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Description**FIELD OF THE INVENTION**

[0001] Various aspects related to drug therapy for the treatment of individuals with developmental disorders, such as autism and the genetic disorder Fragile X Syndrome.

5 BACKGROUND

[0002] Autism Spectrum Disorders (ASDs) are defined by the National Human Genome Research Institute as a broad group of developmental disorders characterized by impaired social interactions, problems with verbal and nonverbal communication and respective behaviors or severely limited
10 activates and interests. Various forms of autism are included in the Diagnostic and Statistical manual of Mental Disorders DSM-IV-TR currently in its forth revised edition and listed as two of five known categories of pervasive developmental disorder. ASDs range from a severe form of the disorder called autistic disorder (or classic autism) to a milder form called Asperger's Disorder. A patient presenting symptoms of either of these disorders, but not meeting the specific criteria for either form, may be said to have pervasive developmental disorder not otherwise specified (PDD-NOS).

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[0003] According to the National Institute for Mental Health an actual diagnosis of autism requires a thorough clinical examination by a physician trained in this area of medicine or even a team of health care professionals. An individual diagnosis is based on observing an individual patient's behaviors and measuring the patient's behavior using such screening tools such as Autism Diagnosis Interview-
20 Revised

[0004] (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS). Comorbid autism such as autism co-diagnosed with conditions such as Down Syndrome or Fragile X Syndrome (FXS) comprise about 15 percent of all forms of autism, the remaining 85 percent of cases is of unknown origin and
25 classified as idiopathic autism.

[0005] Given the profound effects that the most severe forms of autism spectrum disorders, including comorbid and idiopathic forms of the disorder, have on people afflicted with these disorders and the lack of effective treatment options available for these people there is pressing need for materials and
30 methods to treat these patients, various aspects and embodiments presented herein seek to address this need.

[0006] US 2005/171067 A1 discloses antagonists of mGluR5, such as SIB 1893 and MPEP, for the treatment of autism, including autism in patients having fragile X syndrome.

[0007] US 6,890,931 discloses the use of mGluR5 antagonists in the treatment or prevention of neurodegenerative conditions including Fragile X syndrome. In particular US 6,890,931 teaches that such treatments or prevention may employ a compound that antagonizes an mGluR, preferably a compound that antagonizes Group I receptor such as mGluR1, or mGluR5, and even more preferably a compound that is selective for mGluR5.

[0008] "Neuroprotective and abstinence-promoting effects of acamprosate: elucidating the mechanism of action" (De Witte, et al., CNS Drugs; Vol. 19, No. 6; 2005; pages 517-537), "Acamprosate inhibits the binding and neurotoxic effects of trans-ACPD, suggesting a novel site of action at metabotropic glutamate receptors" (Harris Barton, et al.; Alcoholism, Clinical and Experimental Research; Vol. 26, No. 12; December 2002; pages 1779-1793), Littleton (Alcoholism, Clinical and Experimental Research; Vol. 29, No. 5; Supplement May 2005; page 173a), and "Effects of acamprosate on neuronal receptors and ion channels expressed in *Xenopus* oocytes" (Reilly, et al.; Alcoholism, Clinical and Experimental Research; Vol. 32, No. 2; February 2008; pages 188-196), all discuss various properties and biological activities of the homotaurine analogue acamprosate.

SUMMARY

[0009] The invention provides a composition that includes at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt for use in the treatment of a subject having fragile X syndrome.

[0010] The invention also provides a composition that includes at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt, for use in the treatment of a subject having an autism spectrum disorder.

BRIEF DESCRIPTION OF THE FIGURES

[0011] FIG. 1. Table 1.

DESCRIPTION

[0012] For the purposes of promoting an understanding of the principles of the novel technology, reference will now be made to the preferred embodiments thereof, and specific language will be used to describe the same.

[0013] The specification discloses a method of treating a subject having an autism spectrum disorder,

comprising the step of administering to the subject a composition that includes at least one homotaurine analog that decreases neuronal glutamatergic signaling.

[0014] The specification also discloses a method of treating a subject having an autism spectrum disorder, comprising the step of administering to the subject a composition that includes at least one homotaurine analog. The homotaurine analog employed in such methods are homotaurine analogs that can decrease neuronal glutamatergic signaling.

[0015] Autism spectrum disorder is a developmental disorder that affects an individual's ability to communicate, form relationships with others and respond appropriately to the environment. Some individuals with autism spectrum disorder are high functioning, with speech and intelligence within normal range. Other individuals with autism spectrum disorder may be nonverbal and/or have varying degrees of mental retardation. Autism spectrum disorder can include Asperger's syndrome (also referred to as "Asperger's disorder"), idiopathic autism (e.g., autism of unknown origin) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). One of skill in the art would be able to diagnosis an individual with autism spectrum disorder and determine whether the individual has idiopathic autism, PDD-NOS or Asperger's syndrome, employing well-known clinical criteria as described, for example, in Diagnostic and Statistical Manual of Mental Disorders (DSMMD) (4th ed., pp. 70-71) Washington, D.C., American Psychiatric, 1994. Exemplary diagnostic criteria listed in the DSMMD include:

Autistic Disorder

[0016] An autism screening tool must meet all three primary areas defined by the DSM-IV description for autistic disorder (#'s 1-3 under A below) to qualify for a positive rating from First Signs:

1. A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) qualitative impairment in social interaction, as manifested by at least two of the following:

(a) marked impairment in the use of multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

(b) failure to develop peer relationships appropriate to developmental level

(c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)

(d) lack of social or emotional reciprocity

5 (2) qualitative impairments in communication, as manifested by at least one of the following:

(a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)

10 (b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others

(c) stereotyped and repetitive use of language or idiosyncratic language

(d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

15 (3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities as manifested by at least one of the following:

(a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

(b) apparently inflexible adherence to specific, nonfunctional routines or rituals

20 (c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements)

(d) persistent preoccupation with parts of objects

25 B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

[0017] Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS)

[0018] Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS) is a diagnosis often considered for children who show some signs of autism spectrum disorder, but who do not meet the specific diagnostic criteria for other Pervasive Developmental Disorders (PDDs) (see, for

example, Diagnostic and Statistical Manual of Mental Disorders (4th ed., pp. 70-71) Washington, D.C., American Psychiatric, 1994). Deficits in peer relations and unusual sensitivities are generally observed in individuals with PDD-NOS, whereas social skills are generally less impaired than in idiopathic autism.

[0019] This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interests, and activities are present, but the criteria are not met for a specific pervasive developmental disorder, schizophrenia, schizotypal personality disorder, or avoidant personality disorder. For example, this category includes "atypical autism" -- presentations that do not meet the criteria for autistic disorder because of late age of onset, atypical symptomatology, or subthreshold symptomatology, or all or any combination thereof.

[0020] Asperger's Disorder (also referred to herein as "Asperger Syndrome")

[0021] In contrast to individuals with idiopathic autism (autism with unknown origin) individuals with Asperger's syndrome generally do not manifest a delay in spoken language development (see, for example, Diagnostic and Statistical Manual of Mental Disorders (4th ed., pp. 70-71) Washington, D.C., American Psychiatric, 1994). However, they can have serious deficits in social and communication skills; and often have obsessive, repetitive routines and preoccupations with a particular subject matter. Idiosyncratic interests are common and may take the form of an unusual and/or highly circumscribed interest (e.g., in train schedules, the weather).

[0022] An Asperger/HFA screening tool must meet all six areas defined by the DSM-IV description of Asperger Syndrome (A-F below) to qualify for a positive rating from First Signs:

1. A. Qualitative impairment in social interaction, as manifested by at least two of the following:

(1) marked impairment in the use of multiple nonverbal behaviors, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction

(2) failure to develop peer relationships appropriate to developmental level

(3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)

(4) lack of social or emotional reciprocity

- 5 2. B. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

(1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus

(2) apparently inflexible adherence to specific, nonfunctional routines or rituals

- 10 (3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)

(4) persistent preoccupation with parts of objects

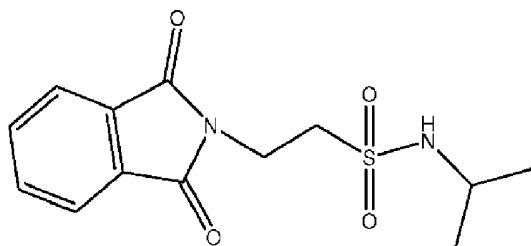
3. C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

- 15 4. D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

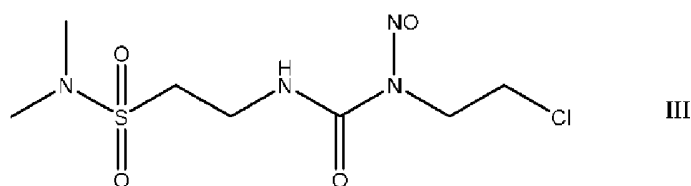
5. E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

- 20 6. F. Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

[0023] "Homotaurine analog," as used herein, means a compound that has a structure that is similar to taurine but differs by at least one element. For example, taltrimide (Formula II), calcium acamprosate (Formula I) and tauromustine (Formula III) are homotaurine analogs (Gupta, R.C., et al., Curr. Medicinal Chem. 12:2021-2039 (2005)).

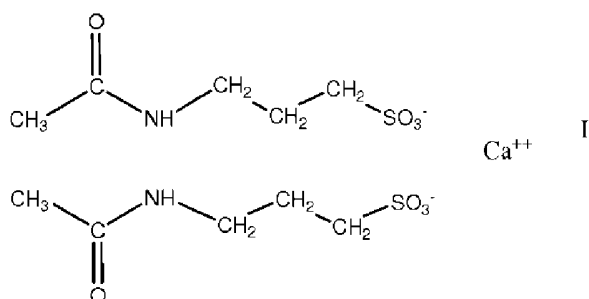


II



[0024] Also disclosed are methods that employ homotaurine analogs (See, for example, U.S. Patent Nos.: 6,391,922 and 5,602,150; U.S. Patent Application Nos.: 2002/0013366, 2002/0119912, 2004/0102525; Harris, B.R., et al., Alcohol Clin Exp Res 26: 1779-1793 (2002); and Pierrefiche, O., et al., Neuropharmacology 47:35-45 (2004)).

[0025] The medical uses of the invention employ the homotaurine analog of Formula I:



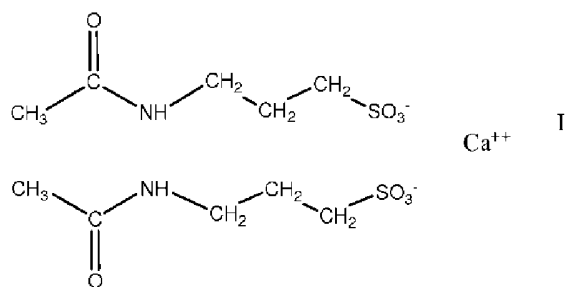
[0026] The chemical name of Formula I is calcium acetylaminopropane sulfonate, calcium bis-acetyl homotaurine or calcium N-acetylhomotaurine. The chemical formula for Formula I is $C_{10}H_{20}N_2O_8S_2Ca$. Formula I is referred to as CAMPRAL® (acamprosate calcium, also referred to herein as "calcium acamprosate"). Formula I decreases neuronal glutamateric signaling.

[0027] "Decreases neuronal glutamatergic signaling," as used herein, means that the homotaurine analog reduces the amount of effect of glutamate on postsynaptic transmission in neurons. A decrease in neuronal glutamatergic signaling can be, for example, consequent to a decrease in release of glutamate from neurons and/or limiting or diminishing the ability of synaptic glutamate to mediate cell signaling in neurons. Techniques to assess whether a homotaurine analog can decrease neuronal glutamateric signaling are well established and known to one of skill in the art and include, for example, the use of paired pulse facilitation to measure glutamate release using electrophysiologic measure, as described, for example, by MacIver, M., et al., Laboratory Investigation 85(Issue 4), pp 823-834 (1996).

[0028] The autism spectrum disorder treated by the medical uses of the invention can include at least one member selected from the group consisting of Asperger's syndrome, an idiopathic autism and a pervasive developmental disorder not otherwise specified (PDD-NOS).

[0029] In an embodiment, the subject that has autism spectrum disorder also has fragile X syndrome.

[0030] The compounds employed in the medical uses of the invention to treat an autism spectrum disorder (Asperger's syndrome, idiopathic autism, PDD-NOS) and/or fragile X syndrome include at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt. In a particular embodiment, the acetylaminopropane sulfonate salt can include a calcium acetylaminopropane sulfonate represented by Formula I:



[0031] The at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt employed in some of the medical uses of the invention (e.g., calcium acetylaminopropane sulfonate, Formula I) can be administered to the subject at a dose of at least one member selected from the group consisting of about a 333 mg dose, about a 666 mg dose, about a 999 mg dose, about a 1332 mg dose, about a 1665 mg dose, about a 1998 mg dose, about a 2331 mg dose, about a 2664 mg dose and about a 2997 mg dose. The at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt (e.g., Formula I) employed in the medical uses of the invention can be administered to the subject in a dose of about 1221 mg/day or in a dose of between about 333 mg/day to about 1999 mg/day. In an embodiment, the subject is administered a dose of the at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt (e.g., Formula I) of about a 333 mg dose. In another embodiment, the subject is administered a dose of the at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt (e.g., Formula I) of about a 666 mg dose.

[0032] The at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt (e.g., Formula I) can be administered to the subject (e.g., a human subject) daily in a single dose or in multiple doses (e.g., two doses, three doses, four doses, five doses, six doses, seven doses, eight doses, nine doses, ten doses) a day. The dosage and frequency of dosing of the subject can within the knowledge of one of skill in the art based on age, other medications

and tolerance of the at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt.

[0033] In another embodiment, the invention is a medical use for treating a subject having fragile X syndrome, utilizing a composition that includes at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt. The at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt employed to treat the subject having fragile x syndrome, autism or a combination of autism and fragile X syndrome can decrease neuronal glutamatergic signaling. The subject having fragile X syndrome treated by the medical uses of the invention can also further have an autism spectrum disorder.

[0034] In yet another embodiment, the invention is a medical use for treating a human having fragile X syndrome, utilizing a composition that includes Formula I, wherein the composition is for administration to the subject in a dose of about 333 mg at a frequency of at least one member selected from the group consisting of two times a day and three times a day. The human treated with Formula I that has fragile X syndrome can further have an autism spectrum disorder.

[0035] In still another embodiment, the invention is a medical use for treating a human having an autism spectrum disorder, utilizing a composition that includes Formula I, wherein the composition is for administration to the subject in a dose of about 333 mg at a frequency of at least one member selected from the group consisting of two times a day and three times a day. The human that has autism spectrum disorder that is treated by administering Formula I can further have fragile X syndrome.

[0036] "Therapeutically effective amount," as used herein, means an amount of a homotaurine analog, such as at least one member selected from the group consisting of an acetylaminopropane sulfonate and an acetylaminopropane sulfonate salt, that diminishes or ameliorates symptoms of at least one condition selected from the group consisting of an autism spectrum disorder and fragile X syndrome. One of skill in the art would be able to determine the therapeutically effective amount of a homotaurine analog for use in the medical uses described herein.

[0037] The medical uses of the invention can further include the use of compositions that treat irritability, anxiety, inattention and hyperactivity in the subjects, as needed (referred to as "additional treatment"). The additional treatment could be for administration before or after administration of the homotaurine analog to the subject. Suitable compositions for administration to the subject in addition to the homotaurine analog can include, for example, aripiprazole and risperidone in subject having autism; selective serotonin reuptake inhibitors (SSRIs) to treat anxiety and stimulants to treat ADHD-like

symptoms in subjects with fragile X syndrome; stimulants, alpha 2-agonists and atomoxetine to manage ADHD-like symptoms and SSRIs; and mirtazapine for anxiety in subjects with idiopathic autism. One of skill in the art would be able to identify subjects who need additional treatment and the additional treatment that is required.

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[0038] FXS represents the most common known cause of autism and related disorders. Approximately 1 in 4 (25%) to 1 in 3 (33%) individuals with FXS additionally meet criteria for autistic disorder (King, State *et al.* 1997; Bailey, Hatton *et al.* 2001; Rogers, Wehner *et al.* 2001). About 2 in 3 (67%) males with FXS are thought to exhibit behavior consistent with the broader autism phenotype (Clifford, Dissanayake *et al.* 2007).

10

[0039] Experiments utilizing cellular and animal modeling, in recent years have contributed to our understanding of the possible etiology of FXS. Some of this work has reported that excessive metabotropic glutamate receptor activation (specifically mGluR5 activation) may be involved in the pathogenesis of FXS (Bear, Huber *et al.* 2004; Bear 2005; Dolen and Bear 2005; Dolen, Osterweil *et al.* 2007; Bear, Dolen *et al.* 2008; Dolen and Bear 2008). In some experiments, the mGluR5 antagonist MPEP (2-methyl-6-phenylethynl)-pyridine) has demonstrated its apparent ability to reverse aspects of the FXS phenotype in animal models for the syndrome (McBride, Choi *et al.* 2005; Yan, Rammal *et al.* 2005; Tucker, Richards *et al.* 2006; Dolen, Osterweil *et al.* 2007).

20

[0040] Fragile X syndrome (FXS) is the most common inherited form of intellectual disability. FXS is the result of an unstable cysteine-guanine-guanine (CGG) trinucleotide repeat expansion (>200 repeats) within the fragile X mental retardation 1 gene (FMR1) promoter region located near the long arm of the X chromosome (Pieretti, Zhang *et al.* 1991). This expansion leads to transcriptional silencing of the FMR1 gene and the absence of fragile X mental retardation protein (FMRP) (Devys, Lutz *et al.* 1993). Due to the location of the FMR1 gene on the X chromosome, females with the full mutation are, in general, more mildly affected than males secondary to potential FMRP production from the non-mutated FMR1 allele. The full mutation gene frequency is about 1/2500 (Hagerman 2008).

25

[0041] FMRP is an RNA binding protein important to dendritic maturity and synaptic plasticity (Greenough, Klintsova *et al.* 2001). This important role in cortical development is likely in part due to the action of FMRP as an end product inhibitor of group 1 metabotropic glutamate receptor (mGluR1 and mGluR5) mediated dendritic RNA translation (Bear, Huber *et al.* 2004; Ronesi and Huber 2008). The impact of excess mGluR activation due to loss of inhibitory FMRP control can be seen in the FMR1 knockout mouse model. In this model, excess hippocampal and cerebellar long term depression (LTD), excess AMPA receptor internalization, abnormal dendritic morphology, and reduced seizure threshold are all consistent with excessive group 1 mGluR activation (Bear, Huber *et al.* 2004).

35

[0042] Some of the treatment implications of excessive mGluR activation have been studied. In the mouse model, mGluR down regulation by treatment with MPEP (2-methyl-6-(phenylethynyl)-pyridine) and other mGluR5 antagonists has been shown to reverse phenotypic characteristics, including audiogenic seizures, altered prepulse inhibition (PPI), and open field hyperactivity (Chuang, Zhao *et al.* 2005; Yan, Rammal *et al.* 2005; de Vrij, Levenga *et al.* 2008). MPEP has rescued aberrant courtship behavior in the *Drosophila* model of FXS (McBride, Choi *et al.* 2005). Genetic down regulation of mGluR5 executed by crossing a FMR1 knockout mouse with a mGluR5 heterozygous knockout resulted in reversal of several FMR1 knockout characteristics, including dendritic spine changes and excess protein synthesis (Dolen and Bear 2008).

[0043] Berry-Kravis and colleagues (2008) conducted a pilot single dose trial of the mGluR5 antagonist fenobam (50-150 mg) focused on tolerability and pharmacokinetic assessment in twelve adults (6 males, 6 females; mean age, 23.9 +/-5.4 years) with full mutation FXS (Berry-Kravis, Hessel *et al.* 2009). Fenobam was generally well tolerated with only 3 (25%) subjects exhibiting mild sedation. Wide inter-subject pharmacokinetic variability was noted. Six (50%) subjects showed at least a 20% improvement in PPI one hour post fenobam dosing. The authors reported that nine (75%) subjects experienced clinical benefit, including reduced hyperactivity and anxiety that was not dose dependent and did not completely correlate with PPI response.

[0044] Acamprosate, calcium acetylhomotaurine, also known as 3-acetamidopropane-1-sulfonic acid, is approved by the United States Food and Drug Administration to administer to patients for the maintenance of abstinence from alcohol in patients with alcohol dependence. See for example, International Publication Number WO 02/102388 A3, incorporated by reference herein in its entirety.

[0045] Recent research into the mechanism of action of acamprosate has focused on mGluR5 antagonism (Harris, Prendergast *et al.* 2002; Blednov and Adron Harris 2008; Gupta, Syed *et al.* 2008). In rat brain specimens, Harris *et al.* (2002) initially demonstrated that acamprosate had binding and functional characteristics consistent with an mGluR antagonist combined with functional similarity to the non-competitive mGluR5 antagonist SIB-1893 (Harris, Prendergast *et al.* 2002). Acamprosate and MPEP have both been associated with increased sedative effects of alcohol and reduced alcohol withdrawal in mice; no effects of acamprosate or MPEP were noted in mGluR5 knockout mice (Blednov and Adron Harris 2008). Gupta and colleagues (2008) demonstrated that acamprosate and MPEP both dose dependently reduced ethanol drinking in the drinking-in-the-dark mouse model (Gupta, Syed *et al.* 2008). In a conflicting report, at concentrations typically achieved in humans, acamprosate did not modulate the function of many neuroreceptors, including mGluR receptors, in an electrophysiological study in *Xenopus* oocytes (Reilly, Lobo *et al.* 2008). Additional preclinical data has pointed to potential weak NMDA receptor antagonism, GABA(A) receptor agonism, and anti-

oxidant effects as potentially contributing to the effect of the drug in early alcohol abstinence (Mann, Kiefer *et al.* 2008).

[0046] In this report, no effects of acamprosate or MPEP were noted in mGluR5 knockout mice

(Blednov and Adron Harris 2008). Also recently, Gupta *et al.* (2008) demonstrated that both acamprosate and MPEP dose dependently reduced ethanol drinking in the drinking-in-the-dark mouse model (Gupta, Syed *et al.* 2008). And MPEP, itself, has been shown to possibly reverse some aspects of the FXS phenotype in several animal models for the condition.

[0047] According to current FDA guidelines acamprosate can be administered to human patients at a dosing level of about 1,998 mg/kg/day which is the U.S. FDA approved dosing of acamprosate used to treat alcohol dependence in adults. The calcium salt of the compound is commercially available and sold in tablets that include about 333 mg of the active ingredient per tablet. Tablets that have an enteric coating are also available to administer to patents that are able to swallow tablets.

[0048] In some embodiments patients already being treated with psychotropic drug use will be allowed to continue to use these drugs throughout the study as long as the dose of psychotropic drugs remains the same during the trial. Experimental primary outcome measures in the studies reported on herein and any ongoing studies and clinical assessments may include tests such as the Clinical Global Impression Improvement (CGI-I) scale (Guy 1976) and the Aberrant Behavior Checklist (ABC) (Aman, Singh *et al.* 1985). The ABC is made up of subscales of behaviors including Social Withdrawal, Irritability, Stereotypy, Hyperactivity, and Inappropriate Speech. The ABC is commonly used in drug trials involving persons with developmental disability and the composite score on the measure has shown good reliability as an outcome measure specifically in persons with FXS (Berry-Kravis, Krause *et al.* 2006). Treatment responses using these tests are determined by scoring the behaviors of the patients' a CGI-I score of "much improved" or "very much improved" and a 25% or greater improvement in the ABC composite score. The tolerability of acamprosate can be readily assessed throughout the course of treatment with the drug via the use of standard side-effect profile checklists at all study visits and by the following baseline and study completion measures: physical examination; laboratory studies including complete blood count, comprehensive metabolic panel, and lipid panel; electrocardiograms.

Experimental

1. Treatment of young adult males presenting with full mutation FXS.

[0049] This study sample included 4 young adult males (mean age, 20.3 years; range, 18-23 years) with full mutation FXS. The parents of each patient gave their written, informed consent for treatment within our clinic. All patients had a comorbid clinical diagnosis of autistic disorder (autism)

utilizing Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria (American Psychiatric Association 2000). Patients A and B had this diagnosis corroborated by the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter et al. 1994). At baseline, each patient had linguistic communication. Two patients (A, B) receiving concomitant psychotropic drugs were continued at the same doses during the trial (see Table 1).

[0050] Acamprosate was initiated at 666 mg every morning and increased in 666 mg increments every 2 weeks as tolerated to a maximum dose of 666 mg three times daily (recommended dose for treatment of alcohol-dependent adults) (Forest Pharmaceuticals 2005). Prior to reaching a maintenance dose, and in between monthly clinic visits, phone calls were made every two weeks to the primary caregiver to assess for treatment response and drug tolerability. Global improvement, as measured by the Clinical Global Impressions-Improvement (Guy 1976) (CGI-I) scale was assigned at the time of last follow-up visit. The CGI-I scale is rated from 1-7 (1= very much improved; 2=much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7= very much worse). The CGI-I ratings described change in target symptoms defined at the baseline visit (see Table 1). Patients were considered treatment responders if assigned a CGI-I score of 1 or 2 at the final follow-up visit. This study was approved by our local Institutional Review Board and, thus, has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

Case 1

[0051] A is a 20-year-old Caucasian male with mild intellectual disability. In addition to the characteristic features of autism (social impairment, communication impairment, repetitive phenomena), A had a history of significant physical aggression, anxiety, inattention, and hyperactivity. Previous trials of aripiprazole and risperidone were unsuccessful in limiting A's aggression. In addition to his current medication regimen, including propranolol, dextroamphetamine, and ziprasidone, a trial of acamprosate targeting aggression and social and communication impairments was initiated. Acamprosate was started at 666 mg every morning and increased to a target dose of 666 mg three times daily over 4 weeks. During the 44-week treatment, A exhibited increased communicative use of language marked by an expanded expressive vocabulary, increased grammatical complexity of speech, and improved pragmatic skills. For example, within 2 weeks of reaching his maximum dose, A reportedly started to appropriately initiate conversation with neighbors as they walked by his home while he was sitting on his front porch. A's increased mean length of utterance when responding to questions was clear at each follow-up visit. Additionally, A exhibited decreased physical aggression, use of foul language, and defiance during the acamprosate trial. He was deemed to be "very much improved" as determined by a CGI-I score of 1. No adverse effects were observed or reported.

Case 2

[0052] B is an 18-year-old Caucasian male with moderate intellectual disability. B had a history of intermittent physical aggression that was reduced significantly with aripiprazole. A trial of acamprosate targeting social skill deficits and communication impairment was begun. At baseline, B exhibited significantly impaired language pragmatics, grammatical complexity of speech, and expressive vocabulary. He would rarely use single words in social settings and only on occasion utilized short sentences with close family members at home. Acamprosate was started at 666 mg every morning and increased to a target dose of 666 mg three times daily over 4 weeks. B experienced nausea and intermittent emesis requiring a dose reduction to 666 mg twice daily. During 40 weeks of acamprosate treatment, he utilized coherent full sentences in social settings for the first time, surprising family friends and peers. During follow-up visits, B's increased grammatical complexity of speech, expressive vocabulary, and pragmatic use of language were all evident. He was deemed to be "very much improved" as determined by a CGI-I score of 1.

Case 3

[0053] C is a 23-year-old Caucasian male with moderate intellectual disability. His primary target symptoms were core symptoms of autism, including social skill deficits and repetitive behavior marked by repetitive questioning. C was unable to tolerate initial dosing of acamprosate monotherapy started at 666 mg every morning due to sedation and emesis. With a dose reduction to 333 mg daily, the sedation and emesis remitted and he continued the drug for 24 weeks. C's language pragmatics was described as improved, marked by an increased ability to convey his needs and interests in socially appropriate ways. He was described as asking more appropriate and not just repetitive questions, and generally "talking more on topic". He was deemed "much improved" as determined by a CGI-I score of 2.

Case 4

[0054] D is an 18-year-old Caucasian male with mild intellectual disability. His primary target symptoms were irritability and core symptoms of PDD-NOS including deficits of social communication. D was dosed up to 666mg three times daily, but developed gastrointestinal upset on three times daily dosing. A dosing change to 999mg twice daily was well tolerated for the duration of a total of 28 weeks of acamprosate treatment. D remained on stable concomitant dosing of aripiprazole, clonidine, and fluoxetine during treatment with acamprosate. During acamprosate treatment, D was described as exhibiting more appropriate use of sentences including use of an expanded vocabulary. D was generally more talkative during treatment. D exhibited reduced irritable behavior throughout acamprosate treatment. He was deemed "much improved" as determined by a CGI-I score of 2.

[0055] The mean final dose of acamprosate for the four young adult male FXS participants was 1415 mg/day (range, 333-1998 mg/day). Patients received the drug for a minimum of 24 weeks (mean duration, 34 weeks; range, 24-44 weeks). All 4 patients were deemed responders. Each subject exhibited positive expressive language change, including elements of improved pragmatics, grammatical complexity, and vocabulary. This increased linguistic communication was not associated with a reduction in gaze aversion or other forms of impaired non-verbal communication. One subject experienced sedation and two experienced nausea and/or emesis which appeared to be dose related.

2. Treatment of juvenile diagnosed with full mutation FXS.

[0056] In this study, acamprosate was initiated at 333 mg every morning and increased in 333 mg increments every 2 weeks as tolerated to a maximum dose of 666 mg three times daily (recommended dose for treatment of alcohol-dependent adults) (Forest Pharmaceuticals 2005). Prior to reaching a maintenance dose, and in between monthly clinic visits, phone calls were made every two weeks to the primary caregiver to assess for treatment response and drug tolerability. Drug dosing was held at a consistent level unless the patient exhibited intolerable side-effects from the therapy. Global improvement, as measured by the Clinical Global Impressions-Improvement (Guy 1976) (CGI-I) scale was assigned at the time of last follow-up visit. The CGI-I scale is rated from 1-7 (1= very much improved; 2=much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7= very much worse). The CGI-I ratings described change in target symptoms defined at the baseline visit (see Table 1). Patients were considered treatment responders if assigned a CGI-I score of 1 or 2 at the final follow-up visit.

Case 5

[0057] E is a 9-year-old Caucasian male with mild intellectual disability and full mutation FXS. His primary target symptoms include social use of language, inattention, hyperactivity, and general social relatedness. E has a comorbid diagnosis of PDD-NOS. E remained on a stable dose of concomitant aripiprazole throughout treatment with acamprosate. E was maintained on a starting dose of acamprosate at 333mg every morning due to sufficient treatment response at this dose over 6 weeks of treatment. During treatment, E was described by his mother as seeming like "his brain has come back." E exhibited improved language pragmatics, improved focus, and remained calmer during use of acamprosate. He was deemed "very much improved" as determined by a CGI-I score of 1.

3. Treatment of juveniles diagnosed with idiopathic autism.

[0058] In this study, acamprosate was initiated at 333 mg every morning and increased in 333 mg increments every 2 weeks as tolerated to a maximum dose of 666 mg three times daily (recommended dose for treatment of alcohol-dependent adults) (Forest Pharmaceuticals 2005). Prior to reaching a

maintenance dose, and in between monthly clinic visits, phone calls were made every two weeks to the primary caregiver to assess for treatment response and drug tolerability. Drug dosing was held at a consistent level unless the patient protested intolerable side-effects due to the therapy. Global improvement, as measured by the Clinical Global Impressions-Improvement (Guy 1976) (CGI-I) scale was assigned at the time of last follow-up visit. The CGI-I scale is rated from 1-7 (1= very much improved; 2=much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7= very much worse). The CGI-I ratings described change in target symptoms defined at the baseline visit (see Table 1). Patients were considered treatment responders if assigned a CGI-I score of 1 or 2 at the final follow-up visit. This study was approved by our local Institutional Review Board and, thus, has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Case 6

[0059] F is a 10-year-old male with idiopathic autistic disorder and mild intellectual disability. His primary target symptoms of treatment were social responsiveness and use of language. He received acamprosate treatment for 14 weeks with a final dosing of 666 mg in the morning, 333mg midday, and 333mg in the evening. F suffered from loose stools during acamprosate treatment. For F acamprosate treatment was associated with improved social responses, increased verbalizations, and improved eye contact. He was deemed "much improved" as determined by a CGI-I score of 2.

Case 7

[0060] G is a 13-year-old male with idiopathic autistic disorder and moderate intellectual disability. His primary target symptoms of treatment were social responsiveness and inattention. He received acamprosate treatment for 10 weeks with a final dosing of 333mg twice daily. G remained on stable dosing of concomitant atomoxetine treatment throughout his acamprosate trial. For G acamprosate treatment was associated with improved attention and mildly improved social behavior. He was deemed "minimally improved" as determined by a CGI-I score of 3.

Case 8

[0061] H is a 12-year-old female with idiopathic autistic disorder and moderate intellectual disability. Her primary target symptoms of treatment were social responsiveness and use of language. She received acamprosate treatment for 28 weeks with a final dosing of 333mg three times daily. She remained on stable dosing of concomitant risperidone and clonidine throughout her treatment with acamprosate. For H acamprosate treatment was associated with increased use of single words, generally improved social communication, and improved eye contact. She was deemed "very much improved" as determined by a CGI-I score of 1.

Case 9

[0062] I is an 11-year-old male with idiopathic autistic disorder and moderate intellectual disability. His primary target symptoms of treatment were social responsiveness and use of language. He received acamprosate treatment for 20 weeks with a final dosing of 333mg three times daily. I remained on stable dosing of concomitant sertraline during his acamprosate trial. For I, acamprosate treatment was associated with initial improvement in social behavior that waned after 8-12 weeks of treatment. I additionally suffered from reduced appetite and gastrointestinal distress during treatment. He was described as "no change" as determined by a CGI-I score of 4.

Case 10

[0063] J is a 6-year-old male with idiopathic autistic disorder and severe intellectual disability. His primary target symptoms of treatment were social responsiveness, inattention, and use of language. He received acamprosate treatment for 20 weeks with a final dosing of 333mg three times daily. For J acamprosate treatment was associated with improved following of directions, improved focus, and increased use of communication with gestures. J suffered from reduced appetite during acamprosate treatment. He was deemed "much improved" as determined by a CGI-I score of 2.

Case 11

[0064] K is an 8-year-old male with idiopathic autistic disorder and moderate intellectual disability. His primary target symptoms of treatment were social responsiveness, inattention, and use of language. He received acamprosate treatment for 30 weeks with a final dosing of 666 mg in the morning, 333mg midday, and 333mg in the evening. K suffered from reduced appetite and gastrointestinal distress that waned after several weeks of treatment with acamprosate. For K acamprosate treatment was associated with increased meaningful use of words, improved social relatedness, and improved focus. He was deemed "much improved" as determined by a CGI-I score of 2.

[0065] The six juveniles (mean age 10.3 years; range 6-13 years) with idiopathic autism were treated with a mean acamprosate dose of 999 mg/day over a mean 20.33 weeks of treatment.

[0066] All but one of the 11 patients treated with acamprosate calcium in this study showed a measurable improvement in standard assessments of functionality. Overall, use of acamprosate was associated with increased use of communicative language in all subjects. In all cases pragmatic language change was noted, as linguistic communication was more social in nature and the content more appropriate to the context of a given discussion. Despite improved pragmatics, nonverbal aspects of social communication including eye gaze, did not appear to change significantly. Acamprosate may

enhance standard measures of expressive language, including assessment of mean length of utterance, vocabulary, and pragmatics of speech, along with systematic measures of interfering behaviors such as aggression.

5 **[0067]** The majority of both adult and juvenile human patients diagnosed with a form of autism spectrum disorder, show measurable improvement when treated with acamprosate. These clinical studies show that acamprosate can improve, for example, social behavior and use of language, resulting in a remarkable treatment for core symptoms of autism and/or fragile X syndrome, including communication and social impairments in these individuals. In addition to these remarkable and
10 unexpected results still other advantages of using acamprosate to treat autism spectrum disorders include the commercial availability of the drug, limited drug-drug interactions given lack of hepatic metabolism, and demonstrated pharmacokinetic and safety profiles in human adults.

[0068] Additional potential properties of acamprosate, including mild NMDA receptor antagonism and
15 GABA(A) agonism, could also be responsible for the treatment response noted. The possible contribution of these non-mGluR5 mediated treatment effects is supported by a report of modest treatment effects with use of the uncompetitive NMDA receptor antagonist memantine in an open-label study in 6 persons with FXS and a comorbid autism spectrum disorder (Erickson, Mullett *et al.* 2009).

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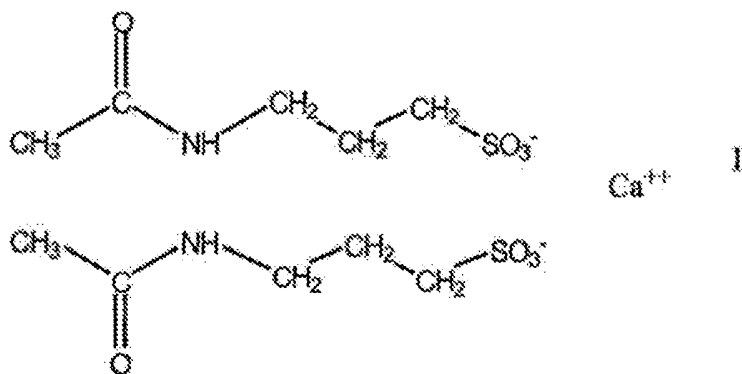
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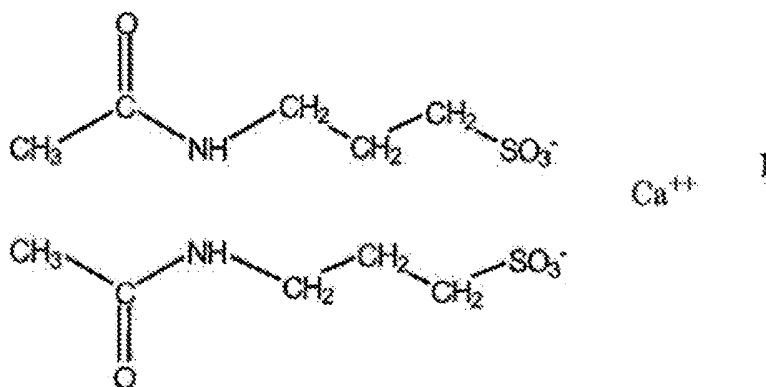
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Patentkrav

1. Sammensætning, der indbefatter mindst ét element udvalgt fra gruppen bestående af acetylamino-propansulfonat og et acetylamino-propansulfonatsalt, til anvendelse i behandlingen af et individ med fragilt X-syndrom.
5
2. Sammensætning, der indbefatter mindst ét element udvalgt fra gruppen bestående af acetylamino-propansulfonat og et acetylamino-propansulfonatsalt, til anvendelse i behandlingen af et individ med en autismespektrumforstyrrelse.
10
3. Sammensætning til anvendelse ifølge krav 2, hvor autismespektrumforstyrrelsen indbefatter Aspergers syndrom.
4. Sammensætning til anvendelse ifølge krav 2, hvor autismespektrumforstyrrelsen indbefatter en idiopatisk autisme.
15
5. Sammensætning til anvendelse ifølge krav 2, hvor autismespektrumforstyrrelsen indbefatter en uspecificeret gennemgribende udviklingsforstyrrelse.
6. Sammensætning til anvendelse ifølge krav 1 eller krav 2, hvor elementet udvalgt fra gruppen bestående af acetylamino-propansulfonat og et acetylamino-propansulfonatsalt reducerer den neuronale glutamaterge signalering.
20
7. Sammensætning til anvendelse ifølge krav 1 eller krav 2,
25 hvor acetylamino-propansulfonatsaltet indbefatter calciumacetylamino-propansulfonat repræsenteret ved formlen I:



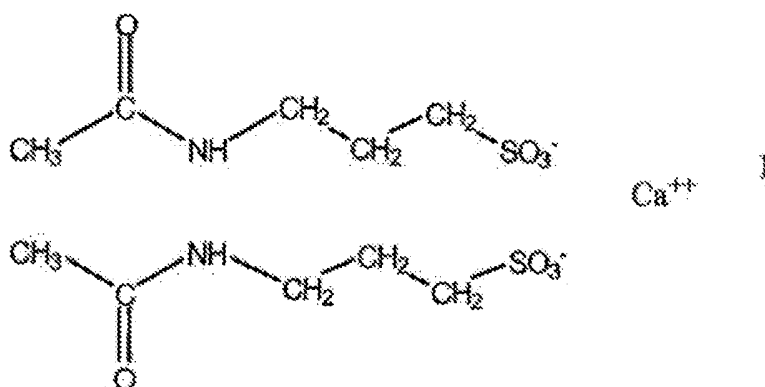
8. Sammensætning til anvendelse ifølge krav 7, hvor calciumacetylamino propansulfonatet er til administration til individet ved en dosis på mindst ét element udvalgt fra gruppen bestående af: en 333 mg dosis; en 666 mg dosis; en 999 mg dosis; en 1332 mg dosis; en 1665 mg dosis; en 1998 mg dosis; en 2331 mg dosis; en 2664 mg dosis og en 2997 mg dosis.
9. Sammensætning til anvendelse ifølge krav 8, hvilken sammensætning er formuleret til daglig administration af dosen til individet i en enkelt dosis.
10. 10. Sammensætning til anvendelse ifølge krav 8, hvilken sammensætning er formuleret til daglig administration af dosen til individet i flere doser, såsom tre doser dagligt.
11. Sammensætning til anvendelse ifølge krav 1 eller krav 2, hvor individet er et menneske.
- 15 12. Sammensætning til anvendelse ifølge krav 10, det indbefatter formelen I:



til anvendelse i behandlingen af et menneske med fragilt X-syndrom, hvor anvendelsen sker ved administration af sammensætningen til det menneskelige individ i en dosis på 333 mg ved en frekvens på mindst ét element udvalgt fra gruppen bestående af to gange dagligt og tre gange dagligt.

5

13. Sammensætning til anvendelse ifølge krav 10, der indbefatter formel I:



- 10 til anvendelse i behandlingen af et menneske med en autismspektrumforstyrrelse, hvor anvendelsen sker ved administration af sammensætningen til det menneskelige individ i en dosis på 333 mg ved en frekvens på mindst ét element udvalgt fra gruppen bestående af to gange dagligt og tre gange dagligt.

- 15 14. Sammensætning til anvendelse ifølge krav 2 eller krav 13, hvor individet endvidere har et fragilt X-syndrom.

15. Sammensætning til anvendelse ifølge krav 1 eller krav 12, hvor individet endvidere har en autismspektrumforstyrrelse.

20

FIG. 1

TABLE 1: Clinical demographics and treatment response data for 3 adult patients with fragile X syndrome (FXS)

Patient no.	Diagnosis	Age (years)	Target Symptoms	Acamprosatedose (mg/day)	Duration of Treatment (weeks)	Concomitant Psychotropic Drugs	Treatment Response (CGI-I)	Adverse Effects
A	FXS, autism, mild intellectual disability	20.8	Aggression, social impairment, communication impairment	1998	20	Dexedrine, propranolol, ziprasidone	1	None
B	FXS, autism, moderate intellectual disability	18	Social impairment, communication impairment	1332	20	Aripiprazole	1	Emesis, nausea
C	FXS, autism, moderate intellectual disability	23.9	Social impairment, repetitive behavior	333	16	None	2	Emesis, sedation