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New Therapeutic Options for Fragile X Syndrome

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Abstract

Purpose of review The purpose of this review is to provide an overview of current research and clinical practice guidelines in fragile X syndrome (FXS) with regard to therapeutic approaches in the management of this condition. The authors summarize and discuss findings from relevant preclinical studies and results from clinical trials in human subjects with FXS. Additionally, we provide an outline of the basic framework for understanding and providing educational and psychosocial supports for these individuals.

Recent findings Current treatments in FXS are largely symptom based and focused on managing associated psychiatric and behavioral co-morbidities. While data from animal studies has been promising in providing targeted treatments to correct the underlying deficits at the cellular level, there have not been as robust findings in human trials. There are several targeted treatments for FXS currently under development.

Summary Individuals with FXS present with several behavioral challenges including anxiety, social withdrawal, ADHD, hyperarousal, self-injury, and aggression. Therapeutic services are often necessary, such as behavioral intervention, speech and language therapy, occupational therapy, and individualized educational support; adjunctive psychopharmacologic treatment is often helpful as well. It is important to address these symptoms and weigh the evidence for the use of medications that target the underlying neurobiology and pathophysiology of the syndrome.

Introduction

- Fragile X syndrome (FXS) was first described in the 1940s and is the most common inherited cause of intellectual disability. Recent estimated prevalence of FXS in males is one in 4000–7000 and one per 8000–11,000 in females [1, 2]. It is caused by an anomalous expansion of the trinucleotide cytosine-guanine-guanine (CGG) repeats due to methylation in the 5′-untranslated region of the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome [3, 4]. In some cases, FXS can be due to other epigenetic mechanisms such as mosaicism, transcriptional silencing of the gene, which occurs in some cells due to either varying size of the repeat expansion or variations in methylation patterns. Mosaicism can result in variability in the production of fragile X mental retardation protein (*FMRP*) [5]. Individuals with greater than 200 CGG repeats have the full mutation. The typical population has fewer than 42 CGG repeats, those with 42–55 CGG repeats are in the indeterminate zone, and premutation carriers have between 55 and 200 repeats. Signs and symptoms of the fragile X family of disorders include the full mutation causing FXS and the premutation which is associated with several additional disorders which can be seen from birth and across the lifespan. Some of the features of this syndrome, however, may be nonspecific, and the phenotypes can be quite broad.
- Autism spectrum disorder (ASD) is a frequent co-morbid condition seen in 30 to 43% of males with FXS and in 16 to 20% of females with FXS [6, 7]. FXS is the most common known single-gene cause of ASD [8]. About 2–8% of individuals with ASD have FXS [9]. Intellectual disability occurs in > 85% of males with FXS and in 20–30% of females with the syndrome [10]. Individuals with FXS also display significant impulsivity, hyperactivity, and inattention, leading to a diagnosis of attention-deficit/hyperactivity disorder (ADHD) in 54–70% of individuals with FXS [11, 12]. Deficits in executive functioning, working and short-term memory, coordination, and processing of sequential information are often seen in FXS [13]. Additionally, difficulties with sleep, anxiety, self-injurious behaviors, and hyperarousal to sensory stimuli, including auditory, visual, and tactile stimuli, also occur [12]. These emotional and behavioral challenges significantly impact academic and daily functioning in individuals with FXS, and current therapeutics are targeted towards addressing these impairments. Recent advances in understanding the neurobiology and pathophysiology of the syndrome based on animal models have led to the development of novel treatments that target the core deficits at the cellular level, including immature synaptic connections, altered synaptic plasticity, and impaired memory formation, which occur due to lack of FMRP [14]. In this article, we provide an overview of current and upcoming medication treatments in FXS, including symptom-based and targeted treatments.

Pharmacologic treatment

As reported in the Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices in 2012, the use of medications to treat the abovementioned psychiatric co-morbidities in FXS is based on FDA-approved treatments for these conditions in the general population or in those with other neurodevelopmental disorders. While these medications have been demonstrated to be effective in retrospective studies and surveys, there is limited research from clinical trials and controlled studies that provides sufficient evidence for prescribing psychotropic medications to individuals with FXS [15•]. It is important to note that individuals with FXS may have an increased susceptibility to developing side effects, hence starting at a low dose with slow titration of the medication is the recommended approach. Targeted, mechanism-based treatments for FXS have shown some benefits in the

Drosophila dfmr1 mutant fly and *Fmr1* knockout (KO) mouse models [16]. Given that maximal improvement in developmental trajectories is seen with treatment at earlier ages in animal models [16, 17], it will be helpful to investigate mechanism-based treatments in younger populations once tolerable safety profiles have been demonstrated in adult trials.

Selective serotonin reuptake inhibitors and other antidepressants

While there is limited research on serotonin in FXS, there are multiple studies that have demonstrated disrupted serotonin synthesis in individuals with ASD [18, 19]. As previously mentioned, there is a significant overlap between ASD and FXS with 30–50% of ASD genes being associated with FMRP [20]. Therefore, there may be rationale for the use of serotonergic agents in FXS. Serotonin is the primary neurotransmitter in the brain responsible for the regulation of mood and affect, and SSRIs are the main treatment for mood and anxiety disorders in the general population as well as in those with neurodevelopmental disorders. Prior reports have demonstrated some improvement in severe, debilitating anxiety symptoms and behavioral challenges in individuals with FXS with the use of fluoxetine and sertraline [21–23]. A retrospective chart review by Winarni and colleagues in 2012 [24] in children with FXS (ages 12–50 months) treated with sertraline demonstrated improvement in expressive and receptive language development. However, a randomized double-blind controlled trial in children with FXS (ages 2–5 years) did not show similar improvements in language and core ASD symptoms (clinicaltrials.gov; NCT01474746).

Antidepressant medications belonging to other classes, such as tricyclic antidepressants, trazodone, and bupropion, may be considered when there are side effects on SSRIs, such as behavioral activation and sleep difficulties. It is important to note that bupropion may lower seizure threshold and is not recommended for use in individuals with FXS who have an active seizure disorder [25].

Antipsychotic medications and mood stabilizers

Children with FXS can present with irritability and aggression, as manifested by self-injurious behaviors and/or aggression towards others. In situations where the aggression is a result of anxiety, SSRIs are useful in the management of these outbursts. In more severe behavioral and mood dysregulation with a greater risk of injury to self and/or others, second-generation antipsychotic medications like risperidone and aripiprazole have been used (Hagerman et al. 2010). These two medications have FDA approval for use in individuals with ASD (ages 6 and up) for the treatment of irritability and often are used in children with FXS with demonstrable benefit. Males with FXS who exhibited aggression, irritability, and aberrant behaviors showed improvement in symptoms on risperidone (Berry-Kravis and Potanos 2004). These findings were similar to those reported by McCracken and colleagues (2002), who reported decreased irritability and aggression in individuals with ASD who did not have FXS. Prior studies have shown that individuals with FXS have response rates for irritability and aggression of over 70% to aripiprazole (Hagerman et al. 2009; Berry-Kravis et al. 2004; Berry-Kravis et al. 2012). Erickson and colleagues (2010; [26]) conducted an open-label study of aripiprazole and found reduced aggression, aberrant social

behaviors, anxiety, distractibility, and mood instability. Lower doses of aripiprazole (2.5–5 mg in adolescents and up to 1 mg in younger children) are recommended in those with FXS due to the risk of activation at higher doses [27]. It is also important to monitor for antipsychotic-related early- and late-onset side effects, including extrapyramidal side effects, metabolic disturbances, lethargy, and withdrawal emergent effects.

Anticonvulsant medications such as valproic acid, lamotrigine, and carbamazepine also have some evidence for mood stabilization and can target aggressive and self-injurious behaviors in individuals with FXS. Administration of lithium carbonate, dosed to achieve blood levels between 0.7 and 1.2 mmol/L, showed improvement in aberrant behaviors, as measured by the Aberrant Behavior Checklist (ABC), Visual Analog Scale for Behavior, scores on the Vineland Adaptive Behavior Scale (VABS), and Clinical Global Impressions Scale-Improvement (CGI-I) in a study conducted in 15 individuals with FXS (ages 6–23) [28]. These results are consistent with other studies conducted in *dfmr1* mutant fly and *Fmr1* KO mouse models that indicated that lithium administration led to reversed physiological, behavioral, cellular, and molecular phenotypes [29].

Stimulant and non-stimulant medications

Attention-deficit hyperactivity disorder (ADHD) is highly prevalent in individuals with FXS, with up to 70% meeting criteria in prior reports [11, 12, 30]. Prominent symptoms include impulsivity, difficulty with sustained attention, and shifting focus. The efficacy of stimulants in treating ADHD in males with FXS has been demonstrated [22, 23]. Hagerman and colleagues [1988; [31]] conducted a small placebo-controlled, crossover study of methylphenidate in boys with FXS and found improvement in hyperactivity, attention, and social functioning. Methylphenidate was more effective than dextroamphetamine in this study. A retrospective chart review [23] of individuals treated in a FXS clinic reported that, while > 70% of individuals prescribed methylphenidate or amphetamines responded to the medications, there were no significant differences between patterns of use or response to the individual medications (56% and 54% responded to methylphenidate and amphetamine salts respectively). The major reasons for treatment failure were lack of effectiveness with no change in symptoms from baseline or side effects such as worsening of irritability and hyperactivity.

There have been few other controlled studies for medications for ADHD in individuals with FXS. Torrioli and colleagues [32] conducted a randomized, double-blind, placebo-controlled, parallel, and multicenter trial utilizing L-acetylcarnitine (LAC) in 51 males with FXS (ages 6–13 years) and found that the group receiving LAC showed greater improvements in hyperactivity and social behavior compared to the placebo group, as rated on the Conners' Global Index (parent report) and the VABS. Alpha-2 agonists such as clonidine and guanfacine have been reported to be effective in the treatment of hyperactive, impulsive, hypersensitive, and aggressive behaviors and may also improve comorbid sleep and anxiety symptoms [33]. However, sedation was a significant side effect in those treated with clonidine [34]. Atomoxetine, a selective norepinephrine reuptake inhibitor, has also been used with some effect in the management of ADHD symptoms in FXS, but it can lead to potential adverse

effects such as worsening of irritability and aggression, which may result in the discontinuation of the medication [25].

Melatonin

Difficulties with sleep are commonly noted in individuals with FXS, with reports of difficulties falling asleep due to hyperarousal at bedtime or in the middle of the night after awakening [35]. Wirojanan and colleagues [2009; [36]] conducted a 4-week, randomized, double-blind, placebo-controlled crossover study in young males with ASD and FXS (ages 2–15.25 years) and noted that melatonin was associated with longer mean sleep duration and shorter mean sleep-onset latency compared to placebo. As noted above, alpha-2 agonists can also be used for management of sleep problems, but at times can be associated with middle insomnia. Sleep problems are also linked to underlying anxiety symptoms which require treatment with agents such as SSRIs.

Metabotropic glutamate receptor 5 antagonists

Upregulation of metabotropic glutamate receptor (mGluR)–mediated processes is theorized to be one of the most significant pathophysiological mechanisms involved in FXS. The various dysfunctions noted in behavioral, electrophysiological, and molecular systems in FXS are postulated to be due to excessive glutamatergic signaling through mGluRs [37]. This leads to increased local mRNA translation at the synaptic junction, which contributes to internalization of AMPA receptors that slow net synaptic maturation through long-term depression (LTD) mediated by mGluR5. This increased internalization of AMPA receptors leads to an increased number of longer immature dendritic spines, which is a possible explanation for the intellectual disability noted in individuals with FXS [38]. mGluRs also increase synthesis of *FMRP* and this mechanism negatively regulates mGluR activity [39]. Features of FXS are postulated to be related to hyperactivity of LTD due to lack of *FMRP*. Dolen and colleagues [2007; [40]] provided evidence in support of this theory by noting that reduction in mGluR5 levels in *FMR1* KO mice led to normalization of mechanisms such as protein synthesis as well as dendritic spines and behavior, which provided the rationale for the use of mGluR5 antagonists in the treatment of FXS. However, findings from KO mouse models may have some limitations in translation to human studies, due to differences in expression of *FMRP* between mouse models and humans during development [41, 42].

Fenobam [N-(3-chlorophenyl)-N0-(4,5-dihydro-1-methyl-4-oxo-1H-imidazole-2-yl)urea], a non-benzodiazepine anxiolytic, has been studied in FXS due to its effects on negative allosteric modulation of mGluR5. An open-label, single-dose trial of fenobam in 12 adults with FXS (ages 18.7–30.7 years) reported that half of the subjects demonstrated an improvement in prepulse inhibition (PPI), a measure of sensory gating [43]. Clinical improvement was noted in areas of hyperarousal and anxiety and better accuracy on a performance task. Fenobam was well tolerated by all participants, and there were no adverse events reported. However, this medication was not considered for further long-term study due to adverse CNS effects such as hallucinations, vertigo, paresthesia, and insomnia noted in non-FXS individuals taking higher doses of the medication, and due to financial challenges faced by the pharmaceutical company [16, 44].

Mavoglurant/AFQ056, which is a noncompetitive mGluR5 antagonist, was evaluated for the treatment of behavioral symptoms in FXS. Jacquemont and colleagues [2011; [45]] conducted a randomized, double-blind, placebo-controlled crossover study in 30 adults with FXS (ages 18–35 years) which did not show a significant difference between mavoglurant and placebo on the primary outcome measure—the Aberrant Behavior Checklist-Community Edition (ABC-C) total score. Secondary outcome measures, such as the CGI, Visual Analog Scale (VAS) of behavior, Social Responsiveness Scale-Adult Research Version (SRS-A), and VABS also failed to show any significant effects. An exploratory analysis in a subset of the study subjects, which included fully methylated male subjects, showed significant improvement in stereotypic behavior, hyperactivity, and inappropriate speech. These findings led to further phase II randomized, double-blind, placebo-controlled, parallel-group studies in adults and adolescents of 12-week duration. The participants were divided into two groups based on full or partial *FMR1* methylation status. In either study, mavoglurant did not show improvements in behaviors compared to placebo on any of the primary or secondary outcome measures. An open-label continuation of mavoglurant over the next year demonstrated some improvements in behavior and cognition based on family report, but these findings were not controlled and not adequately measured on any of the standardized scales [46].

Basimglurant/RO4917523 is a novel mGlu5 negative allosteric modulator, which has been studied in animal models of depression and has resulted in improved wakefulness and anxiolysis [47]. A study in *FMR1* KO mice using CTEP, a selective mGluR5 inhibitor and a close chemical analog of basimglurant, showed improvements in LTD, protein synthesis, and audiogenic seizures [48]. Results from preclinical trials utilizing CTEP [48, 49] laid the foundation for a 6-week, randomized, double-blind, placebo-controlled trial in 40 adults with FXS (ages 18–49 years). Participants received daily doses of 0.1, 0.5, 1.0, or 1.5 mg, and although the study was not sufficiently powered to detect a significant difference, trends for clinical improvements were noted, but this data has not yet been published [50]. A phase II investigation of the safety and efficacy on the treatment of behavioral symptoms in 183 adults and adolescents with FXS (ages 14–50 years) assessed change from baseline in behavioral symptoms using the Anxiety Depression and Mood Scale (ADAMS) total score [50]. While there were improvements noted in behaviors from baseline with basimglurant administration over 12 weeks, the 1.5-mg group showed less improvement compared to placebo and the 0.5-mg group was inferior to placebo in the ADAMS total score. Additionally, due to presence of adverse events such as hallucinations/psychosis experienced by three participants, it was concluded that basimglurant did not demonstrate significant benefit compared to placebo.

γ-Aminobutyric acid modulators

Dysfunction in GABAergic signaling in various regions of the CNS has been demonstrated in several preclinical studies in FXS and is believed to contribute to deficits at the cellular level as well as to deficits in behavioral symptoms [51–54]. Results from a PET study that quantified GABA-A receptors in individuals with FXS (ages 16–55 years) indicated a reduction in GABA-A binding potential

throughout the CNS [55]. Studies conducted in animal models of FXS using GABA-A agonists have shown improvements in behavior, such as anxiety and hyperactive behaviors, as well as neuronal excitability measures [53, 56]. Ganaxolone, a synthetic allosteric modulator of the steroid allopregnanolone and a positive allosteric modulator at the GABA-A receptor, demonstrated improvements in KO mouse models on measures of repetitive and stereotypic behaviors and seizures [53, 56]. A randomized, double-blind, placebo-controlled, crossover trial involving 51 children with FXS (ages 6–17 years) did not reveal any statistically significant improvements in primary or secondary outcome measures—the CGI-I and the Pediatric Anxiety Rating Scale-R [57]. A subset of the study subjects, which included children with higher baseline anxiety and lower full-scale IQs, revealed positive trends for improved symptoms of anxiety, attention, and hyperactivity.

GABA-B receptors lead to a decrease in presynaptic release of glutamate, which contributes to an increase in the inhibitory effect of the GABAergic system and also decreases the input from excessive mGluR activation, leading to improved neurobehavioral functioning in FXS [16, 58]. Arbaclofen is an active enantiomer of racemic baclofen and a GABA-B agonist. In the *FMR1* KO mouse, Henderson and colleagues [2012; [59]] demonstrated arbaclofen-reduced neuronal hyperexcitability, which contributed to reduced susceptibility to the development of seizures and improvement in neuronal abnormalities. As a result of these positive findings, a randomized, double-blind, placebo-controlled, multi-site crossover study was conducted in 63 subjects (ages 3 to 39 years) [60]. All participants received flexible dose titration of the medication over a 4-week period, but in this trial, they did not show a significant difference from placebo on the primary outcome measure, the ABC-I. Post hoc analyses conducted utilizing the ABC-social avoidance scale and VAS showed significant improvements, while another post hoc analysis in a subset of subjects with more severe social impairment showed improvements in the VABS-II socialization and ABC-Social Avoidance Scale. Subsequently, two other phase 3 placebo-controlled trials were conducted using flexible dosing in adult and adolescent subjects (aged 12–50 years) and fixed dosing in children (ages 5–11 years) [61]. These trials included 119 and 159 subjects respectively, and while there were no serious adverse events reported in either study, some somatic and neurobehavioral side effects were noted in both arbaclofen and placebo arms. In the adult/adolescent trial, no significant improvements were noted in any of the outcome measures. The highest dosing group in the child study showed a positive trend on the ABC- Social Avoidance and Hyperactivity subscales compared to placebo and on some secondary outcome measures as well. No further studies were conducted by the sponsoring pharmaceutical company.

Acamprosate, a calcium salt of N-acetylhomotaurinate and a GABA agonist, has activity at both GABA-A and GABA-B receptors. It is a compound that has been FDA approved for relapse prevention in the treatment of alcohol dependence. In a study conducted in *FMR1* KO mice, acamprosate improved anxiety-like behaviors, hyperactivity, and some electrophysiological and molecular pathology seen in FXS [62]. An open-label study conducted by Erickson and colleagues [2010; [63]] in three individuals with FXS plus ASD showed improved linguistic communication and clinical benefit on the CGI-I. A follow-up prospective open-label 10-week trial of the medication in 12 youths (ages 6–17 years) found that acamprosate was associated with CGI-I of "very much

improved" or "much improved" in 75% of subjects [64]. Additionally, improvements in various secondary outcome measures including the ABC, CGI-Severity, SRS, ADHD Rating Scale, and VABS subscales were noted. Acamprosate was found to be safe in all subjects and was found to stabilize elevated levels of soluble amyloid precursor protein (sAPP) and sAPP-alpha. sAPP and sAPP-alpha are known to be elevated in ASD [65, 66], and the authors propose that these could be potential biomarkers to assess treatment response in future research studies. A current phase II 10 week, double-blind placebo-controlled trial of acamprosate is underway. Results are awaited at this time (clinicaltrials.gov; NCT01911455).

Minocycline

FMRP has also been associated with negative regulation of matrix metalloproteinase-9 (MMP-9), leading to elevated MMP-9 which is associated with immature dendritic spine morphology [16, 67]. Minocycline, a tetracycline antibiotic used for the treatment of acne, is known to inhibit MMP-9 activity, and studies conducted in FMR1 KO mice found that minocycline led to improvements in measures of anxiety, cognition, and maturation of dendritic spines [67, 68]. Utari and colleagues [2010; [69]] conducted a survey of 50 individuals with FXS (ages 0.3–25 years) who received minocycline for at least 2 weeks and noted improvements in language and behavioral functioning based on reports by family members. An open-label pilot trial was conducted in 20 individuals with FXS (ages 13–32 years) and demonstrated improvements in ABC-C Irritability Subscale, VAS, and CGI scores. These findings paved the way for a randomized, double-blind, placebo-controlled trial in 55 children and adolescents with FXS (ages 3.5–16 years). Improvements were seen in CGI-I but not on any of the other behavioral outcome measures [70]. Minocycline was safe overall and well-tolerated by the study subjects. One subject had a seizure while on placebo. Other adverse events noted in studies have been gastrointestinal side effects and seroconversion to positive antinuclear antibody (ANA). Minocycline attenuated altered event-related potentials (ERPs) with improvements in habituation in a subgroup of 12 subjects in which ERPs were measured [71].

Memantine

Memantine (3,5-dimethyladamantan-1-amine), a noncompetitive antagonist at the NMDA receptor, is FDA approved for the treatment of Alzheimer's disease. It has been suggested that NMDA receptor dysfunction may be present in individuals with FXS, but there is insufficient evidence to support this, based on existing studies in preclinical models which suggest that effects may vary depending on the developmental stage and brain region [72–74]. An open-label trial of > 34.7 weeks in six individuals with FXS plus ASD (aged 13–22 years) demonstrated improvement in four subjects on the CGI-1, but two subjects discontinued treatment due to increased irritability [75].

Lovastatin

Lovastatin, an HMG-CoA reductase inhibitor used to treat hyperlipidemia and hypercholesterolemia, has demonstrated effects on intracellular signaling. Protein upregulation noted in FXS is hypothesized to be due to downstream

consequences of increased ERK1/2 activity which has been demonstrated in FXS mouse models and human brain tissue (Hou et al., 2006; Price et al., 2007). In FMR1 KO mice, lovastatin inhibited Ras, reduced increase in basal ERK activation, lowered protein synthesis to wild type levels, and ameliorated FXS audiogenic seizure susceptibility [76]. An open-label trial was conducted by Caku and colleagues [2014; [77]] in 15 individuals with FXS (ages 6–31 years) and significant improvements were noted after 4 and 12 weeks of treatment. The ABC-C, CGI, and VABS-II scores improved from week 4 to week 12. Lovastatin also reduced excessive ERK activity as measured in platelets and this correlated with behavioral improvement on the ABC-C.

Other supportive treatments and interventions

Although there is a wide range of phenotypic variation seen in individuals with FXS, the majority of them have difficulties with executive function, auditory and sensory processing, complex reasoning, mathematical skills, socialization, and communication [13]. Additionally, the presence of hypotonia and joint laxity in individuals with FXS can lead to difficulties with academic performance requiring fine motor skills (handwriting and speed) and various gross and fine motor activities needed for coordination. Behavioral and adaptive functioning challenges noted in individuals with FXS can be addressed by interventions provided by an interdisciplinary team comprised of individuals from child psychiatry/mental health, educators and school personnel, occupational therapy, speech/language pathology, and caregivers, as recommended by the Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices. A comprehensive evaluation is especially useful when behavioral, educational, and short and long-term treatment goals and plans are being made. As part of this approach (described below), a number of components are helpful to include in order to evaluate the needs of each individual. A detailed psychoeducational assessment analyzes the underlying cognitive processes that can impact performance. It uses data that assesses the individual's ability to process information and should be conducted and updated at least every 3 years, unless otherwise not recommended. A functional behavioral assessment (FBA) conducted by a school professional such as a behavioral therapist or psychologist aims to determine the antecedents or function of a particular behavior. Results obtained from this analysis can help determine alternative or replacement behaviors and consequences that will help eliminate or not maintain the challenging behaviors.

Special Education Services are provided to children and adolescents with FXS as a part of the Individuals with Disabilities Education Act (IDEA) of 2004. These services are available in school settings and are provided by members of the interdisciplinary team. The Individualized Education Program (IEP) is the legal document that outlines the process that guides the child's educational program and services and is developed after assessments are conducted by the interdisciplinary team. Based on the needs of the child identified during these assessments along with input and approval from parents, the IEP is constructed. Use of various assistive technologies at school can help children improve their functional abilities. For example, use of a special chair to aid with positioning

and posture can help a child with low muscle tone. Access to school counselors is also provided, which can assist with behavioral and mood symptoms as well as the development of social skills by use of group-based therapies. Physical and occupational therapists design and implement interventions that focus on achieving optimal functional outcomes and provide support with gross and fine motor skills. Speech/language pathologists not only assess for deficits in receptive and expressive language skills, but also refer for medical assessments when necessary and provide therapeutic services. Parent counseling and training is also an integral part of the supports and services that are valuable in the management of individuals with FXS. Parents are provided with information about the child's condition, and they are connected with support groups, advocacy services, and financial advisors and obtain referrals for professional services. Parents and caregivers often find that therapy services for themselves are helpful to get additional support around the management of the unique challenges of individuals with FXS.

Emerging therapies

There are several investigational drug therapies underway that are based on the identification of the underlying biochemical mechanisms in FXS. In this section, a brief overview of clinical trials in FXS obtained from the US National Institutes of Health index of clinical trials (www.clinicaltrials.gov) is provided. These studies are limited to those that are in the recruitment phase; studies with results have been discussed in prior sections.

- NCT03722290 is a trial being conducted at Université de Sherbrooke, which is examining the role of metformin, a widely prescribed drug for type II diabetes in children and adults that can correct various neurological and behavioral FXS phenotypes by normalizing ERK signaling and EIF4E phosphorylation and lowering expression of MMP9 to normal. The study will administer metformin orally at 250 mg (twice a day) for the first week followed by metformin 500 mg (twice a day) for the next 8 weeks.
- NCT03140813 is a double-blind, placebo-controlled two-dose crossover study being conducted at the Cincinnati Children's Hospital Medical Center, which is investigating the safety, tolerability, and pharmacodynamics of treatment with oral administration of AZD7325, which is a high affinity, selective modulator of the $GABA_A$ receptor system, with differential binding and modulatory properties dependent on the particular $GABA_A$ subtype. All participants will orally receive AZD7325 at 5 mg BID, 15 mg BID, and placebo BID.
- NCT03697161 is a multi-site phase 2, randomized, double-blind, parallel-group study sponsored by Ovid Therapeutics that aims to assess the safety, tolerability, and efficacy of oral OV101 (gaboxadol), a GABA-A receptor antagonist, in FXS. Participants will receive OV101 once daily, twice daily, or three times daily.

- NCT03569631 is a randomized, double-blind, two-period crossover study being conducted at Rush University Medical Center, which aims to explore the effects of BPN14770, an allosteric inhibitor of phosphodiesterase E4D, which has been shown to have beneficial effects on memory in mouse models. Participants will receive 25 mg BPN14770 capsules or matching placebo capsules during period 1, followed by the opposite treatment during period 2. One capsule will be taken twice daily during both double-blind periods.
- NCT03614663 is a randomized, double-blind, placebo-controlled, multi-site study, to assess the efficacy and safety of ZYN002, a pharmaceutically manufactured CBD, formulated as a transdermal gel, for the treatment of anxiety and behavioral challenges in children and adolescents with FXS. If the participants weigh less than or equal to 35 kg, they will receive two sachets of the gel twice a day (one sachet approximately every 12 h) or placebo, and if they weigh more than 35 kg, they will receive four sachets of gel per day (two sachets approximately every 12 h) or placebo.
- NCT02747394 will evaluate the efficacy of Cogmed, a cognitive training program proven to enhance working memory and executive/frontal function in a variety of clinical populations, in individuals with FXS, which is being conducted at the University of California, Davis. Participants will undergo 5 days per week for 5–6 weeks of parent-aided visual working memory training, consisting of adaptive Cogmed or nonadaptive Cogmed.
- NCT03510156 is an interventional study being conducted at Stanford University that aims to assess the effectiveness of administering a standardized function-based behavioral treatment for problem behaviors in FXS using telemedicine. Participants will be randomly assigned to receive the behavioral analytic treatment or observation.
- NCT02616796 is an interventional study conducted at Stanford University that aims to evaluate a 2–3 day treatment probe targeted to improving social gaze behavior in children with FXS. The investigators will use the principles of Applied Behavior Analysis (ABA) to shape appropriate social skills and examine the effects of this treatment probe on brain and behavior.

Compliance with Ethical Standards

Conflict of Interest

Isha Jalnapurkar has no potential conflicts of interest relevant to this article.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

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