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Advances in the Understanding of the Gabaergic Neurobiology of *FMR1* Expanded Alleles Leading to Targeted Treatments for Fragile X Spectrum Disorder

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Abstract

Fragile X spectrum disorder (FXSD) includes: fragile X syndrome (FXS), fragile X-associated tremor ataxia syndrome (FXTAS) and fragile X-associated primary ovarian insufficiency (FXPOI), as well as other medical, psychiatric and neurobehavioral problems associated with the premutation and gray zone alleles. FXS is the most common monogenetic cause of autism (ASD) and intellectual disability (ID). The understanding of the neurobiology of FXS has led to many targeted-treatment trials in FXS. The first wave of phase II clinical trials in FXS were designed to target the mGluR5 pathway; however the results did not show significant efficacy and the trials were terminated. The advances in the understanding of the GABA system in FXS have shifted the focus of treatment trials to GABA agonists, and a new wave of promising clinical trials is under way. Ganaxolone and allopregnanolone (GABA agonists) have been studied in individuals with FXSD and are currently in phase II trials. Both allopregnanolone and ganaxolone may be efficacious in treatment of FXS and FXTAS, respectively. Allopregnanolone, ganaxolone, riluzole, gaboxadol, tiagabine, and vigabatrin are potential GABAergic treatments. The lessons learned from the initial trials have not only shifted the targeted system, but also have refined the design of

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CONFLICT OF INTEREST

Dr. Hagerman has received funding from Novartis, Roche, Neuren, and Alcobra for treatment trials in fragile X syndrome. She has also consulted with Roche/Genentech, Alcobra, and Novartis regarding treatment trials in fragile X syndrome.

clinical trials. The results of these new trials will likely impact further clinical trials for FXS and other genetic disorders associated with ASD.

Keywords

GABA; GABAA; GABA system; Fragile X Spectrum Disorder; FXSD; Fragile X Syndrome; FXS; Fragile X-associated Tremor Ataxia Syndrome; FXTAS; Targeted treatments; Clinical trials; ASD treatments; Autism

INTRODUCTION

The recently proposed term “fragile X spectrum disorder” (FXSD) highlights the continuity of clinical phenotypes from the gray zone (45-54 CGG repeats in the promoter of the *FMR1* gene, located in the X chromosome) throughout the premutation range (55-200) and into the full mutation range (>200). The FXSD term emerged due to an overlap of symptoms across the CGG repeat range, CGG repeat range. Developmental problems similar to those with fragile X syndrome (FXS) including intellectual disability (ID), autism spectrum disorders (ASD) and seizures can occur in some children with the premutation [1-3]; and FXTAS, typically associated with the premutation, has now been observed in individuals with the gray zone mutation [4,5] and full mutation with lack of methylation or mosaicism [6-8].

Since the initial description of the fragile X syndrome (FXS) by Lubs and colleagues [9] almost five decades ago, considerable advances in the understanding of the phenotype-genotype and the neurobiology of FXS have been made. FXS is the leading mono- genic form of ASD and ID in males and presents with typical facial dymorphism in the majority of older individuals but in only 30% of children. Intellectual disability occurs in 85% of males (mean IQ is 40) and 25% of females (IQ below 70). In addition, about 60% of males with FXS have a diagnosis of ASD [10, 11]. The physical features are long and narrow face, large and prominent ears, high arched palate, hyperextensible finger joints, pectus excavatum, flat feet, soft skin and mitral valve prolapse. Other signs include low muscle tone, seizures and pubertal macroorchidism [12-14]. Studies show that the clinical features of individuals with FXS [14, 15] are the result of the FMRP (*FMR1* encoded protein) deficit [16] seen in the full mutation [17] and abnormal methylation of the promoter and the gene [18, 19]. Males with the full mutation have little or absent production of *FMR1* mRNA and FMRP [20]. Females have variable levels of *FMR1* mRNA and FMRP, related to the X- chromosome activation ratio (the percentage of cells with the normal X as the active X chromosome) [21].

FMRP, an RNA binding protein, is in part a key translational suppressor and a transport regulator of several mRNAs that are important for synaptic plasticity [22]. FMRP acutely regulates metabotropic glutamate receptor (mGluR)-stimulated protein synthesis and long-term synaptic depression (mGluR-LTD) [23]. In the absence of FMRP, there is an increased number of long and immature dendritic spines of neurons in the *Fmr1* knockout (KO) mice [24, 25]. The mGluR5 pathway plays a role on the development of long-term depression (LTD) in FXS, which in turn weaken long-term memory consolidation [26-28]. These advances in understanding the neurobiology of FXS have led to studies of targeted treatments that can rescue many features of FXS in the *Fmr1* KO mice and in other animal

models [22, 29-33]. In the past decade, human clinical trials for FXS based on the use of mGluR5 antagonists were conducted; however, due to their lack of efficacy these trials were abandoned [32, 34, 35]. Since then, the focus has shifted to the GABA system [36]. Studies in the *Fmr1* KO mouse demonstrated down-regulation of the GABA system with decreased levels of many of the GABA receptors and proteins that are related to the synthesis and metabolism of GABA [30, 37, 38]. These findings have led to clinical trials of GABAergic drugs in FXS. In this review we will discuss the GABA deficits observed in FXSD as well as and potential GABAergic compounds and ongoing related clinical trials.

In 1991 the second FXSD fragile X-associated primary ovarian insufficiency (FXPOI) was described and was linked to the premutation allele [39, 40]. About 20% of female carriers have FXPOI, which is defined as menopause before the age of 40. The mechanism that causes FXPOI is not known, but it has been proposed that the premutation leads to the accumulation of ovarian toxic products [41, 42]. The third FXSD, also linked to the premutation allele, was described in 2001 [43] and subsequently named fragile X- associated tremor ataxia syndrome (FXTAS) [44, 45].

Clinical features of FXTAS include progressive kinetic tremor, gait ataxia, executive function and memory deficits, peripheral neuropathy, and parkinsonism; with associated variable features, such as cognitive decline into dementia, dysautonomia, and psychiatric problems, including depression, apathy, and anxiety [43, 46- 48]. Many individuals with the premutation develop neurological and cognitive problems—including executive function deficits, memory problems, neuropathy, immune mediated problems, migraines, hypertension, and psychiatric symptoms, particularly anxiety—before the onset of tremor and ataxia [49-55]. Neuroimaging in FXTAS reveals white matter disease and diffusion tensor imaging (DTI) abnormalities of both the cerebellum and cerebrum [56- 61]; atrophy of the basal ganglia and brain stem [61, 62], cerebellum spongiosis [59,63,64], demyelination in the white matter, and iron accumulation in choroid plexus and basal ganglia [65]. The pathological hallmark of FXTAS is the presence of intranuclear inclusions in neurons and astrocytes throughout the central nervous system and peripheral nervous system [62, 66, 67]. Peripheral organ inclusions are found in the gastro-intestinal system, heart, testicles, adrenals and pancreas; and their presence correlate to many of the symptoms that are commonly seen in carriers, including cardiac arrhythmias, hypertension, irritable bowel syndrome, erectile dysfunction, and low testosterone levels [66, 68]. Although FXTAS is a disorder associated with aging in carriers of the *FMR1* premutation, FXTAS can occur earlier in adult life, particularly if another disease process is occurring, such as substance abuse that may exacerbate the pathological process of FXTAS [69-71].

FXTAS is thought to be the result of mRNA toxicity from the elevated *FMR1* mRNA levels, a chronic DNA damage repair mechanism, and in part to lower FMRP levels [72]. The elevated levels of mRNA can form hairpin structures which are sticky and lead to the sequestration of many proteins that are important for neuronal function and the formation of pathognomonic inclusion bodies in neurons and astrocytes throughout the CNS, the peripheral nervous system, and other organs [8, 73]. Animal model studies show that mouse hippocampal premutation neurons have a cluster burst firing activity related to the GABA deficits; and allopreg- nanolone, a GABAA agonist, eliminates the abnormal burst firing

[74]. A clinical trial of allopregnanolone in premutation carriers with FXTAS is under development and portends the potential use of GABAergic treatments in premutation carriers.

GABA IN THE CORTEX

While the glutamatergic hypothesis of FXS proposes an exaggerated excitatory mGluR signaling, the GABAergic hypothesis is anchored in decreased GABA signaling. These two hypotheses combined suggest that an excitatory/inhibitory imbalance underlies the pathophysiology of FXS. GABA is the major inhibitory neurotransmitter in the adult mammalian brain and is synthesized and released by interneurons in the cerebral cortex. These interneurons are the only source of GABA and the main provider of inhibitory signaling to the cerebral cortex. All interneurons in the cortex are inhibitory with the exception of spiny stellate cells. Inhibitory interneurons include a wide variety of subpopulations that can be classified based on their morphology, marker expression, and electrophysiological properties. GABA is synthesized by two isoforms of glutamic acid decarboxylase (GAD), GAD65 and GAD67. Both isoforms are present in most interneurons, but GAD67 is located the cytoplasm, whereas GAD65 is located in membranes and nerve endings. It has been suggested that GAD67 preferentially synthesizes cytoplasmic GABA, while GAD65 synthesized GABA for vesicular release [75]. Therefore, the level of expression of GAD65 vs. that of GAD67 could be an indicator of interneuronal capacity to produce and release GABA. GABA is secreted into the synaptic space and binds to transmembrane receptors in pre- and postsynaptic neuronal processes, normally inducing hyperpolarizing events. There are two GABA receptors, the ionotropic GABAA receptor and the metabotropic GABAB receptor. In the adult brain, GABA acts primarily through activation of the fast-hyperpolarizing GABAA receptors that are ligand-gated chloride ion channels comprised of a, B, y and 8 subunits in a heteropentameric structure [76, 77]. GABAB receptors are responsible for the later and slower component of inhibitory transmission [78] and are composed of two subunits, 1 and 2. GABA is released into the extracellular space, where there is reuptake by the GABA transporter GAT1 to the intracellular space. The balance between the different components of the GABA system modulates the inhibitory state of the CNS circuitry and an alteration of this balance induces a change of the excitatory/inhibitory balance in the brain and therefore circuitry malfunction.

GABA SYSTEM RELATED TREATMENT FOR FXS

Animal Models

The standard animal model for the study of FXS is the *Fmr1* KO mouse. Studies investigating the amount of the GABA neurotransmitter in the *Fmr1* KO mice have not come into an agreement. While, an increase in the amount of GABA was described in brainstem [79], a decrease in GABA has been noted in the cortex and cerebellum in these mice [37, 80]. The number of GABA-synthesizing cells, the inhibitory interneurons, was reported unchanged in the cortex; however the number of a specific type of interneuronal subpopulation, the PV+ cells, were decreased in the cortex of *Fmr1* KO mice [37, 81]. Increasing evidence also sup- ports a role for GABAA receptors in the pathophysiology of FXTAS [82]. *Fmr1* KO mice present with underexpression of a series of messengers and

proteins of GABA receptor subunits (a to p subunits in cortex, hippocampus, cerebellum, and other brain region [83-89]. It has been suggested that the absence of FMRP in mice leads to dysregulation of the mRNAs of some GABAA receptors that would normally be bound to it [36]. GABA transporter proteins (GAT1-4), GABA degradation enzymes (succinate semialdehyde dehydrogenase and GABA transaminase), and GABA receptor-clustering proteins (gephyrin) have also been studied in the *Fmr1* KO mice, being mostly down-regulated [82, 84]. However, the level of GAD65/67 protein was increased in the cortex, hippocampus, brainstem and cerebellum [87, 88], while it was reported to be decreased in the amygdala of the *Fmr1* KO mice [37]. A GABAB receptor subunit is also down-regulated in the *Fmr1* KO mice [90]. The expression of genes encoding enzymes and proteins important in the synthesis, transport, and degradation of GABA or related to the clustering of GABAA receptors has also been examined in FXTAS. Cerebellar RNA over-expression of several GABAA receptor subunits (a1, a3, a4, B1, B2 and y2) and proteins involved in the GABA metabolism (GAD1, ssadh and gephyrin) in a CGG repeat premutation knock-in mouse, a model for FXTAS, was reported [82]. Because no differential expression of the GABA-related genes was observed in the cerebellum of the knock- in premutation mouse, the authors speculated that it is unlikely that a reduction of FMRP levels is responsible for these findings and hypothesized that it may be due to an RNA effect [82]. More studies are needed in order to understand the state of the GABAergic system in both FXS and FXTAS. Unfortunately, similar studies in postmortem tissue of patients with FXS are lacking at this point. Studies in humans are necessary in order to better understand these diseases and generate novel and efficient treatments for FXS and premutation involvement.

One of the main targets for treatments for FXS is the GABAA receptor. Several modulators of GABAA activity have been tested in preclinical studies in the *Fmr1* KO mice, including gaboxadol, and neurosteroids such as allopregnanolone or similar synthetic steroids. Gaboxadol is a superagonist of 8 containing GABAA receptor [91]. Gaboxadol-treated *Fmr1* KO mice experienced an in- crease in the axon-potential threshold and a decrease of hyperactivity [92]. Additionally, alphaxalone and ganaxolone, synthetic neurosteroids, prevented seizures and corrected repetitive behavior in the *Fmr1* KO mice [93]. The GABAB receptor has also been targeted for treatment in the *Fmr1* KO mouse and in patients. Arbaclofen, a selective GABAB agonist, reversed social behavior deficits and elevated protein synthesis in *Fmr1* KO mice [94, 95].

No GABA-related preclinical treatments have been performed for FXTAS. However, Zhengyu Cao and collaborators evaluated the influence of allopregnanolone, a positive allosteric modulator of the postsynaptic GABAA receptors [96], on the electric firing pattern of premutation hippocampal neurons [74]. They found that allopregnanolone suppressed the clustered burst firing pattern of premutation hippocampal neurons, reducing the spike rate as well as the mean burst duration, in a concentration dependent and reversible manner. Allopregnanolone and ganaxolone are agonists (allosteric modulators) of GABAA receptors [97, 98] that are currently being studied as a FXS treatment in humans. Acomprosate, riluzole, gaboxadol, tiagabine, and vigabatrin are other potential GABAergic treatments.

HUMAN STUDIES

(Table **1**. summarizes the studies in individuals with FXSD).

Acamprosate

Acamprosate, an FDA-approved drug for the maintenance of abstinence from alcohol use in adults, is an agent with potential pleiotropic effects impacting glutamate and GABA neurotransmission [99]. In animal studies, acamprosate acts as an antagonist at the NMDA glutamate receptor and exhibits GABAA agonism [99, 100]. The open-label treatment with acamprosate in three patients with FXS and a comorbid diagnosis of ASD showed that all three patients improved in linguistic communication [101].

A prospective open-label 10-week trial of acamprosate was also conducted in 12 youth aged 6-17 years (mean age: 11.9 years) with FXS. Acamprosate use (mean dose: 1,054 ± 422 mg/day) was generally safe and well tolerated and was associated with a significant improvement in social behavior and a reduction in inattention/hyperactivity. An increase in brain-derived neurotrophic factor (BDNF) occurred with treatment and BDNF may be a useful bio- marker in future acamprosate studies [102].

Arbaclofen

Arbaclofen, a selective GABAB agonist, was evaluated in a randomized, double-blind, placebo-controlled crossover study in 63 subjects (55 male), ages 6 to 39 years, with FXS. A post-hoc subgroup of 27 subjects with more severe social impairment showed improvements on the Vineland II-Socialization raw score, on the ABC-Social Avoidance scale, and on all global measures. In this exploratory study, arbaclofen did not show a benefit on irritability in FXS [103]. This study led to an 8-week open-label trial enrolling 32 children and adolescents with either Autistic Disorder or Pervasive Developmental Disorder-Not Otherwise Specified without FXS, and a score 2:17 on the Aberrant Behavior Checklist (ABC)- Irritability subscale [104]. Arbaclofen was generally well tolerated. The most common adverse events were agitation and irritability, which typically resolved without dose changes, and were often felt to represent spontaneous variation in underlying symptoms. Improvements were observed on several outcome measures in this exploratory trial, including the ABC-Irritability (the primary end- point) and the Lethargy/Social Withdrawal subscales, the Social Responsiveness Scale, the CY-BOCS-PDD, and clinical global impression scales. However, a subsequent 12-week double-blind controlled trial of arbaclofen in individuals with ASD aged 5 to 21 did not demonstrate efficacy [105], leading to the dissolution of the company. The phase III double-blind controlled trial of arbaclofen in adults with FXS also did not demonstrate efficacy; however, the controlled trial in children with FXS aged 5 to 11 did demonstrate limited efficacy in two secondary measures (ABC FX-Irritability scale and the parent stress scale), although the primary outcome measure, ABC FX-Social Avoidance Scale, did not demonstrate efficacy [106]. Although arbaclofen may have limited efficacy in young children with FXS, it is no longer available for research study.

Allopregnanlone

Allopregnanolone is a neurosteroid and positive modulator of GABAA receptors. Functions associated with this compound in- clude stimulation of neurogenesis in the hippocampus [107], reversal of hippocampal-dependent learning and memory problems [108], neuroprotection by reducing the expression of the proapoptotic protein caspase 3 [109, 110] and inhibiting the mitochondrial permeability transition pores, a key process in the intrinsic pathway of apoptosis [111]. As previously mentioned, preliminary data demonstrate abnormal network bursting activity in hippocampal neurons cultured from premutation mice in addition to up-regulation of several proteins that are related to the RNA toxicity caused by the elevated *FMR1* mRNA seen in premutation carriers [74]. Both the RNA toxicity and the persistent bursting are a plausible mechanism for neurodegeneration that may lead to the neurological symptoms in FXTAS. Allopregnanolone, by potentiating GABAA-receptor signaling, has been shown to eliminate the up-regulation of proteins and the abnormal neuronal bursting in premutation neurons that leads to neuroprotection [74, 112].

Since Alzheimer's disease (AD) is sometimes associated with FXTAS [55, 113], and postmortem neuropathological studies of brains of individuals with FXTAS have demonstrated changes consistent with AD, it is important to review some of the studies of allopregnanolone in AD. Preliminary data demonstrated in an AD mouse model and human progenitor cells that allopregnanolone improved neuronal proliferation [114], reversed neurogenic and cognitive deficits [115], promoted regeneration and reduced beta-amyloid burden [116], restored hippocampal dependent learning, and improved memory and survival [108]. In addition, allopregnanolone is reduced in the prefrontal and temporal cortex in AD. Currently this drug is being studied in AD (ClinicalTrials.gov Identifier: NCT02221622), traumatic brain injury (ClinicalTrials.gov Identifier: NCT01673828) and mild traumatic brain injury (ClinicalTrials.gov Identifier: NCT01336413).

In summary, allopregnanolone can prevent neuronal loss and also stimulate the generation of new neurons from neural stem and progenitor cells. This compound is considered a targeted treatment for FXTAS and may counteract the development of neurological disability by improving executive function deficits, memory deficits, and psychiatric symptoms, particularly anxiety (a hallmark of premutation carriers) [50].

Currently, there is an IND for an open trial to assess the safety and efficacy of allopregnanolone as a new treatment for adults with FXTAS and neurological problems. Premutation carriers ages 50- 85 who present with tremor and/or ataxia in addition to executive function deficits will be enrolled. The participants will receive escalating doses of allopregnanolone IV infusions once a week for three weeks to reach the highest tolerated dose and continue for 12 weeks. Primary outcome measures include the California Verbal Learning Test. Secondary end points are other cognitive measures, such as the Behavioral Dyscontrol Scale (BDS-2), CANTAB battery, COWAT, ERP measures, and a tremor/balance measure, the CATSYS, used in previous treatment studies of FXTAS [117]. It is hoped that this treatment will stabilize the progression of FXTAS and improve memory and executive function deficits in addition to anxiety that these carriers have.

Ganaxolone

Ganaxolone, also known as CCD-1042, is a 3B-methylated synthetic analog of the progesterone metabolite allopregnanolone, which is a neuroactive steroid, and is a potent and selective positive allosteric modulator of the GABAA receptor [98]. Ganaxolone is beneficial for the treatment of seizures in children and adults [87, 96, 98, 118, 119] and also has sedative and anxiolytic effects. Unlike benzodiazepines, there does not appear to be tolerance to the anticonvulsant effects of ganaxolone [118, 120, 121]. In humans, ganaxolone is well tolerated [118, 121-125], with side- effects including sedation, dizziness, fatigue, and headache. Six hundred thirty one adults (males and females, age 18 to 69 years old) and 79 pediatric subjects (males and female, age 6 months to 15 years) have been exposed to ganaxolone [126]. There were 214 subjects in Phase I studies and 498 in Phase II epilepsy and migraine studies. The epilepsy studies involved more than 100 patients and generated data supportive of ganaxolone's efficacy and safety in the treatment of both children and adults suffering from refractory epilepsy. In a placebo-controlled adult epilepsy trial, adverse events were similar to placebo. Overall, ganaxolone was considered to be well tolerated in clinical trials, and the evidence of efficacy in epilepsy was sufficient for the drug to be advanced to additional clinical testing. However it has never been tested as an anxiolytic. As previously mentioned, ganaxolone is considered a targeted specific treatment of FXS because the GABAA receptors are dramatically down-regulated in FXS together with other proteins involved in the metabolism of GABA. Recent evidence indicates that deficits in GABA-mediated inhibition may underlie many of the key symptoms in FXS, including seizures, anxiety, and autistic behaviors [82,84,93,127]. As GABAA receptors are the major inhibitory receptors in the brain and are specifically involved in processes that are disturbed in fragile X, including neuronal excitability (leading to enhanced seizure susceptibility), anxiety, sleep, and learning, enhancement of the function of GABAA receptors may have major therapeutic benefits for FXS. Currently, there is a phase II proof-of-concept clinical trial of ganaxolone being conducted. This study is a double-blind, randomized, placebo-controlled, crossover trial to investigate ganaxolone treatment in children and adolescents with FXS (ClinicalTrials.gov Identifier: NCT01725152). Sixty subjects (aged 6-17 years) are being randomized to receive either ganaxolone or placebo for six weeks and then crossed over to the opposite treatment for another six weeks. The aims of the study are to assess the safety, tolerability, and efficacy of ganaxolone for treatment of anxiety and attention in individuals with FXS. The hypothesis is that ganaxolone treatment compared to placebo will improve anxiety and attention as measured by the several neuropsychological and psychometric tests. The ganaxolone oral suspension dose is titrated from 3 mg/kg up to 12 mg/kg, with maximum of 1500 mg/day; the placebo and ganaxolone are given in three divided doses daily. The primary outcome measure used is the Clinical Global Impression- Improvement scale (CGI-I). Secondary outcome measures include Pediatric Anxiety Rating Scale (PARS), Visual Analog Scale, Aberrant Behavior Checklist and the Swanson, Nolan, and Pelham-IV questionnaire (SNAP-IV). Other outcome measures are the KiTAP-Test of Attentional Performance for Children, social gaze (eye tracking) and event-related brain potentials (ERP). The study was started in 2012 and it will be completed in 2015.

Riluzole

Riluzole is hypothesized to have an inhibitory effect on glutamate release, block excitotoxic effects of glutamate, and potentiate postsynaptic GABAA receptor function. The pleiotropic effects of riluzole may antagonize common mechanisms underlying chronic cerebellar ataxia, a debilitating and untreatable consequence of various diseases including FXTAS. In a randomized, double-blind, placebo-controlled pilot trial, 40 patients presenting with cerebellar ataxias of different etiologies (one of them with FXTAS) were randomly assigned to riluzole (100 mg/day) or placebo for 8 weeks. The number of patients with a 5-point drop in the International Cooperative Ataxia Rating Scale (ICARS) was significantly higher in the riluzole group than in the placebo group after 4 weeks. The participant with FXTAS showed the aforementioned improvement [128]. In a second trial, riluzole was associated with clinical response in 1 of 6 adult subjects with FXS (17%), in a six-week open- label prospective pilot study (100 mg/day). Significant improvement was only noted on the ADHD Rating Scale-IV (which became non-significant when corrected for multiple comparisons). Overall, riluzole use was not associated with significant clinical improvement in FXS [129].

CONCLUDING REMARKS

Even though many targeted clinical trials have been completed, the treatment of children with FXS continues to require special education, speech and language therapy, behavioral intervention, sensory integration, occupational therapy, and physical therapy. In addition, a variety of medications other than targeted treatments such as stimulants, guanfacine, aripiprazole, rispiradone and selective serotonin reuptake inhibitors (SSRIs) are also required [130]. In regards to FXTAS there is currently no disease-modifying intervention although, several medications can help with the symptomatic treatment [55, 131, 132]. There are many challenges at many levels in the discovery of efficacious medications that target specific protein deficits related to genetic syndromes such as FMRP in FXS.

FMRP has many functions, although it mainly acts as a translational repressor; FMRP can also enhance translation, transport and stabilize mRNAs among other functions. FMRP is thought to enhance GABA-receptors expression, so that its absence will lower GABA receptors. Neurobiological studies have demonstrated GABA deficits in both those with FXS and premutation disorders including FXTAS. The advances in the understanding of the GABA system and neurobiology in FXS is now leading to a new wave of clinical trials, and the experience of the previous trials has help researchers and physician scientists to make modifications in the design of the trials that may potentially identify specific benefits in the target population. The criteria for inclusion and outcome measures in clinical trials, in particular, are areas of active research.

The GABAergic compounds described here, particularly the neurosteroids, will hopefully demonstrate safety and efficacy in the studies of FXSD including both those with FXS and premutation disorders. Both allopregnanolone and ganaxolone hold promise to treat FXSDs, and studies with gaboxidol are planned. It is important to remark that other agents that indirectly influence the GABA deficits in FXS include the IGF-1 analogue, which is currently undergoing multicenter trials in FXS [133, 134], and cannabinoids [135], for

which trials will begin soon in FXS. It is likely that GABAergic agents will continue to be part of a multimodality treatment for FXSDs for many years to come. The results of these new trials will likely impact further trials for FXSD and other genetic or idiopathic disorders. Further studies are needed to determine the safety and efficacy of GABA-agonist treatments for FXSD. The future looks promising for GABA-agonist compounds for FXSD including FXS and FXTAS.

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Table 1

Summary of current and potential GABAergic compounds in FXSD

Drug	Efficacy in FXSD
Acamprosate	Improvements in language and behavior [101] Improvements in social behavior and inattention/hyperactivity [102]
Arbaclofen	Improvements in social function and behavior in children with FXS [103]
Allopregnanolone	Initiating for adults with FXTAS
Ganaxolone	Ongoing study in children with FXS (ClinicalTrials.gov Identifier: NCT01725152)
Gaboxadol	No studies but recently licensed for initiation of phase 1 and 2 studies in FXS and Angelman syndrome
Riluzole	Clinical response in 1/6, Improvements in attention and hyperactivity, correction in ERK activation (open label) [129]. One patient with FXTAS improved in the ICARS [128]
Tiagabine	No studies
Vigabatrin	No studies