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(54) **Title:** NOVEL METHODS

(57) **Abstract:** Provided are novel methods comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof.



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NOVEL METHODS

[0001] This application claims priority to U.S. Provisional Application No. 61/913,886 filed on December 9, 2013, the contents of which are hereby incorporated by reference.

BACKGROUND

[0002] Fragile X-associated disorders are a family of genetic conditions that may affect individuals in a variety of ways. The three fragile X-associated disorders are fragile X syndrome (FXS), fragile X-associated tremor/ataxia syndrome (FXTAS), and fragile X-associated primary ovarian insufficiency (FXPOI). The conditions are all caused by changes in the fragile X mental retardation 1 (FMR1) gene, located on the X chromosome. In most people, the FMR1 gene contains approximately 5-44 repeats of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region.

[0003] Fragile X syndrome (FXS) is the most common inherited form of intellectual disability worldwide. FXS is characterized by an expansion to more than 200 repetitions of the CGG trinucleotide, resulting in loss or significant reduction of expression of the FMR1 gene product, fragile X mental retardation protein (FMRP).

[0004] In addition to their intellectual development disability, individuals with FXS may display associated physical features such as large ears, long face, macrocephaly, and macroorchidism. Individuals with FXS may also exhibit one or more of hyperactivity, impulsivity, multiple anxiety symptoms, repetitive/perseverative stereotypic behaviors, unstable affect, aggression, and self-injurious behavior. Males are generally more severely affected than females when carrying the mutation (heterozygous females may appear phenotypically unaffected, but may suffer reproductive abnormalities).

[0005] FXTAS is caused by a moderate expansion (55-200 repeats; premutation range) of the CGG trinucleotide in the FMR1 gene. FXTAS is an adult onset neurodegenerative disorder, e.g., occurring over 50 years of age. Affected individuals may exhibit one or more of action tremor, Parkinsonism, sensory neuropathy, cognitive dysfunction (e.g., executive impairment and dementia), anxiety, irritability, agitation, hostility, obsessive-compulsiveness, apathy, and depression.

[0006] FXPOI affects women and is also caused by a moderate expansion (55-200 repeats; premutation range) of the CGG trinucleotide in the FMR1 gene. Some women with about 44 to 54 CGG repeats may also have features of FXPOI. Affected women may exhibit intermittent and unpredictable menses, with eventual early cessation. FXPOI may also be associated with late-onset Parkinson-like neurological problems (fragile X-associated tremor ataxia syndrome, or FXTAS) including executive function deficits, tremor, ataxia, neuropathy, and brain atrophy.

[0007] In treating fragile X-associated disorders, such as FXS, it has been observed that while available agents may improve some symptoms, they aggravate others.

[0008] For instance, stimulants, such as methylphenidate and amphetamines, have been used in individuals with FXS. However, concerns about stimulants include risk of abuse, dependency, and diversion as well as potential neurotoxic effects of amphetamines. In addition, individuals with FXS treated with stimulants have reported increased anxiety, irritability, mood lability, perseveration, hyperactivity, and/or aggressive tendencies.

[0009] Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, have also been used in individuals with FXS. It has been reported, however, that in some individuals, especially children, SSRIs caused behavioral activation (increase in activity level that does not include any real change in mood, impulse control, or a change in the child's demeanor or other behaviors), which can aggravate preexisting symptoms of hyperactivity and disinhibited behaviors.

[0010] Aripiprazole has also been tried in individuals with FXS. It has been reported, however, that some individuals with FXS failed treatment predominately due to aggravation of aggressive, perseverative, and irritable behavior.

[0011] Atomoxetine, a selective norepinephrine reuptake inhibitor, has also been tried in individuals with FXS. Compared to stimulants, advantages of atomoxetine may include lack of abuse potential and once-daily dosage. Six trials of atomoxetine in individuals with FXS, however, were unsuccessful, with the majority failing due to aggravation of irritable, moody, and aggressive behaviors.

[0012] Attention-deficit/hyperactivity disorder (ADHD) and anxiety disorders occur together in 25%-33% of patients. However, as discussed above, concerns about treatment with

stimulants include risk of abuse, dependency, and diversion as well as potential neurotoxic effects of amphetamines. In addition, stimulants may exacerbate anxiety.

[0013] Accordingly, there remains a need for methods to treat the manifold symptoms associated with a fragile X-associated disorder such as FXS. There also remains a need for methods to treat ADHD co-morbid with anxiety.

BRIEF SUMMARY

[0014] Provided is a method of treating a fragile X-associated disorder comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof.

[0015] Further provided is a method of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.

[0016] Further provided is a method of treating autism spectrum disorder (ASD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.

[0017] Further provided is a method of treating a fragile X-associated disorder comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient was refractory to a prior course of treatment for the fragile X-associated disorder.

[0018] Further provided is a method of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder.

[0019] 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

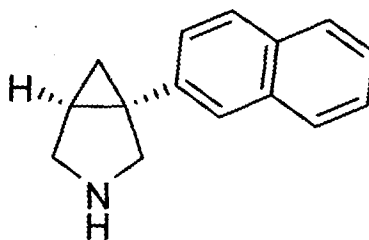
and specific examples, while indicating the preferred embodiment of this disclosure, are intended for purposes of illustration only and are not intended to limit the scope of this disclosure.

DETAILED DESCRIPTION

[0020] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, 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] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, also known as (+)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, is shown as Formula I below.



Formula I

[0023] “(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane” and “(+)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane” are used interchangeably herein.

[0024] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is an unbalanced triple reuptake inhibitor with the most potency towards norepinephrine reuptake (NE), one-sixth as much towards dopamine reuptake (DA), and one-fourteenth as much towards serotonin reuptake (5-HT).

[0025] Although individuals with a fragile X-associated disorder, such as FXS, may exhibit symptoms similar to ADHD, their response to treatment is somewhat different. Thus, while stimulants have been used in individuals with FXS, such treatment may not be optimal because of the sensitivity of individuals with FXS to dopaminergic medications. For instance, individuals with FXS treated with stimulants have shown increased anxiety, irritability, mood

lability, perseveration, hyperactivity, and/or aggressive tendencies. Stimulants also have substance abuse concerns.

[0026] Meanwhile a drug with minimal to no effect on dopamine may not provide optimal treatment for FXS either. For instance, six trials of atomoxetine, a selective norepinephrine reuptake inhibitor, in individuals with FXS, were unsuccessful, with the majority failing due to aggravation of irritable, moody, and aggressive behaviors.

[0027] Compared to atomoxetine, (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane also enhances dopamine function, but without the pronounced dopaminergic activities of stimulants. Thus, in individuals with FXS, the unbalanced norepinephrine-dopamine-serotonin reuptake inhibition profile of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may affect the norepinephrine, dopamine, and serotonin circuitries without causing the increased anxiety, irritability, mood lability, perseveration, hyperactivity, and/or aggressive tendencies that have been seen with stimulants in individuals with FXS and without triggering substance abuse associated with dopamine seen with stimulants. In addition, the multi-functional effects of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may be useful in treating the manifold symptoms associated with a fragile X-associated disorder such as FXS. Further, affecting the norepinephrine, dopamine, and serotonin circuitries with one drug may avoid pharmacologic drug-drug interactions (DDIs). For instance, administering two drugs with different effects on the norepinephrine, dopamine, and/or serotonin circuitries may result in off-target interactions potentially leading to undesirable and unexpected changes in norepinephrine, dopamine, and/or serotonin levels.

[0028] It has been reported that cytochrome P450 enzyme isoforms (CYPs), which catalyze oxidative reactions, account for the metabolism of 75% of all drugs, and in particular, about 80% of drugs cleared by CYPs are metabolized by four CYP isoforms – CYP3A4, CYP2D6, CYP2C9 and CYP2C19. Thus, these four CYPs are potential candidates for DDIs. Physicians consider potential DDIs and metabolic pathway(s) when selecting treatments. (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is primarily metabolized by monoamine oxidase A (MAO A) which may spare the liver and may reduce drug-drug interactions if (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is used in a combination therapy, e.g., with a drug that is metabolized by CYPs, e.g., mavoglurant.

[0029] In individuals having ADHD with co-morbid anxiety, stimulants may exacerbate anxiety. In addition, administering two drugs with different effects on the norepinephrine, dopamine, and/or serotonin circuitries may result in off-target interactions potentially leading to undesirable and unexpected changes in norepinephrine, dopamine, and/or serotonin levels.

[0030] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane enhances dopamine function, but without the pronounced dopaminergic activities of stimulants. In addition, the multi-functional effects of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may be useful in treating ADHD with co-morbid anxiety. Further, affecting the norepinephrine, dopamine, and serotonin circuitries with one drug may avoid pharmacologic drug-drug interactions (DDIs).

[0031] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane may be synthesized as described in U.S. Patent No. 8,461,196 or International Publication No. WO 2013/019271, both of which are incorporated herein by reference in their entirety.

[0032] As used herein, “substantially free of the corresponding (-) enantiomer” means more of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane than the corresponding (-) enantiomer, i.e., (1S,5R)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane. In some embodiments, “substantially free of the corresponding (-) enantiomer” means containing no more than 20% w/w (weight/weight) of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 10% w/w of the corresponding (-) enantiomer, in free or pharmaceutically acceptable salt form, e.g., no more than 5% w/w 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.

[0033] As used herein, “(1R,5S)-1-(naphthalen-2-yl)-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.

[0034] As used herein, “(1R,5S)-1-(naphthalen-2-yl)-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

anhydrides), 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, including, for example, polymorphs, solvates (including hydrates), unsolvated polymorphs (including anhydrides), and conformational polymorphs, as well as mixtures thereof, unless a particular crystalline form is referred to.

[0035] Crystalline and amorphous forms of (1R,5S)-1-(naphthalen-2-yl)-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.

[0036] As used herein, "substantially free of other polymorphic forms" means that the crystalline material contains no more than 10% w/w of any other crystalline form, e.g., no more than 5% w/w of any other crystalline form, no more than 2% w/w of any other crystalline form, e.g., no more than 1% w/w of any other crystalline form.

[0037] (1R,5S)-1-(naphthalen-2-yl)-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*.

[0038] As used herein, the term "patient" includes human or non-human (i.e., animal) patient. In some embodiments, patient encompasses both human and nonhuman. In some embodiments, patient means a nonhuman. In other embodiments, patient means a human.

[0039] 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.

[0040] 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.

[0041] As used herein, “autism spectrum disorder,” includes autistic disorder (classic autism), Asperger’s disorder (Asperger syndrome), pervasive developmental disorder not otherwise specified (PDD-NOS), Rett’s disorder (Rett syndrome), and childhood disintegrative disorder (CDD).

[0042] As used herein, “a patient that was refractory to a prior course of treatment for a fragile-X associated disorder” refers to a patient who has previously been treated one or more times for a fragile-X associated disorder, i.e., a patient that has not responded to a prior course of treatment, that responded in an unsatisfactory manner to a prior course of treatment, that was unable to tolerate a prior course of treatment, and/or that otherwise responded in an unsatisfactory manner to a prior course of treatment. A prior course of treatment may include, but is not limited to, an anti-depressant (e.g., a selective serotonin reuptake inhibitor), a stimulant, and/or an antipsychotic (e.g., a typical and/or atypical antipsychotic). A patient that was refractory to a prior course of treatment for a fragile-X associated disorder may have been refractory for any reason. In some embodiments, a patient that was refractory to a prior course of treatment for a fragile-X associated disorder may have failed to respond or failed to respond sufficiently to a prior course of treatment for the fragile-X associated disorder. In other embodiments, a patient that was refractory to a prior course of treatment for a fragile-X associated disorder may have initially responded to treatment. In some embodiments, a patient that was refractory to a prior course of treatment for a fragile-X associated disorder may have been unable to continue taking the prior course of treatment due to intolerance of the prior course of treatment because of side effects including, but not limited to, increased anxiety, irritability, mood lability, perseveration, hyperactivity, aggressive tendencies, and/or disinhibited behaviors and/or sexual dysfunction, weight gain, insomnia, dry mouth, constipation, nausea and vomiting, dizziness, memory loss, agitation, anxiety, sedation, headache, urinary retention, and/or abdominal pain. An unsatisfactory or failed response may be determined by any means generally used, including patient self-reporting and/or clinical observation.

[0043] ADHD includes three sub-types: predominantly inattentive type, predominantly hyperactive-impulsive type, and combined type.

[0044] Anxiety may be characterized by feelings of tension and worried thoughts. Anxiety disorders may cause recurring intrusive thoughts or concerns. Anxiety disorders include

generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder, phobias, and post-traumatic stress disorder.

[0045] Provided is a method (Method 1) of treating a patient having a fragile X-associated disorder comprising administering to the patient in need thereof a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

[0046] Further provided is Method 1 as follows:

- 1.1 Method 1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 1.2 Method 1 or 1.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 1.3 Method 1, 1.1, or 1.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 1.4 Any of Methods 1 or 1.1-1.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 1.5 Any of Methods 1 or 1.1-1.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 1.6 Any of Methods 1 or 1.1-1.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 1.7 Any of Methods 1 or 1.1-1.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 1.8 Method 1.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.

- 1.9 Method 1.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
- 1.10 Any of Methods 1 or 1.1-1.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.
- 1.11 Any of Methods 1 or 1.1-1.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 1.12 Any of Methods 1 or 1.1-1.11 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 1.13 Any of Methods 1 or 1.1-1.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 1.14 Any of Methods 1 or 1.1-1.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 1.15 Any of Methods 1 or 1.1-1.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 1.16 Any of Methods 1 or 1.1-1.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.

- 1.17 Any of Methods 1 or 1.1-1.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 1.18 Any of Methods 1 or 1.1-1.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.
- 1.19 Any of Methods 1 or 1.1-1.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
- 1.20 Any of Methods 1 or 1.1-1.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
- 1.21 Any of Methods 1 or 1.1-1.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 1.22 Any of Methods 1 or 1.1-1.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 1.23 Any of Methods 1 or 1.1-1.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic

- acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.
- 1.24 Any of Methods 1 or 1.1-1.23 further comprising administering an mGluR5 antagonist.
- 1.25 Method 1.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 1.26 Method 1.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof.
- 1.27 Any of Methods 1 or 1.1-1.26 further comprising administering a GABA-B agonist.
- 1.28 Method 1.27 comprising administering arbaclofen.
- 1.29 Any of Methods 1 or 1.1-1.28 further comprising administering a GABA modulator.
- 1.30 Method 1.29 comprising administering acamprosate.
- 1.31 Any of Methods 1 or 1.1-1.30 further comprising administering minocycline.
- 1.32 Any of Methods 1 or 1.1-1.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 1.33 Any of Methods 1 or 1.1-1.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 1.34 Method 1.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 1.35 Method 1.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 1.36 Any of Methods 1 or 1.1-1.35 wherein the fragile X-associated disorder is fragile X syndrome (FXS).
- 1.37 Any of Methods 1 or 1.1-1.35 wherein the fragile X-associated disorder is fragile X-associated tremor/ataxia syndrome (FXTAS).
- 1.38 Any of Methods 1 or 1.1-1.35 wherein the fragile X-associated disorder is fragile X-associated primary ovarian insufficiency (FXPOI).
- 1.39 Any of Methods 1 or 1.1-1.35 wherein the fragile X-associated disorder is associated with an expansion to 40, e.g., 44 or more, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.
- 1.40 Any of Methods 1 or 1.1-1.39 wherein the treatment improves one or more symptoms associated with the fragile X-associated disorder.
- 1.41 Method 1.40 wherein the one or more symptoms comprise one or more of cognitive impairment, anxiety, hyperactivity, impulsivity, repetitive/perseverative stereotypic behaviors, unstable affect, aggression, and self-injurious behavior.

[0047] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating a patient having a fragile X-associated disorder, e.g., for use in Method 1, e.g., Methods 1.1-1.41.

[0048] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 a patient having a fragile X-associated disorder, e.g., for use in Method 1, e.g., Methods 1.1-1.41.

[0049] Also provided is a method (Method 2) of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.

[0050] Further provided is Method 2 as follows:

- 2.1 Method 2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 2.2 Method 2 or 2.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 2.3 Method 2, 2.1, or 2.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 2.4 Any of Methods 2 or 2.1-2.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 2.5 Any of Methods 2 or 2.1-2.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 2.6 Any of Methods 2 or 2.1-2.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 2.7 Any of Methods 2 or 2.1-2.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 2.8 Method 2.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.

- 2.9 Method 2.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
- 2.10 Any of Methods 2 or 2.1-2.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.
- 2.11 Any of Methods 2 or 2.1-2.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 2.12 Any of Methods 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 2.13 Any of Methods 2 or 2.1-2.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 2.14 Any of Methods 2 or 2.1-2.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 2.15 Any of Methods 2 or 2.1-2.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 2.16 Any of Methods 2 or 2.1-2.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.

- 2.17 Any of Methods 2 or 2.1-2.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 2.18 Any of Methods 2 or 2.1-2.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.
- 2.19 Any of Methods 2 or 2.1-2.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
- 2.20 Any of Methods 2 or 2.1-2.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
- 2.21 Any of Methods 2 or 2.1-2.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 2.22 Any of Methods 2 or 2.1-2.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 2.23 Any of Methods 2 or 2.1-2.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic

- acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.
- 2.24 Any of Methods 2 or 2.1-2.23 further comprising administering an mGluR5 antagonist.
- 2.25 Method 2.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 2.26 Method 2.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof.
- 2.27 Any of Methods 2 or 2.1-2.26 further comprising administering a GABA-B agonist.
- 2.28 Method 2.27 comprising administering arbaclofen.
- 2.29 Any of Methods 2 or 2.1-2.28 further comprising administering a GABA modulator.
- 2.30 Method 2.29 comprising administering acamprosate.
- 2.31 Any of methods 2 or 2.1-2.30 further comprising administering minocycline.
- 2.32 Any of Methods 2 or 2.1-2.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 2.33 Any of Methods 2 or 2.1-2.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 2.34 Method 2.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 2.35 Method 2.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 2.36 Any of Methods 2 or 2.1-2.35 wherein the fragile X-associated disorder is fragile X syndrome (FXS).
- 2.37 Any of Methods 2 or 2.1-2.35 wherein the fragile X-associated disorder is fragile X-associated tremor/ataxia syndrome (FXTAS).
- 2.38 Any of Methods 2 or 2.1-2.35 wherein the fragile X-associated disorder is fragile X-associated primary ovarian insufficiency (FXPOI).
- 2.39 Any of Methods 2 or 2.1-2.35 wherein the fragile X-associated disorder is associated with an expansion to 40, e.g., 44 or more, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.

[0051] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating attention-deficit/hyperactivity disorder (ADHD) in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 2, e.g., Methods 2.1-2.39.

[0052] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 attention-deficit/hyperactivity disorder (ADHD) in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 2, e.g., Methods 2.1-2.39.

[0053] Also provided is a method (Method 3) of treating autism spectrum disorder (ASD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-

azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.

[0054] Further provided is Method 3 as follows:

- 3.1 Method 3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 3.2 Method 3 or 3.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 3.3 Method 3, 3.1, or 3.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 3.4 Any of Methods 3 or 3.1-3.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 3.5 Any of Methods 3 or 3.1-3.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 3.6 Any of Methods 3 or 3.1-3.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 3.7 Any of Methods 3 or 3.1-3.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 3.8 Method 3.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
- 3.9 Method 3.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
- 3.10 Any of Methods 3 or 3.1-3.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.

- 3.11 Any of Methods 3 or 3.1-3.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 3.12 Any of Methods 3 or 3.1-3.11 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 3.13 Any of Methods 3 or 3.1-3.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 3.14 Any of Methods 3 or 3.1-3.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 3.15 Any of Methods 3 or 3.1-3.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 3.16 Any of Methods 3 or 3.1-3.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.
- 3.17 Any of Methods 3 or 3.1-3.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 3.18 Any of Methods 3 or 3.1-3.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.

- 3.19 Any of Methods 3 or 3.1-3.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
- 3.20 Any of Methods 3 or 3.1-3.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
- 3.21 Any of Methods 3 or 3.1-3.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 3.22 Any of Methods 3 or 3.1-3.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 3.23 Any of Methods 3 or 3.1-3.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filizole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.

- 3.24 Any of Methods 3 or 3.1-3.23 further comprising administering an mGluR5 antagonist.
- 3.25 Method 3.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 3.26 Method 3.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof.
- 3.27 Any of Methods 3 or 3.1-3.26 further comprising administering a GABA-B agonist.
- 3.28 Method 3.27 comprising administering arbaclofen.
- 3.29 Any of Methods 3 or 3.1-3.28 further comprising administering a GABA modulator.
- 3.30 Method 3.29 comprising administeringacamprosate.
- 3.31 Any of Methods 3 or 3.1-3.30 further comprising administering minocycline.
- 3.32 Any of Methods 3 or 3.1-3.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 3.33 Any of Methods 3 or 3.1-3.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 3.34 Method 3.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 3.35 Method 3.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than

about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 3.36 Any of Methods 3 or 3.1-3.35 wherein the fragile X-associated disorder is fragile X syndrome (FXS).
- 3.37 Any of Methods 3 or 3.1-3.35 wherein the fragile X-associated disorder is fragile X-associated tremor/ataxia syndrome (FXTAS).
- 3.38 Any of Methods 3 or 3.1-3.35 wherein the fragile X-associated disorder is fragile X-associated primary ovarian insufficiency (FXPOI).
- 3.39 Any of Methods 3 or 3.1-3.35 wherein the fragile X-associated disorder is associated with an expansion to 40, e.g., 44 or more, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.

[0055] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating autism spectrum disorder in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 3, e.g., Methods 3.1-3.39.

[0056] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 autism spectrum disorder in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 3, e.g., Methods 3.1-3.39.

[0057] Also provided is a method (Method 4) of treating a patient having a fragile X-associated disorder comprising administering to the patient in need thereof a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, wherein the patient was refractory to a prior course of treatment for the fragile X-associated disorder.

[0058] Further provided is Method 4 as follows:

- 4.1 Method 4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 4.2 Method 4 or 4.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 4.3 Method 4, 4.1, or 4.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 4.4 Any of Methods 4 or 4.1-4.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 4.5 Any of Methods 4 or 4.1-4.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 4.6 Any of Methods 4 or 4.1-4.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 4.7 Any of Methods 4 or 4.1-4.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 4.8 Method 4.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
- 4.9 Method 4.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
- 4.10 Any of Methods 4 or 4.1-4.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.
- 4.11 Any of Methods 4 or 4.1-4.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 4.12 Any of Methods 4 or 4.1-4.11 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 4.13 Any of Methods 4 or 4.1-4.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 4.14 Any of Methods 4 or 4.1-4.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 4.15 Any of Methods 4 or 4.1-4.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt forms.
- 4.16 Any of Methods 4 or 4.1-4.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.
- 4.17 Any of Methods 4 or 4.1-4.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 4.18 Any of Methods 4 or 4.1-4.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.
- 4.19 Any of Methods 4 or 4.1-4.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
- 4.20 Any of Methods 4 or 4.1-4.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.

- 4.21 Any of Methods 4 or 4.1-4.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 4.22 Any of Methods 4 or 4.1-4.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 4.23 Any of Methods 4 or 4.1-4.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.
- 4.24 Any of Methods 4 or 4.1-4.23 further comprising administering an mGluR5 antagonist.
- 4.25 Method 4.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 4.26 Method 4.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof

- 4.27 Any of Methods 4 or 4.1-4.26 further comprising administering a GABA-B agonist.
- 4.28 Method 4.27 comprising administering arbaclofen.
- 4.29 Any of Methods 4 or 4.1-4.28 further comprising administering a GABA modulator.
- 4.30 Method 4.29 comprising administering acamprosate.
- 4.31 Any of Methods 4 or 4.1-4.30 further comprising administering minocycline.
- 4.32 Any of Methods 4 or 4.1-4.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 4.33 Any of Methods 4 or 4.1-4.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 4.34 Method 4.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 4.35 Method 4.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 4.36 Any of Methods 4 or 4.1-4.35 wherein the fragile X-associated disorder is fragile X syndrome (FXS).
- 4.37 Any of Methods 4 or 4.1-4.35 wherein the fragile X-associated disorder is fragile X-associated tremor/ataxia syndrome (FXTAS).
- 4.38 Any of Methods 4 or 4.1-4.35 wherein the fragile X-associated disorder is fragile X-associated primary ovarian insufficiency (FXPOI).
- 4.39 Any of Methods 4 or 4.1-4.35 wherein the fragile X-associated disorder is associated with an expansion to 40, e.g., 44 or more, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.
- 4.40 Any of Methods 4 or 4.1-4.39, wherein the treatment improves one or more symptoms associated with the fragile X-associated disorder.
- 4.41 Method 4.41 wherein the one or more symptoms comprise one or more of cognitive impairment, anxiety, hyperactivity, impulsivity, repetitive/perseverative stereotypic behaviors, unstable affect, aggression, and self-injurious behavior.

[0059] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating a patient having a fragile X-associated disorder, wherein the patient was refractory to a prior course of treatment for the fragile X-associated disorder, e.g., for use in Method 4, e.g., Methods 4.1-4.41.

[0060] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 a patient having a fragile X-associated disorder, wherein the patient was refractory to a prior course of treatment for the fragile X-associated disorder, e.g., for use in Method 4, e.g., Methods 4.1-4.41.

[0061] Also provided is a method (Method 5) of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder.

[0062] Further provided is Method 5 as follows:

- 5.1 Method 5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 5.2 Method 5 or 5.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 5.3 Method 5, 5.1 or 5.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 5.4 Any of Methods 5 or 5.1-5.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 5.5 Any of Methods 5 or 5.1-5.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 5.6 Any of Methods 5 or 5.1-5.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 5.7 Any of Methods 5 or 5.1-5.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 5.8 Method 5.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
- 5.9 Method 5.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.
- 5.10 Any of Methods 5 or 5.1-5.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.
- 5.11 Any of Methods 5 or 5.1-5.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 5.12 Any of Methods 5 or 5.1-5.11 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 5.13 Any of Methods 5 or 5.1-5.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 5.14 Any of Methods 5 or 5.1-5.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 5.15 Any of Methods 5 or 5.1-5.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 5.16 Any of Methods 5 or 5.1-5.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.
- 5.17 Any of Methods 5 or 5.1-5.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 5.18 Any of Methods 5 or 5.1-5.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.
- 5.19 Any of Methods 5 or 5.1-5.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.

- 5.20 Any of Methods 5 or 5.1-5.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
- 5.21 Any of Methods 5 or 5.1-5.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 5.22 Any of Methods 5 or 5.1-5.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 5.23 Any of Methods 5 or 5.1-5.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.
- 5.24 Any of Methods 5 or 5.1-5.23 further comprising administering an mGluR5 antagonist.

- 5.25 Method 5.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 5.26 Method 5.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof
- 5.27 Any of Methods 5 or 5.1-5.26 further comprising administering a GABA-B agonist.
- 5.28 Method 5.27 comprising administering arbaclofen.
- 5.29 Any of Methods 5 or 5.1-5.28 further comprising administering a GABA modulator.
- 5.30 Method 5.29 comprising administering acamprosate.
- 5.31 Any of Methods 5 or 5.1-5.30 further comprising administering minocycline.
- 5.32 Any of Methods 5 or 5.1-5.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 5.33 Any of Methods 5 or 5.1-5.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 5.34 Method 5.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 5.35 Method 5.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%,

e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 5.36 Any of Methods 5 or 5.1-5.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X syndrome (FXS).
- 5.37 Any of Methods 5 or 5.1-5.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated tremor/ataxia syndrome (FXTAS).
- 5.38 Any of Methods 5 or 5.1-5.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated primary ovarian insufficiency (FXPOI).
- 5.39 Any of Methods 5 or 5.1-5.35 wherein the patient has a fragile X-associated disorder, e.g., a fragile X-associated disorder associated with an expansion to 40, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.
- 5.40 Any of Methods 5 or 5.1-5.39 wherein the ADHD is predominantly inattentive type.
- 5.41 Any of Methods 5 or 5.1-5.39 wherein the ADHD is predominantly hyperactive-impulsive type.
- 5.42 Any of Methods 5 or 5.1-5.39 wherein the ADHD is combined type.

[0063] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating attention-deficit/hyperactivity disorder (ADHD) wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 5, e.g., Methods 5.1-5.42.

[0064] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 attention-deficit/hyperactivity disorder (ADHD) wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 5, e.g., Methods 5.1-5.42.

[0065] Also provided is a method (Method 6) of treating an autism spectrum disorder comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder.

[0066] Further provided is Method 6 as follows:

- 6.1 Method 6 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
- 6.2 Method 6 or 6.1 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
- 6.3 Method 6, 6.1 or 6.2 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
- 6.4 Any of Methods 6 or 6.1-6.3 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 6.5 Any of Methods 6 or 6.1-6.4 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 6.6 Any of Methods 6 or 6.1-6.5 wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
- 6.7 Any of Methods 6 or 6.1-6.6 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
- 6.8 Method 6.7 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
- 6.9 Method 6.8 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.

- 6.10 Any of Methods 6 or 6.1-6.9 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is crystalline.
- 6.11 Any of Methods 6 or 6.1-6.10 comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 6.12 Any of Methods 6 or 6.1-6.11 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 6.13 Any of Methods 6 or 6.1-6.11 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 6.14 Any of Methods 6 or 6.1-6.11 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 6.15 Any of Methods 6 or 6.1-6.10 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
- 6.16 Any of Methods 6 or 6.1-6.15 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.
- 6.17 Any of Methods 6 or 6.1-6.16 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.
- 6.18 Any of Methods 6 or 6.1-6.17 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.

- 6.19 Any of Methods 6 or 6.1-6.18 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
- 6.20 Any of Methods 6 or 6.1-6.19 comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
- 6.21 Any of Methods 6 or 6.1-6.20 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
- 6.22 Any of Methods 6 or 6.1-6.21 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
- 6.23 Any of Methods 6 or 6.1-6.22 wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol, methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filizole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.

- 6.24 Any of Methods 6 or 6.1-6.23 further comprising administering an mGluR5 antagonist.
- 6.25 Method 6.24 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
- 6.26 Method 6.25 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof
- 6.27 Any of Methods 6 or 6.1-6.26 further comprising administering a GABA-B agonist.
- 6.28 Method 6.27 comprising administering arbaclofen.
- 6.29 Any of Methods 6 or 6.1-6.28 further comprising administering a GABA modulator.
- 6.30 Method 6.29 comprising administering acamprosate.
- 6.31 Any of Methods 6 or 6.1-6.30 further comprising administering minocycline.
- 6.32 Any of Methods 6 or 6.1-6.31 further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
- 6.33 Any of Methods 6 or 6.1-6.32 wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
- 6.34 Method 6.33 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
- 6.35 Method 6.34 wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than

about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

- 6.36 Any of Methods 6 or 6.1-6.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X syndrome (FXS).
- 6.37 Any of Methods 6 or 6.1-6.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated tremor/ataxia syndrome (FXTAS).
- 6.38 Any of Methods 6 or 6.1-6.35 wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated primary ovarian insufficiency (FXPOI).
- 6.39 Any of Methods 6 or 6.1-6.35 wherein the patient has a fragile X-associated disorder, e.g., a fragile X-associated disorder associated with an expansion to 40, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.
- 6.40 Any of Methods 6 or 6.1-6.39 wherein the patient has autistic disorder.
- 6.41 Any of Methods 6 or 6.1-6.39 wherein the patient has Asperger's disorder (Asperger syndrome).
- 6.42 Any of Methods 6 or 6.1-6.39 wherein the patient has pervasive developmental disorder not otherwise specified (PDD-NOS).
- 6.43 Any of Methods 6 or 6.1-6.39 wherein the patient has Rett's disorder (Rett syndrome).
- 6.44 Any of Methods 6 or 6.1-6.39 wherein the patient has childhood disintegrative disorder (CDD).

[0067] Also provided is use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating an autism spectrum disorder wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 6, e.g., Methods 6.1-6.44.

[0068] Also provided is a pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 an autism spectrum disorder wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 6, e.g., Methods 6.1-6.44.

[0069] Any of the preceding methods, e.g., Method 1, e.g., Methods 1.1-1.41, or, e.g., Method 2, e.g., Methods 2.1-2.39, or, e.g., Method 3, e.g., Method 3.1-3.39, or, e.g., Method 4, e.g., Methods 4.1-4.41, or, e.g., Method 5, e.g., Method 5.1-5.42, or, e.g., Method 6, e.g., 6.1-6.44, or any of the preceding uses or pharmaceutical compositions wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is different, e.g., lower, than the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, administered to a patient without a fragile X-associated disorder, e.g., fragile X syndrome. In some embodiments, provided is Method 2, e.g., Methods 2.1-2.39, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to treat attention-deficit/hyperactivity disorder (ADHD) in a patient with a fragile X-associated disorder, e.g., fragile X syndrome (FXS), is different, e.g., lower, than the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, administered to treat attention-deficit/hyperactivity disorder (ADHD) in a patient without a fragile X-associated disorder, e.g., fragile X syndrome.

[0070] Any of the preceding methods, e.g., Method 1, e.g., Methods 1.1-1.41, or, e.g., Method 2, e.g., Methods 2.1-2.39, or, e.g., Method 3, e.g., Method 3.1-3.39, or, e.g., Method 4, e.g., Methods 4.1-4.41, or, e.g., Method 5, e.g., Method 5.1-5.42, or, e.g., Method 6, e.g., Method 6.1-6.44, or any of the preceding uses or pharmaceutical compositions wherein the patient exhibits one or more of hyperactivity, impulsivity, inattention, impaired working memory, irritability, depression, dysthymia, impaired executive function (e.g., reasoning, planning, problem solving), mood lability, anxiety, repetitive/perseverative stereotypic behaviors, unstable affect, aggression, and self-injurious behavior.

[0071] 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 a fragile X-associated disorder, e.g., fragile X syndrome, are indicated to be obtained on oral administration at dosages of the order from about 0.01 to 2.0 mg/kg. An indicated daily dosage for oral administration may be in the range of from about 0.75 mg to 200 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier therefor.

[0072] (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, may be administered by any suitable route, including orally, parenterally, transdermally, or by inhalation, including by sustained 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, which provides therapeutically effective levels of (1R,5S)-1-(naphthalen-2-yl)-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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.

[0073] In some embodiments, (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is released from a composition and delivered into the blood plasma or other target site of activity in the subject (including, but not limited to, areas of the brain such as the prefrontal cortex, frontal cortex, thalamus, striatum, ventral tegmental area, other cortical areas, hippocampus, hypothalamus, or nucleus accumbens) in a sustained release profile characterized in that from about 0% to 20% of the active compound is released and delivered (as determined, e.g., by measuring blood plasma levels) within 0 to 2 hours, from 20% to 50% of the active compound is released and delivered within about 2 to 12 hours, from

50% to 85% of the active compound is released and delivered within about 3 to 20 hours, and greater than 75% of the active compound is released and delivered within about 5 to 18 hours.

[0074] In some embodiments, the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30% of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition. In some embodiments, the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition. In some embodiments, the C_{\max} (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition. In some embodiments, the C_{\max} (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is about 20-50%, e.g., is about 30-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in

free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.

[0075] In some embodiments, the pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, e.g., a sustained release pharmaceutical composition, comprises a lubricant, e.g., magnesium stearate, a carrier, e.g., lactose monohydrate, or a combination thereof.

[0076] Pharmaceutical compositions comprising (1R,5S)-1-(naphthalen-2-yl)-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. Thus, oral dosage forms may include tablets, capsules, solutions, suspensions, and the like.

[0077] 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.

EXAMPLE

Example 1

[0078] Sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride

Ingredient	Concentration (%W/W)	Tablet Unit Weight (mg)
(1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride	25%	100
Lactose, Monohydrate, NF Hypromellose, NF (as 50/50 premix - RetaLac®)	74.5%	298

Magnesium Stearate, NF (Hyqual® Vegetable source)	0.5%	2
Total	100%	400

CLAIMS**WHAT IS CLAIMED IS:**

1. A method of treating a patient having a fragile X-associated disorder comprising administering to the patient in need thereof a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
2. A method of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.
3. A method of treating autism spectrum disorder (ASD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the patient has a fragile X-associated disorder.
4. A method of treating a patient having a fragile X-associated disorder comprising administering to the patient in need thereof a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, wherein the patient was refractory to a prior course of treatment for the fragile X-associated disorder.
5. A method of treating attention-deficit/hyperactivity disorder (ADHD) comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder.
6. A method of treating an autism spectrum disorder comprising administering a therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, to a patient in need thereof wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder.

7. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is substantially free of the corresponding (-) enantiomer.
8. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 20% w/w of the corresponding (-) enantiomer.
9. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, comprises less than or equal to 10% w/w of the corresponding (-) enantiomer.
10. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
11. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
12. The method of any of the preceding claims, wherein the therapeutically effective amount of (1R,5S)-1-(naphthalen-2-yl)-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.
13. The method of any of the preceding claims, wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane is in pharmaceutically acceptable salt form.
14. The method of claim 13, wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is an acid addition salt.
15. The method of claim 14, wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane in pharmaceutically acceptable salt form is (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane hydrochloride.

16. The method of any of the preceding claims comprising administering 1 mg to 1800 mg, e.g., 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., 50 mg to 1000 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 750 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, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
17. The method of any of the preceding claims 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 (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
18. The method of any of claims 1-16 comprising administering 50 mg to 600 mg, e.g., 100 mg to 600 mg, e.g., 100 mg to 400 mg, e.g., 100 mg to 200 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
19. The method of any of claims 1-16 comprising administering 5 mg to 500 mg, e.g., 5 mg to 10 mg, e.g., 10 mg to 25 mg, e.g., 30 mg to 50 mg, e.g., 10 mg to 300 mg, e.g., 25 mg to 300 mg, e.g., 50 mg to 100 mg, e.g., 100 mg to 250 mg, e.g., 250 mg to 500 mg, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
20. The method of any of claims 1-15 comprising administering 0.5 mg/kg to 20 mg/kg per day, e.g., 1 mg/kg to 15 mg/kg per day, e.g., 1 mg/kg to 10 mg/kg per day, e.g., 2 mg/kg to 20 mg/kg per day, e.g., 2 mg/kg to 10 mg/kg per day, e.g., 3 mg/kg to 15 mg/kg per day, of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form.
21. The method of any of the preceding claims comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once, twice, three, or four times daily.
22. The method of any of the preceding claims comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, once daily.

23. The method of any of the preceding claims comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, twice daily.
24. The method of any of the preceding claims comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, three times daily.
25. The method of any of the preceding claims comprising administering (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, four times daily.
26. The method of any of the preceding claims wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with another drug.
27. The method of any of the preceding claims wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with an mGluR1 antagonist, an mGluR2/3 antagonist, an mGluR5 antagonist, an AMPA receptor positive modulator, an NMDA receptor antagonist, a tetracycline antibiotic, an α 2-adrenergic agonist, an antipsychotic, an anti-depressant (e.g., a selective serotonin reuptake inhibitor (SSRI), a serotonin-norepinephrine reuptake inhibitor (SNRI), or a tricyclic anti-depressant), a benzodiazepine, an anti-convulsant, a mood stabilizer, a gamma-aminobutyric acid (GABA) agonist e.g., a GABA-B agonist, a GABA modulator, a stimulant, a β -blocker, a hormone, or a combination thereof.
28. The method of any of the preceding claims wherein (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered concurrently or sequentially, in either order, with fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), CX516, memantine, acamprosate, minocycline, clonidine, guanfacine, aripiprazole, risperidone, citalopram, escitalopram, fluoxetine, sertraline, fluvoxamine, paroxetine, trazodone, bupropion, imipramine, amitriptyline, venlafaxine, nefazodone, duloxetine, venlafaxine, carbamazepine, lamotrigine, valproic acid, sodium valproate, lithium, quetiapine, folic acid, L-acetylcarnitine, melatonin, arbaclofen, donepezil hydrochloride, alpha-tocopherol,

- methylphenidate, amphetamine mixed salts (e.g., Adderall), dextroamphetamine, risperidone, olanzapine, ziprasidone, buspirone, filuzole, metadoxine, primidone, topiramate, estradiol, cyclic medroxyprogesterone, or a combination thereof.
29. The method of any of the preceding claims further comprising administering a mGluR5 antagonist.
30. The method of claim 29 comprising administering fenobam, mavoglurant (AFQ056), dipraglurant, RO4917523, STX107, 2-methyl-6-phenylethynyl pyridine (MPEP), or a combination thereof.
31. The method of claim 30 comprising administering RO4917523, mavoglurant (AFQ056), or a combination thereof.
32. The method of any of the preceding claims further comprising administering a GABA-B agonist.
33. The method of claim 32 comprising administering arbaclofen.
34. The method of any of the preceding claims further comprising administering a GABA modulator.
35. The method of claim 34 comprising administering acamprosate.
36. The method of any of the preceding claims further comprising administering minocycline.
37. The method of any of the preceding claims further comprising a non-pharmacological intervention, e.g., a modification in the home environment, a more tailored behavioral intervention and classroom environment, language and occupational therapy, an attention to social factors, sensory integration therapy, or a combination thereof.
38. The method of any of the preceding claims, wherein the (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is administered in a sustained release pharmaceutical composition.
39. The method of claim 38, wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of the sustained release pharmaceutical composition is less than about 80%, e.g., less than about 75%, e.g., less than about 60%, e.g., less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-80%, e.g., is about 30-80%, e.g., is about 20-70% e.g., is about 30-70%, e.g., is about 30-60%, e.g., is about 30-

- 50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
40. The method of claim 39, wherein the C_{\max} of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, provided after administration of a sustained release pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, is less than about 50%, e.g., less than about 40%, e.g., less than about 30%, e.g., is about 20-50%, e.g., is about 20-50%, e.g., is about 30-40%, of the C_{\max} obtained after administering an equivalent dose of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in an immediate release pharmaceutical composition.
41. The method of any of claims 1-40, wherein the patient has a fragile X-associated disorder, e.g., fragile X syndrome (FXS).
42. The method of any of claims 1-40, wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated tremor/ataxia syndrome (FXTAS).
43. The method of any of claims 1-40, wherein the patient has a fragile X-associated disorder, e.g., fragile X-associated primary ovarian insufficiency (FXPOI).
44. The method of any of claims 1-40, wherein the patient has a fragile X-associated disorder, e.g., a fragile-X associated disorder associated with an expansion to 40, e.g., 44 or more, e.g., 50 or more, e.g., 54 or more, e.g., 80 or more, e.g., 100 or more, e.g., 200 or more repeats, of the cytosine guanine guanine (CGG) trinucleotide within the 5' untranslated region of the FMR1 gene located on the X chromosome.
45. The method of any of claims 1-44, wherein the method improves one or more symptoms associated with the fragile X-associated disorder.
46. The method of claim 45, wherein the one or more symptoms comprise one or more of cognitive impairment, anxiety, hyperactivity, impulsivity, repetitive/perseverative stereotypic behaviors, unstable affect, aggression, and self-injurious behavior.
47. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating a

- patient having a fragile X-associated disorder, e.g., for use in Method 1, e.g., Methods 1.1-1.41.
48. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 a patient having a fragile X-associated disorder, e.g., for use in Method 1, e.g., Methods 1.1-1.41.
49. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament, for treating attention-deficit/hyperactivity disorder (ADHD) in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 2, e.g., Methods 2.1-2.39.
50. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 attention-deficit/hyperactivity disorder (ADHD) in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 2, e.g., Methods 2.1-2.39.
51. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating autism spectrum disorder in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 3, e.g., Methods 3.1-3.39.
52. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 autism spectrum disorder in a patient in need thereof, wherein the patient has a fragile X-associated disorder, e.g., for use in Method 3, e.g., Methods 3.1-3.39.
53. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating a patient having a fragile X-associated disorder, wherein the patient was refractory to a prior course of treatment for the a fragile X-associated disorder, e.g., for use in Method 4, e.g., Methods 4.1-4.41.

54. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 a patient having a fragile X-associated disorder, wherein the patient was refractory to a prior course of treatment for the a fragile X-associated disorder, e.g., for use in Method 4, e.g., Methods 4.1-4.41.
55. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating attention-deficit/hyperactivity disorder (ADHD) wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 5, e.g., Methods 5.1-5.42.
56. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 attention-deficit/hyperactivity disorder (ADHD) wherein the ADHD is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 5, e.g., Methods 5.1-5.42.
57. Use of (1R,5S)-1-(naphthalen-2-yl)-3-azabicyclo[3.1.0]hexane, in free or pharmaceutically acceptable salt form, in the manufacture of a medicament for treating an autism spectrum disorder wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 6, e.g., Methods 6.1-6.44.
58. A pharmaceutical composition comprising (1R,5S)-1-(naphthalen-2-yl)-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 an autism spectrum disorder wherein the autism spectrum disorder is co-morbid with one or both of anxiety and depression (e.g., depression), e.g., in a patient with a fragile X-associated disorder, e.g., for use in Method 6, e.g., Methods 6.1-6.44.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/69401

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/13, 31/135, 31/403 (2015.01)

CPC - A61K 31/13, 31/135, 31/403

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)

IPC(8): A61K 31/13, 31/135, 31/403 (2015.01)

CPC: A61K 31/13, 31/135, 31/403 USPC: 514/412

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATSEER (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC); ProQuest; Google Scholar; IP.com; KEYWORDS: azabicyclo hexane, naphthalen 2 yl, azabicyclo 3 1 0 hexane, 1R 5S, tripl* reuptak* inhibit*, unbalanc* tripl* reuptak* inhibit*, ADHD, depression, anxiety, autism, monoamin* neurotransmit*, autism* spectr* disorder, fragil* X syndrom*, anxiet* disorder*, refractor* treat*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/019271 A1 (NEUROVANCE) 07 February 2013; paragraphs [0008]-[0009], [0011], [0036], [0058], [0062]; claim 1	1-6, 7/1-6, 47-58
Y	US 2011/0034565 A1 (REGAN, C et al.) 10 February 2011; paragraphs [0025], [0033], [0039], [0047], [0049], [0138], [0154], [0193]-[0194], [0272], [0291]; claim 19	1-6, 7/1-6, 47-58
Y	US 2012/0258994 A1 (MCKINNEY, AA et al.) 11 October 2012; paragraphs [0002], [0007], [0014], [0051]	4, 7/4, 53-54
A	THERAVANCE, Theravance Announces Initiation of Phase 2 Study With Its MARIN Compound, TD-9855, for the Treatment of ADHD, Theravance Press Release, pages 1-2, 2011; [retrieved on 2015-02-17]. Retrieved from the Internet: <URL: http://www.marketwired.com/press-release/theravance-announces-initiation-phase-2-study-with-its-marin-compound-td-9855-treatment-nasdaq-thrx-1597199.htm >; entire document	1-6, 7/1-6, 47-58
A	WO 2012/118563 A2 (VANDERBILT UNIVERSITY) 07 September 2012; paragraphs [0008]-[0010], [0246], [0253], [0257], [0260], [0262]-[0263], [0273]-[0274]	1-6, 7/1-6, 47-58

☐ 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

21 February 2015 (21.02.2015)

Date of mailing of the international search report

18 MAR 2015

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US14/69401

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.: 8-46
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:

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.:

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.