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Treatment of the psychiatric problems associated with fragile X syndrome

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Abstract

Purpose of review—This work reviews recent research regarding treatment of fragile X syndrome (FXS), the most common inherited cause of intellectual disability and autism spectrum disorder. The phenotype includes anxiety linked to sensory hyperarousal, hyperactivity, and attentional problems consistent with attention deficit hyperactivity disorder and social deficits leading to autism spectrum disorder in 60% of boys and 25% of girls with FXS.

Recent findings—Multiple targeted treatments for FXS have rescued the phenotype of the *fmr1* knockout mouse, but few have been beneficial to patients with FXS. The failure of the metabotropic glutamate receptor 5 antagonists falls on the heels of the failure of Arbaclofen's efficacy in children and adults with autism or FXS. In contrast, efficacy has been demonstrated in a controlled trial of minocycline in children with FXS. Minocycline lowers the abnormally elevated levels of matrix metalloproteinase 9 in FXS. Acamprosate and lovastatin have been beneficial in open-label trials in FXS. The first 5 years of life may be the most efficacious time for intervention when combined with behavioral and/or educational interventions.

Summary—Minocycline, acamprosate, lovastatin, and sertraline are treatments that can be currently prescribed and have shown benefit in children with FXS. Use of combined medical and behavioral interventions will likely be most efficacious for the treatment of FXS.

Keywords

fragile X syndrome; GABA agonists; mGluR5 antagonists; minocycline; omega 3; sertraline

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Conflicts of interest

Randi Hagerman has received funding from Novartis, Roche/Genentech, Seaside Therapeutics Neurpharm, Curemark, Forest, and Alcobra for treatment studies in fragile X syndrome, autism and Down's syndrome. She has also consulted with Roche/Genentech, Novartis, and Alcobra regarding treatment studies in Fragile X syndrome. Jonathan Polussa does not have any conflicts.

INTRODUCTION

Fragile X syndrome (FXS) has led the way for targeted treatments regarding neurodevelopmental disorders [1]. Perhaps, this is because the gene and causative mutation, the Cytosine, Guanine, Guanine (CGG) expansion in *FMR1* was discovered in 1991, and the knockout mouse model for FXS was developed early so that the last decade of research has assessed new treatments that target the neurobiological abnormalities of FXS. This most common cause of intellectual disability and autism is caused by a full mutation in *FMR1*, meaning greater than 200 CGG repeats in the promoter region leading to methylation and the silencing of transcription. Since *FMR1* is at Xq27.3, FXS is a sex-linked disorder and men are affected more severely than women. The dysmorphic facial features include narrow face and prominent ears, recently reviewed by Heulens *et al.* [2], although for many, these features may be hard to distinguish from the general population. Over 85% of men will have an intelligence quotient (IQ) between 20 and 70, whereas only 25% of women will have intellectual disability with an IQ less than 70. However, learning disabilities are seen in over 70% of women and psychiatric problems including anxiety, compulsive behaviour, and attention deficit hyperactivity disorder (ADHD) are seen in the majority of men and women with FXS [3].

Anxiety is a key feature in FXS and in comparison to age-matched boys with autism without FXS anxiety was higher in those with FXS and there was a significant association between social avoidance and autism in FXS that was not seen in those with autism without FXS [4▪▪]. Autism spectrum disorder (ASD) occurs in approximately 60% of boys and 20% of girls [3,4▪▪]; however, boys with FXS and autism demonstrated a greater interest in social interactions than boys with autism without FXS, but overall more anxiety [4▪▪]. Therefore, anxiety is an important target for treatment in FXS.

Fragile X mental retardation 1 protein (FMRP), the protein normally produced by *FMR1*, but deficient or missing in FXS, is a regulator of translation that controls most of the proteins important for synaptic plasticity [5]. There is significant overlap between the genes associated with ASD and the genes whose translation is controlled by FMRP [6▪▪,7]. When FMRP is deficient, there is up-regulation of many proteins, including those that internalize AMPA receptors leading to enhanced long term depression (LTD), in addition to matrix metalloproteinase 9 (MMP9) that is important for synapse formation, GSK3β, Arc, STEP, Map1B, αCaMKII, post synaptic density 95, Shank 1, SAPAP1-3, and many others [6▪▪,8]. Dendritic spine morphology is dysregulated in FXS, leading to immature, elongated spines [9▪] that can be rescued by targeted treatments described below.

The metabotropic glutamate receptor 5 (mGluR5) theory of intellectual disability in FXS explained the immature synaptic connections seen in both animal models and humans with FXS as secondary to enhanced LTD produced by up-regulation of LTD proteins that internalized AMPA receptors and weakened the synaptic connections [8]. This theory led to the treatment of FXS by mGluR5 antagonists which would reverse the LTD and rescue the synaptic phenotype in FXS. Such was the case in the animal models that were treated with mGluR5 antagonists including MPEP, fenobam, AFQ056 (Mavoglurant; Novartis pharmaceuticals), and RO491756 (Basimglurant; Hoffman-LaRoche pharmaceuticals)

[8,10]. However, the human trials discussed below have not met efficacy criteria and therefore further studies have been stopped in 2014.

The gamma amino butyric acid (GABA) system is basically down-regulated in FXS and this has led to the use of $GABA_A$ and $GABA_B$ agonists in both animal models and human trials in FXS. The preliminary study of Arbaclofen (STX209) demonstrated benefit in a subgroup of patients with FXS, particularly those with ASD or social avoidance on the Aberrant Behavior Checklist (ABC) [11]. Therefore, a subsequent phase 2 open-label trial was initiated to assess long-term benefit, and two phase 3 multicenter studies were initiated in both adolescents and adults (209FX301; aged 12–50; $n = 120$; Clinical Trials.gov identifier: NCT01282268) and in children aged 5–11 years (209FX302; $n = 172$; Clinical Trials.gov identifier: NCT01325220). These studies involved 8 weeks of treatment vs. placebo, with the first 4 weeks involving escalation of the dose followed by 4 weeks of stable dose of Arbaclofen/placebo (maximal dose was 10 mg three times a day). The phase 2 controlled trial in ASD without FXS did not demonstrate efficacy on the primary outcome measure and the publicity of the failed autism trial led to failure of the company financially and the fragile X trials were halted. The results of the two phase 3 controlled trials were presented at the National Fragile X Foundation International Conference in Anaheim in July 2014 [12]. Neither of the phase 3 trials of FXS met their primary outcome measure of significant improvement in Social Avoidance Scale on the fragile X ABC [13] that had demonstrated a beneficial outcome in the initial phase 2 trial once the data were reanalyzed. However, the children's trial (209FX302) demonstrated significant efficacy on secondary measures, so it appears that Arbaclofen may be more effective in young children with FXS, although it is currently unavailable.

Ganaxolone, a neurosteroid that is a $GABA_a$ agonist is in a phase 2 double-blind crossover trial in children with FXS aged 6–17 years at the MIND Institute (http://www.clinicaltrials.gov; NCT01725152), but results will not be known for another year.

Additional agents have been tried in children with FXS including minocycline and sertraline, with good results reviewed below. Up-and-coming agents have been introduced this year in animal studies, and these results which will eventually move into clinical trials are discussed below.

MINOCYCLINE

Minocycline is an antibiotic used in the treatment of acne in adolescence. Minocycline lowers MMP9 level that is too high in FXS [14▪]. The recent publication of a double-blind crossover controlled trial of minocycline lasting 3 months for each arm of treatment was carried out in 55 children aged 3.5–16 years with FXS. Forty-eight patients completed this trial and efficacy was demonstrated on the primary outcome measure of the Clinical Global Impression Scale (CGI-I) and on the secondary measure of the Visual Analogue Scale (VAS) targeting mood and anxiety [15▪]. Side-effects were not significantly different compared to placebo in this study. However, minocycline can cause graying of the permanent teeth and sometimes darkening of the nails, skin, or gums with long-term use. In addition, a positive antinuclear antibody (ANA) can occur in a subgroup of patients treated with minocycline, so

the ANA should be checked every 6 months to 1 year for safety. A rare side-effect of a lupus-like syndrome with rash and swollen joints can develop with minocycline treatment. Another rare side-effect includes headaches caused by pseudotumor cerebri, meaning increased intracranial pressure. Minocycline is available clinically and can be prescribed for those with FXS, but families should be warned that if headache, rash, swollen joints, or an increasing ANA titer develop, then the minocycline should be discontinued. Event-related potential (ERP) studies have demonstrated improvements in habituation to a passive odd ball auditory paradigm in 12 patients with FXS (eight males and four females; mean age 10.5 years) who underwent the minocycline controlled trial [16▪▪]. After 3 months of minocycline treatment, the elevated N1 and P2 amplitudes over the temporal regions typical for FXS normalized and habituation significantly improved compared to placebo [16▪▪]. This study demonstrates that ERPs are a sensitive and feasible biomarker that can be utilized as an outcome measure in treatment trials in children with FXS.

The very recent report of the cross between an MMP9 knockout mouse with an *fmr1* knockout mouse leading to the rescue of the FXS phenotype in the offspring emphasizes the importance of the MMP9 pathway in the phenotype of FXS [17▪]. Therefore, further studies are needed in young children with FXS who are treated early so that the appropriate synaptic connections can be developed early on.

LOVASTATIN

The recent study by Osterweil *et al.* [18▪▪] represents another targeted treatment that can down-regulate the excessive protein synthesis that occurs in FXS. They studied the enhanced activity of the Ras/MAPK pathway in FXS and found that lovastatin, an HMG-CoA reductase inhibitor used to treat hypercholesterolemia in children and adults, can correct excessive Ras activity in the *fmr1* knockout mouse model similar to what lovastatin can do in the mouse model of neurofibromatosis (NF1). They demonstrated that lovastatin treatment corrected the excessive extra cellular receptor kinase-mediated protein synthesis and blocked mGluR5-mediated epileptiform bursting in the *fmr1* knockout hippocampal neurons. Lovastatin also dampened the hyperexcitability seen in the visual cortex in the knockout mouse. In addition, they rescued the seizure phenotype in the live knockout mouse. These studies have stimulated human trials of lovastatin and preliminary results of an open-label trial in children with FXS in Canada demonstrated positive results [19].

ACAMPROSATE

Acamprosate is a $GABA_a$ agonist that is US Food and Drug Administration (FDA)-approved for maintenance of abstinence in adults with alcohol dependence. However, acamprosate has potential antagonism at mGluR5 receptors with similar effects to mGluR5 antagonists in the rodent models of alcoholism [20]. Acamprosate also binds at spermidine-sensitive NMDA glutamate receptors where it can enhance activation at low glutamate concentrations and cause inhibition at high glutamate concentrations. Erickson *et al.* [21] initially carried out an open-label study in three young adults with FXS and saw not only improvements in the CGI-I in all patients but unexpected improvements in language. They have recently reported a 10-week open-label acamprosate trial in 12 children (6–17 years; mean age 11.9 years)

with FXS. Nine of the 12 children (75%) demonstrated significant improvement in the CGI-I and additional standardized scales improved capturing benefits in ADHD symptoms and social interactions. They also demonstrated a deficit in brain derived neurotropic factor (BDNF) measured in blood at baseline and they saw a significant increase in this biomarker with acamprosate treatment, although the improvement in BDNF levels did not correlate with treatment response measures [22▪]. Currently, a multicenter controlled trial of acamprosate is being carried out in individuals with FXS (http://www.clinicaltrials.gov; NCT01911455).

CANNABINOIDS

The endocannabinoid system is a modulator of synaptic plasticity, anxiety, and seizure activity, and Maccarrone *et al.* [23,24] were the first to show that FMRP is a regulator of the endocannabinoid system in the striatum. Pharmacological blockade of the endocannabinoid receptor CBR1 by rimonabant has been shown to normalize cognitive impairment, reduce susceptibility to seizures, and normalize mammalian target of rapamycin (mTOR) signaling in knockout mice [25▪]. Recent study by Straiker *et al.* [26] have demonstrated broad effects on the endocannabinoid system by the loss of FMRP in the knockout mouse that changes with age. Initially, there appears to be overproduction of the 2-arach-idonoylglycerol (2AG) neurotransmitter leading to enhanced cannabinoid inhibition of excitatory neurotransmission in hippocampal neuron of the knockout mouse; then there is a gradual desensitization of CB1 receptors with age and a decline in cannabinoid signaling [26]. Although there appears to be the potential for therapeutic manipulation of the cannabinoid system in FXS, there is no consensus regarding whether a blockade or enhancement of one or the other receptor (CB1 or CB2) and the appropriate age that would be acceptable for studies of patients with FXS.

OMEGA 3 AND OTHER NEUTRACEUTICALS

There is significant evidence from knockout mouse studies that additives to the diet including alpha-tocopherol (vitamin E) and N-acetyl cysteine (NAC) [27], melatonin (also an antioxidant) [28] and just recently long chain polyunsaturated fatty acids (PUFAs or omega 3s) can rescue some of the phenotypic abnormalities seen in FXS [29▪▪]. Presumably these benefits with antioxidants are related to the enhanced oxidative stress seen in the knockout mice [30]. The omega 3 study supplemented knockout mice from the time of weaning to adulthood with a diet enriched with omega 3s, including more n-3 long-chain PUFAs such as 20:5 n-3 (eicosapentaenoic acid), 22:6 n-3 (docosahexaenoic acid) compared to the control diet, which was isocaloric with equal amounts of lipid including a normal amount of PUFAs. The PUFA-enriched diet in the knockout mice led to improvement in the affiliation deficit when interacting with female mice, improvement in excessive self-grooming, changes in various cytokine/chemokine levels, and normalization of the BDNF deficit seen in the dentate gyrus of the knockout mice compared to control mice [29▪▪]. These findings are compelling because such supplements are easy to recommend, although studies of patients with FXS have not been completed. A randomized controlled trial of alpha tocopherol (10 mg/kg/day) combined with vitamin C (10 mg/kg/day) is currently

being carried out in Spain by de Diego-Otero *et al.* [31] lasting 12–24 weeks for boys with FXS aged 6–18 years (ClinicalTrials.gov Identifier: NCT01329770).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Metabolomic studies show down-regulation of the enzymes that metabolize tryptophan to serotonin in the blood of individuals with both genetic and idiopathic forms of ASD [32]. Further evidence of serotonin deficits have been found in positive electron tomography studies of children with autism between the age of 2 and 6 years [33]. Such studies and clinical experience led to the treatment of young children with FXS with sertraline to improve anxiety, sensory hyperarousal, and language deficits [34]. In a retrospective review of 45 patients with FXS (18 months to 6 years), there was a significant benefit in the trajectory of both receptive and expressive language as measured by the Mullen Scales of Early Learning (MSEL) in those treated with sertraline compared to those not treated with sertraline [34]. These data stimulated a controlled trial of low-dose sertraline (2.5–5.0 mg/day) treatment in young children with FXS between the age of 24–68 months at the MIND Institute (Clinical-Trials.gov identifier: NCT01474746). Preliminary data after the first 30 children completed the study demonstrated significant improvement on the CGI-I in those treated with sertraline [35]. Selective serotonin reuptake inhibitors (SSRIs) are known to stimulate neurogenesis and increase BDNF which is low in FXS [36]. In addition, sertraline specifically enhances dopamine levels in the striatum [37] and has neuroprotective and procognitive effects in young mice [38]. Both of these strengths can be very important for young children with FXS who have evidence of oxidative stress.

ENVIRONMENTAL ENRICHMENT

A recently published paper by Oddi *et al.* [39▪▪] has demonstrated that enrichment in early development in the knockout mouse by the introduction of a nonlactating female to the mother– pup pair from birth to 3 months of age had significant positive effects on the time the mother spent with the babies and also on the adult phenotype of the knockout mouse. Specifically, this enriched environment eliminated the hyperactivity, rescued the social deficits, and eliminated the cognitive deficits in two hippocampal phenotypes, the Y maze and the contextual freezing deficits in the adult knockout mouse. In addition, there was rescue of the immature spine morphology in apical and basal dendrites in the hippocampus in the adult knockout mouse [39▪▪]. This work points to the importance of early intervention and builds on the previous work of environmental enrichment through physical toys [40] by showing that another adult, apart from the mother, is an important form of enrichment. This enrichment is reminiscent of the benefits of early intervention with a therapist who can enhance the mother's interaction with her child as is seen in the Early Start Denver Model with long-lasting consequences in children with autism [41].

COMBINATION TREATMENTS

An exciting result in the knockout mouse model was published in 2014 by Lim *et al.* [42▪], demonstrating that combining low-dose serotonin 5 HT2B agonist with a dopamine (DA-1) agonist led to improvements in normalizing protein kinase B (PKB) signaling and rescued

the associative learning deficit in the knockout mouse compared to controls. Basically, the NMDA-R-dependent long-term potentiation (LTP) is reduced in the knockout mouse [43] due to a selective impairment of signal transduction between Ras and P13K/PKB that impairs GluA1-dependent plasticity in the knockout mouse [44]. It has been known for years that children with FXS respond best to low doses of stimulants combined with an SSRI, typically sertraline [45], and now the animal studies demonstrate that this cocktail works best in a low dose compared to a high dose. In the absence of FMRP, many of the proteins belonging to the NMDA-R–Ras–PI3K/PKB signaling interactome are dysregulated [6▪▪, 42▪]. Lim *et al.* show that synaptic Ras signal transduction is impaired even though the basal Ras activity is up-regulated in knockout mice. Knockout mice have reduced maximal PI3K/PKB activity compared to wild-type mice. The rescue of synaptic plasticity and associative learning with the cocktail occurred via stimulating PI3K/PKB signaling dynamics and thus restoring PI3K/PKB signaling-dependent synaptic GluA1 trafficking. This GluA1-dependent rescue is consistent with the findings that the knockout mice have a predominant deficit in GluA1-dependent synaptic plasticity [44] and synaptic GluA1 delivery is required for associative learning [42▪].

Seese *et al.* have also recently demonstrated that the spacing of learning trials also has a profound effect on long-term memory in the knockout mouse [46]. Instead of one long training session which promotes LTP in the wild-type mouse, the knockout mouse has robust long-term memory only when the training is divided into three short sessions each separated by 1 h. This basic research should be translated into the school for those with FXS.

CONCLUSION

The concept of combined treatments working best in FXS will likely be studied further, particularly combining medications that have different mechanisms of action, for example, minocycline and ganaxolone or minocycline and sertraline [47]. In addition, expanding combinations to include medications that will improve synaptic plasticity with innovative learning programs is essential if reversal of cognitive and behavioral impairment is to be achieved in FXS [48]. An example of an intensive learning program that is helpful for ADHD symptoms in children with FXS is CogMed, a digital program for improving attention and learning in children with ADHD [49]. Another example is an intensive digital reading program, such as Head-Sprout, because the enhancement of reading can be important for improving the verbal IQ in children with FXS [50]. We are in a new age for improving cognitive and behavioral problems in those with neurodevelopmental disorders and the plethora of new targeted treatments for many disorders in addition to FXS, such as Rett syndrome, ASD, Down’s syndrome, and many others will dramatically increase in the next few years [51].

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KEY POINTS

- Minocycline is available by prescription and has demonstrated efficacy for improving behavior in children with FXS.
- The mGluR5 antagonists have not demonstrated efficacy in controlled trials in FXS.
- There is both animal evidence and clinical evidence that combining treatments, such as the use of a stimulant and an SSRI, can be helpful in the treatment of FXS.
- Research regarding the combined effects of behavioral/learning intervention and medication intervention is greatly needed in the fragile X field.