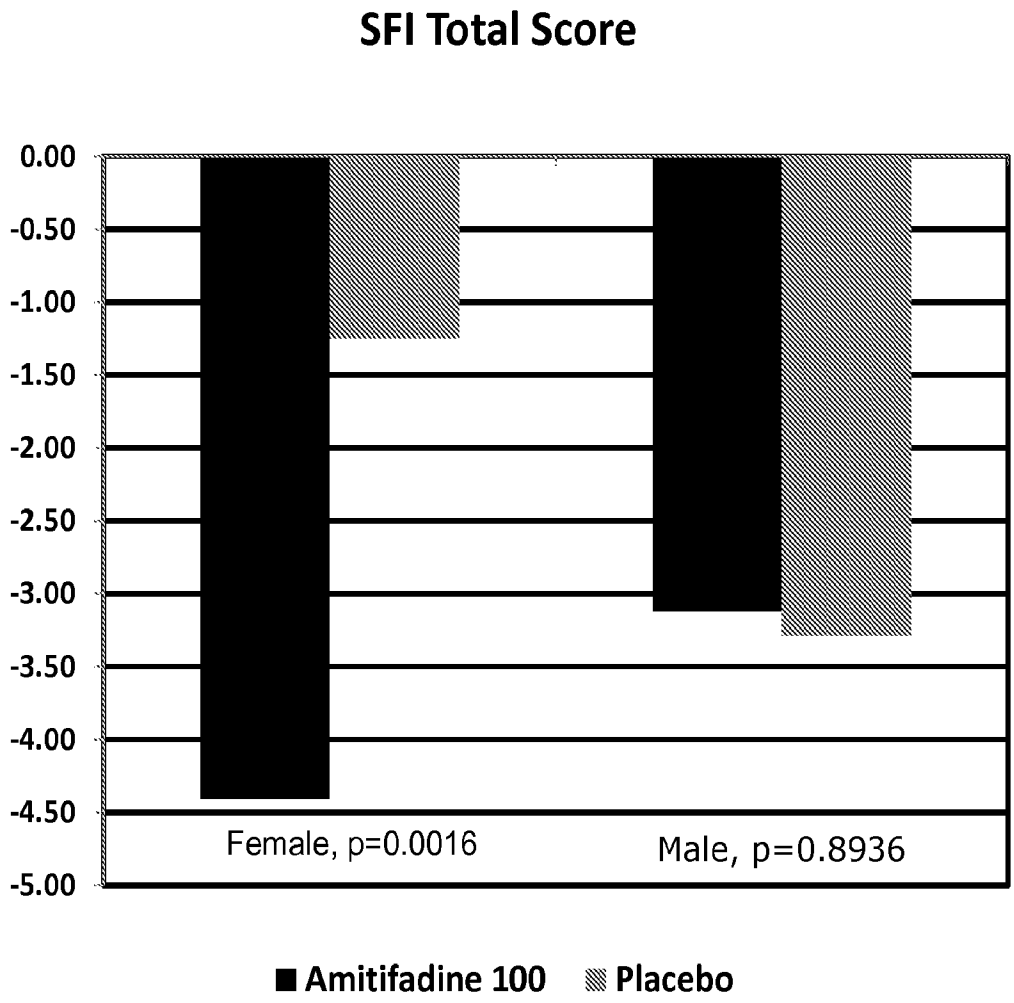

SFI Total Score
0.00
-0.50
-1.00
-1.50
-2.00
-2.50
-3.00
-3.50
-4.00
-4.50
-5.00
Female, p=0.0016
Male, p=0.8936
Amitifadine 100
Placebo

FIGURE 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/65095

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 57/00; A61K 31/67 (2015.01)
CPC - C07D 495/04; C07D 335/06; C07F 9/6561
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
CPC: C07D 495/04; C07D 335/06; C07F 9/6561
IPC (8): A01N 57/00; A61K 31/67 (2015.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/96,100

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Thomson innovation (US Grant , AU Innov , CA App , US App , AU Grant , FR App , EP Grant , AU App , DE Util , EP App , GB App , DE Grant , WO App , CA Grant , DE App , JP App , KR Grant , KR App , Other , JP Util , KR Util , CN Util , JP Grant , CN Grant , CN App , VN Grant , MY Grant , TH Grant),Google, sciencedirect. Terms: azabicyclo* *phenyl s

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Tran et al., 'Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial', Journal of Psychiatric Research 46 (2012) 64-71	1-4, 35-36, 38, 41 and 44
Y	US 2010/0029740 A1 (Bonanomi et al.) 04 February 2010 (04.02.2010) entire document especially	1-4, 35-36, 38, 41 and 44
Y	2008/0045725 (Murry et al.) 21 February 2008 (21.02.2008) entire document especially para [0003]-0027]	1-4, 35-36, 38, 41 and 44
Y	WO 2010/130672 (Bonanomi et al.) 18 November 2010 (18.11.2010) entire document especially abstract; page 1, ln 19 to page 4, ln in 7	1-4, 35-36, 38, 41 and 44
Y	US 2010/0016401 A1 (Aissaoui et al.) 21 January 2010 (21.01.2010) entire document especially para [0058]; [0101]; [0102]-[0336]	1-4, 35-36, 38, 41 and 44
A	US 8,283,474 B2 (Capelli et al.) 09 October 2012 (09.10.2012) entire document	1-4, 35-36, 38, 41 and 44

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2015 (22.03.2015)	07 APR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/65095

Box III: lack of unity:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-4, 35-36, 38, 41 and 44, directed to a method of prophyalaxis or treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane

Group II: Claims 37, 40, 43 and 46, directed to a pharmaceutical composition comprising (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane

Group III: Claims 39, 42, and 45, directed to the manufacture of a medicament using (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special technical features:

The special technical feature of Group I is a method of prophyalaxis or treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane, not required by groups II and III

The special technical feature of Group III is a manufacture of a medicament using (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane, not required by groups I and II

Common technical features:

Groups I- III share the technical feature of treatment of female sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3 .1.0]hexane, in free or pharmaceutically acceptable salt form. Groups II and III share the additional technical feature of method 2 or 2.1-2.30. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being disclosed by the document entitled 'Efficacy and tolerability of the novel triple reuptake inhibitor amitifadine in the treatment of patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial' by Tran et al. (hereinafter 'Tran'). Tran teaches treatment of sexual dysfunction comprising administering a therapeutically effective amount of (+)-1-(3,4-dichlorophenyl)-3- azabicyclo[3 .1.0]hexane (amitifadine), in free or pharmaceutically acceptable salt form (page 65, col 1, para 5, Amitifadine ((1R,5S)-(+)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexane hydrochloride..; page 68, col 2, para 2, ..as predicted (Skolnick, 2005), treatment with amitifadine was not associated with changes in sexual function. Of most interest, patients who had preserved sexual functions at baseline did not experience worsening in their sexual function. This is an important feature of amitifadine since sexual dysfunction has been reported with many existing antidepressants and sexual dysfunction is a cause of non-compliance and early treatment failure), but does not specifically teach treating female sexual dysfunction. Since Tran teaches amitifadine is effective for treating sexual dysfunction, it would have been obvious to one of skill in the art to try for female sexual dysfunction. Tran does not specifically teach the method 2 or 2.1-2.30, but it would have been obvious to one of skill in the art to identify such methods by routine experimentation in an attempt to identify the most effective dosage regimen for improved treatment

Groups I-III, therefore, lack unity under PCT Rule 13.2, because they do not share a same or corresponding special technical feature providing a contribution over the prior art.

Note: claims 5-34 are determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 14/65095

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-34
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
—please see supplemental box —

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-4, 35-36, 38, 41 and 44

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.