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FRAGILE X SYNDROME: PSYCHIATRIC MANIFESTATIONS, ASSESSMENT AND EMERGING THERAPIES

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Abstract

Fragile X Syndrome (FXS), the most common inherited cause of intellectual disabilities, is an X-linked dominant disorder caused by the amplification of a CGG repeat in the 5' untranslated region of the fragile X mental retardation gene 1 (*FMRI*). Prevalence estimates of the disorder are approximately 1/3600. Psychiatric manifestations of the disorder include anxiety, attention deficit hyperactivity disorder, autism, mood instability and aggression. In this article we review the above psychiatric manifestations and challenges to accurate assessment. We also discuss how the neurobiological underpinnings of these symptoms are beginning to be understood and can help guide treatment.

Keywords

assessment; fragile X syndrome; neurobiology; psychiatric symptoms; treatment

INTRODUCTION

Fragile X Syndrome (FXS) is an X-linked dominant disorder caused by the amplification of a CGG repeat in the 5' untranslated region of the fragile X mental retardation 1 gene (*FMRI*). These CGG repeats disrupt synthesis of the fragile X protein (FMRP) known to be essential for brain function and growth [1]. The resulting syndrome is the most common inherited cause of intellectual disability with a prevalence estimate of 1/3600–4000 [2, 3]. The cognitive, behavioral and physical phenotype varies by sex, with males more severely affected because they have only one X chromosome [4]. Physical characteristics may include a long, narrow face, high arched palate, prominent ears, and enlarged testicular volume in post-pubescent males [4]. The FXS phenotype typically involves a variety of psychiatric symptoms, including features of autism, attention deficit/hyperactivity disorder, anxiety, and aggression. These symptoms can have a profound impact on daily functioning,

disrupting schooling as well as family life, and lead to significant parenting challenges [5]. The manifestations, assessment and treatment of these psychiatric symptoms in FXS patients are the focus of the present paper.

PSYCHIATRIC MANIFESTATIONS

Attention Deficit Hyperactivity Disorder

Beginning in the 1980s, hyperactivity and concentration difficulty were noted to be some of the most prominent psychiatric symptoms in FXS with most males meeting formal criteria for ADHD [6, 7]. Cross-sectional studies with parent and teacher ratings show a 59% incidence of ADHD [8]. According to a recent national parent survey of 976 full mutation males and 259 full mutation females, 84% of males and 67% of females had been diagnosed or treated for attention problems [9]. While attention deficits persist, hyperactivity tends to decrease with age and is independent of intellectual level [10,11]. Hyperactivity generally emerges around preschool age with a steady decline as body mass increases [11,12]. Hypoactivity is often seen in very young children with FXS [4].

Anxiety and avoidant behavior

Individuals with FXS display a wide range of anxiety symptoms that fit multiple different types of anxiety disorders of the Diagnostic and Statistical Manual IV (DSM IV) [13]. In a recent study of the prevalence of anxiety disorders in a group of 58 males and 39 females with FXS (ages 5.0–33.3 years old) 86.2% of males and 76.9% of females met criteria for at least one anxiety disorder. The most common disorders were specific phobia (51.4% of females, 64.9% of males), social phobia (55.3% of females, 60.3% of males), and selective mutism (21.1% in females and 28.1% in males) [13]. These rates are significantly higher than the 10.5% overall rate of anxiety disorders found in individuals with intellectual disability (ID) [14]. Evidence for obsessive compulsive disorder (OCD) and compulsive behaviors alone have also been shown. In a study using the Compulsive Behavior Checklist (n=60, ages 5–20) 18.4% of females and 27.3% of males met full criteria for obsessive compulsive disorder [15]. However, compulsive behavior alone was seen in 72% of males and 55% of females [15]. This suggests that compulsive behavior is quite common in FXS and could have a different underlying cause when compared to OCD. Supporting this idea are observations that a child with FXS may derive pleasure from repetitive behaviors such as watching the same video or perseverating on topics. This is distinct from the ego-dystonic obsessions and compulsions classically described in OCD and has led some to hypothesize that the compulsive behaviors seen in FXS are associated with the repetitive behaviors characteristic of autism in FXS [10].

In addition to anxiety disorders there is a classically described set of behavioral features in FXS which includes poor eye contact, gaze aversion and shyness. This suggests a high level of anxiety, particularly in social interactions [4]. In an early study of the psychological profile of FXS, “timid” behavior was noted in 47.6%, “fearful” behavior was seen in 28.5%, whereas “low stress tolerance” and “sensitive” behavior were each observed in 24% of individuals [6]. Additionally there is a characteristic turning away during introduction or while shaking hands in greeting, which appears to function as avoidance of eye contact [16].

This gaze aversion often appears different from the lack of eye contact seen in autism as it is often displayed by children who are otherwise socially engaged and affectionate [17]. The timid behavior, fearfulness and gaze avoidance can be thought of as avoidant behaviors in general and are quite common in both males and females [12, 18].

Autism spectrum disorders

An association between autism and FXS was first noted in the early 1980s and identification of the disorder has steadily increased with more consistent use of formal testing. Current estimates of the percentage of patients with FXS who have autism are now around 30–35% [19–21]. However, prevalence varies a great deal by gender. In a study of 47 girls and 73 boys with FXS, 35.1% of boys and 4.3% of girls met autism criteria based on the Social Communication Questionnaire and Autism Diagnostic Observation Schedule [20]. Autistic behavior is more frequently observed in the youngest males with FXS and those who are moderately intellectually impaired [11]. In early studies the most prominent autistic features described were lack of eye contact, stereotyped movements and echolalia [7]. However, lack of eye contact in this population is common [22] and difficulty establishing and maintaining eye-gaze in social interactions has been associated with increased levels of the stress hormone cortisol or autonomic reactivity in individuals with FXS; as such, gaze aversion in this population may be a coping mechanism for social anxiety rather than a symptom solely associated with autism [23–26]. Other common autistic features include perseverative behaviors or speech, sensory hypersensitivity, and stereotypic or repetitive motor behaviors such as hand flapping and hand biting [4]. Notably, analysis of the symptom profile in children with FXS who are diagnosed with autism reveals lower rates of impairment in communication and reciprocal social interaction than reference autism samples in one study [20] but not in others [21]. Of the individuals who are diagnosed with autism and FXS, impairment in social interaction is prominent [27] and these individuals function at significantly lower levels of development with a decreased growth rate [28]. The relatively high frequency of autism in FXS may eventually provide clues into the genetic pathogenesis of some forms of idiopathic autism [29].

Mood instability and aggression

Males with FXS rarely meet formal criteria for a diagnosis of a major mood disorder because their mood lability is fleeting and their sleep difficulties are rarely associated with an abnormal mood state [10]. However, irritability accompanied by self-injurious behavior and aggressive outbursts is common, with early studies noting “rage attacks” in 43% [6] and aggression in 9 out of 13 boys [7]. In a more recent study of 31 boys and 29 girls, self-injurious behavior was noted in 58% of boys and 17% of girls [15]. These episodes appear to be provoked by stressors and generally occur in unfamiliar environments [10]. Initial temper tantrums tend to evolve over time into destructive, aggressive and self-injurious behavior as children with FXS grow older [30]. Females with FXS have significantly higher rates of major depression, dysthymia, and depression not otherwise specified when compared to age- and IQ- matched females without FXS [18].

ASSESSMENT AND SPECIAL CHALLENGES

Assessment of psychiatric symptoms in patients with FXS is complicated by limitations in accuracy of self-report and insight, atypical manifestation of some symptoms in the context of ID, and the relative lack of validated assessment tools. For example, limited expressive language and social reciprocity impairments often prevent reliable communication of symptoms, necessitating reliance on caregiver reporting, which can be biased. Depression might be revealed by withdrawal or increased aggression rather than by report of sadness, anhedonia, or irritability. Diagnostic overshadowing occurs when psychiatric symptoms are not appreciated as a co-morbid problem in a patient with intellectual disability, but are attributed only to the disability itself. Modifications to the Diagnostic and Statistical Manual (DSM) for persons with ID have been published [31, 32] providing needed guidance for psychiatric assessment. However, the diagnostician must be cognizant that the validity of DSM symptom clusters may not always apply to a genetic disorder such as FXS.

In a study aiming to characterize the anxiety disorders in FXS (also described above) [13], the Anxiety Disorders Interview Schedule for DSM-IV: Parent Report Version [33] algorithm was somewhat modified to account for limited language and overlapping symptoms with autism. The study demonstrated an anxiety disorder rate of 77% of females and 83% of males with FXS, with good cross-validity with an anxiety screen previously validated for ID [34]. Measures such as the Aberrant Behavior Checklist (ABC) [35] are helpful in persons with ID for identifying severity of maladaptive behaviors, which often strongly associate with psychiatric disorders. However, our recent detailed psychometric analysis of the ABC in patients with FXS revealed a factor structure that differentiated significantly from the original ABC subscales, which were validated on patients with idiopathic or mixed ID [36]. This work shows that the way in which psychiatric or behavioral symptoms cluster together may vary depending on the etiology of ID and specific phenotypes. As such, diagnostic algorithms may not always detect clinically significant expressions of the behavioral phenotype or their specificity may be reduced.

The diagnosis of autism in the context of FXS is complicated and sometimes confounded by prominent and phenotypic features of social anxiety, over-arousal, hyperactivity, distractibility, and repetitive behaviors. All of these symptoms can occur in patients with FXS without autism spectrum disorders. Therefore, many individuals score highly on standardized, in-clinic measures such as the ADOS [37] despite high social motivation and awareness in daily life. Thus, it is critical to consider both performance on standardized measures and information gathered through careful diagnostic interviewing before forming a diagnostic impression of autism.

Finally, it is important to recognize that the psychiatric symptoms present in patients with FXS are not necessarily reflective only of their *FMRI* mutation. These individuals are likely to be affected by many of the same risk and protective factors for psychiatric disease as others in the general population. For example, in a study of child behavioral problems in families affected by FXS, the quality of the home environment as well as parental psychiatric symptoms were associated with child behavior problems in *both* children with FXS and unaffected siblings [38]. Background genes known to be associated with anxiety

and mood may also modify FXS phenotype expression, and perhaps even treatment response [39]. As such, it is important to consider the entire family history of psychiatric disorders and family dynamics in order to best conceptualize the etiology and treatment of psychiatric symptoms in the patient with FXS.

NEUROBIOLOGICAL UNDERPINNINGS OF FXS AND TARGETED TREATMENTS

The use of psychotropic medications in FXS has not been thoroughly studied, but the available evidence for their use is summarized in Table 1 [40–48]. Only two controlled studies have been carried out regarding treatment of ADHD in FXS, one utilizing stimulants [41] and the other with L-acetylcarnitine [48]. The former study demonstrated efficacy of stimulants and this has been supported by cohort studies of the largest clinical programs for FXS [40, 43]. Most patients with ADHD and FXS who are 5 or older respond well to stimulants; if response is lacking or significant aggression is present, low dose aripiprazole can be utilized. This recommendation has been supported by an open trial [45] and by consensus of the Fragile X Clinical and Research Centers (FXCRC) of the National Fragile X Foundation [49]. The use of selective serotonin reuptake inhibitors (SSRIs) for anxiety is supported by large surveys of clinical populations, [40, 43] a retrospective review [50] and the consensus of the FXCRC [49].

Although standard psychopharmacological medication is helpful for symptom management, recent research has focused on targeted treatments and alternative agents such as minocycline and antioxidants. The clear molecular basis for FXS has spurred this promising research. FMRP is a critical protein for many activities of the neuron, including mRNA transport and stability [51] and regulation of mRNA translation, including repression and activation of translation [51, 52]. When FMRP is missing or deficient in FXS, the overall result is up-regulation of the metabotropic glutamate receptor 5 (mGluR5) pathway [53] and down-regulation of the GABA_A pathway, which leads to hyperexcitable neuronal networks. The success of the mGluR5 antagonists and GABA agonists in animal models of FXS has led to human trials in both children and adults with FXS [54, 55].

The first mGluR5 antagonist that was tried in humans was fenobam; 12 adults with FXS were given one dose of fenobam orally. The baseline deficit of prepulse inhibition, a measure of hyperexcitability, was significantly improved with this single dose and behavior appeared to be improved [56]. This study was focused on pharmacokinetics and safety, which were established, but further studies were not carried out with fenobam because the pharmaceutical manufacturing company dissolved.

The mGluR5 antagonist AFQ056 was studied in a controlled, double-blind trial in adults with FXS in Europe. Efficacy was demonstrated in those with a fully methylated mutation using the Aberrant Behavior Checklist (ABC) total score and the Clinical Global Impression Scale (CGI) as the primary outcome measures [57]. Those who were mosaic from CGG repeat size or methylation status had a variable response but, did not, as a group, demonstrate efficacy. However, the success of AFQ056 in the fully methylated patients has led to further, currently ongoing, controlled trials at multiple centers internationally.

Another mGluR5 antagonist, RO4917523, is currently undergoing controlled trials at multiple centers in the US and internationally. We are eagerly awaiting results regarding efficacy of mGluR5 antagonists on behavioral measures, although benefits in the cognitive realm are also expected, particularly with long-term therapy combined with educational interventions. There is hope that these targeted treatments can strengthen synaptic connections in children and adults with FXS, as they do in the animal models for FXS [58]. Additionally, it is hoped that cognitive outcomes will improve when these treatments are paired with focused educational interventions.

There are two current trials of treatments for FXS targeting the GABA neurotransmitter system. Arbaclofen is the R-isomer of baclofen and a GABA_B agonist that works at a presynaptic receptor, lowering the level of glutamate at the synapse. This, in turn, lowers the mGluR5 activation seen in FXS and thereby lowers the level of excess proteins produced by up-regulation of the mGluR5 pathway in FXS. There is an increased level of proteins produced in the hippocampus in the absence of FMRP because FMRP typically inhibits protein translation [59]. In 60 patients with FXS (ages 6 to 40), an initial, double-blind, cross-over study of Arbaclofen, with each phase lasting 4 weeks, demonstrated efficacy in those with FXS and autism and also in those with significant social withdrawal [60]. The success of this trial stimulated further controlled studies in children and adults with FXS at multiple centers. In addition, positive preliminary data in patients with autism has stimulated controlled trials in idiopathic autism without FXS. An additional study of ganaxolone, a neurosteroid and GABA_A agonist, is currently taking place at the M.I.N.D. Institute. It includes a double-blind, controlled trial of an oral preparation of ganaxolone in children 6 to 17 years old with FXS. Ganaxolone has been shown to reduce seizures in the FMRP knock-out (KO) mouse model [54]. Taurine is another GABA_A agonist that could be beneficial. It is likely that the combination of a GABA_A agonist with an mGluR5 antagonist will be helpful in FXS; however, not enough evidence exists to date.

Minocycline, an antibiotic related to tetracycline, came to clinical use in the 1960s, for treatment of acne in adolescents in the general population. A study by Bilousova and colleagues [61] demonstrated that levels of matrix metalloproteinase 9 (MMP9), one of a family of proteins important for synaptic plasticity, was too high in the FMRP KO mouse. Treatment with minocycline for one month after birth lowered MMP9 levels and normalized synaptic connections in the FMRP KO mouse. This generated excitement in the fragile X community since minocycline is currently available and can be prescribed. A subsequent survey of minocycline use in children and adults with FXS suggested efficacy without significant side effects [62]. Subsequently, an open trial by Paribello and colleagues [63] in adolescents and young adults with FXS demonstrated improvements in language and several behavioral areas. This work has stimulated a controlled trial of minocycline in children ages 3 ½ to 16 years old with FXS at the M.I.N.D. Institute. A subgroup of patients with FXS who take minocycline develop a positive antinuclear (ANA) titer, although associated clinical symptoms are rare [63]. The use of minocycline in young children who do not yet have their permanent teeth is likely to cause graying of the permanent teeth when they emerge. This has to be explained in detail to the families because dental plating is necessary to correct this problem cosmetically. Minocycline can also cause gastrointestinal symptoms;

treatment with a probiotic usually alleviates these symptoms, since it replaces the normal intestinal flora that is diminished by minocycline treatment.

A number of additional targeted treatments and antioxidants have been in preliminary studies for FXS; details regarding these agents can be found in Hagerman et al. [58]. The future treatment of FXS looks exciting as targeted treatments are developed to help with the psychiatric symptoms and the cognitive deficits that are intrinsic to this disorder.

CONCLUSION

Fragile X syndrome, the most common inherited form of intellectual disability, is associated with anxiety, attention deficit hyperactivity disorder, impulsivity, autism, mood instability, and aggression. Appropriate assessment of these symptoms is important but can be challenging in the majority of patients with intellectual impairment. There is limited research to support the use of psychotropic medication in this population, but current studies provide some guidelines for treatment. In the future, there is hope that targeted treatments may improve outcomes significantly.

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References

1. Bassell GJ, Warren ST. Fragile X syndrome: loss of local mRNA regulation alters synaptic development and function. *Neuron*. 2008; 60(2):201–14. [PubMed: 18957214]
2. Crawford DC, Meadows KL, Newman JL, et al. Prevalence of the fragile X syndrome in African-Americans. *Am J Med Genet*. 2002; 110:226–33. [PubMed: 12116230]
3. Crawford D, Acuna JM, Sherman SL. FMR1 and the fragile X syndrome: Human genome epidemiology review. *Genet Med*. 2001; 3(5):359–371. [PubMed: 11545690]
4. Hagerman, RJ. Physical and behavioral phenotype. In: Hagerman, RJ.; Hagerman, PJ., editors. *Fragile X syndrome: Diagnosis, treatment and research*. 3. Baltimore: Johns Hopkins University Press; 2002. p. 3-109.
5. Hall SS, Burns DD, Reiss AL. Modeling family dynamics in children with fragile X syndrome. *J Abnorm Child Psychol*. 2007; 35(1):29–42. [PubMed: 17165142]
6. Fryns JP, Jacobs J, Kleczkowska A, van den Berghe H. The psychological profile of the fragile X syndrome. *Clin Genet*. 1984; 25(2):131–4. [PubMed: 6705249]
7. Largo RH, Schinzel A. Developmental and behavioural disturbances in 13 boys with fragile X syndrome. *Eur J Pediatr*. 1985; 143(4):269–75. [PubMed: 2580709]
8. Sullivan K, Hatton D, Hammer J, et al. ADHD symptoms in children with FXS. *Am J Med Genet*. 2006; 140(21):2275–88. [PubMed: 17022076]
9. Bailey DB Jr, Raspa M, Olmsted M, Holiday DB. Co-occurring conditions associated with FMR1 gene variations: findings from a national parent survey. *Am J Med Genet*. 2008; 146A(16):2060–9. [PubMed: 18570292]
10. Tranfaglia MR. Fragile X syndrome: a psychiatric perspective. *Results Probl Cell Differ*. 2012; 54:281–95. [PubMed: 22009359]

11. Borghgraef M, Fryns JP, Dielkens A, Pyck K, Van den Berghe H. Fragile (X) syndrome: a study of the psychological profile in 23 prepubertal patients. *Clin Genet.* 1987; 32(3):179–86. [PubMed: 3621665]
12. Einfeld S, Tonge B, Turner G. Longitudinal course of behavioral and emotional problems in fragile X syndrome. *Am J Med Genet.* 1999; 87(5):436–9. [PubMed: 10594885]
13. Cordeiro L, Ballinger E, Hagerman R, Hessel D. Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: prevalence and characterization. *J Neurodev Disord.* 2011; 3(1):57–67. [PubMed: 21475730]
14. Dekker MC, Koot HM. DSM-IV disorders in children with borderline to moderate intellectual disability. I: prevalence and impact. *J Am Acad Child Adolesc Psychiatry.* 2003; 42(8):915–22. [PubMed: 12874493]
15. Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behavior in children and adolescents with fragile X syndrome. *Am J Ment Retard.* 2008; 113(1):44–53. [PubMed: 18173299]
16. Wolff PH, Gardner J, Paccla J, Lappen J. The greeting behavior of fragile X males. *Am J Ment Retard.* 1989; 93(4):406–11. [PubMed: 2522786]
17. Bregman JD, Leckman JF, Ort SI. Fragile X syndrome: genetic predisposition to psychopathology. *J Autism Dev Disord.* 1988; 18(3):343–54. [PubMed: 3170453]
18. Freund LS, Reiss AL, Abrams MT. Psychiatric disorders associated with fragile X in the young female. *Pediatrics.* 1993; 91(2):321–9. [PubMed: 8380924]
19. Harris SW, Hessel D, Goodlin-Jones B, et al. Autism profiles of males with fragile X syndrome. *Am J Ment Retard.* 2008; 113(6):427–38. [PubMed: 19127654]
20. Hall SS, Lightbody AA, Hirt M, Rezvani A, Reiss AL. Autism in fragile X syndrome: a category mistake? *J Am Acad Child Adolesc Psychiatry.* 2010; 49(9):921–33. [PubMed: 20732628]
21. Rogers SJ, Wehner DE, Hagerman RJ. Behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *J Dev Behav Pediatr.* 2001; 22(6):409–17. [PubMed: 11773805]
22. Garrett AS, Menon V, MacKenzie K, Reiss AL. Here's looking at you, kid: Neural systems underlying face and gaze processing in fragile X syndrome. *Arch Gen Psychiatry.* 2004; 61(3):281–288. [PubMed: 14993116]
23. Hall S, DeBernardis M, Reiss A. Social escape behaviors in children with fragile X syndrome. *J Autism and Dev Disord.* 2006; 36:935–947. [PubMed: 16897394]
24. Hessel D, Glaser B, Dyer-Friedman J, et al. Cortisol and behavior in fragile X syndrome. *Psychoneuroendocrinology.* 2002; 27(7):855–872. [PubMed: 12183220]
25. Hessel D, Glaser B, Dyer-Friedman J, Reiss AL. Social behavior and cortisol reactivity in children with fragile X syndrome. *J Child Psychol Psychiatry.* 2006; 47(6):602–610. [PubMed: 16712637]
26. Farzin F, Rivera SM, Hessel D. Brief report: visual processing of faces in individuals with fragile X syndrome: an eye tracking study. *J Autism Dev Disord.* 2009; 39:946–952. [PubMed: 19399604]
27. Kaufmann WE, Cortell R, Kau AS, et al. Autism spectrum disorder in fragile X syndrome: communication, social interaction, and specific behaviors. *Am J Med Genet.* 2004; 129A:225–34. [PubMed: 15326621]
28. Bailey DB Jr, Hatton DD, Skinner M, Mesibov G. Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *J Autism Dev Disord.* 2001; 31(2):165–74. [PubMed: 11450815]
29. Bertone A, Hanck J, Kogan C, Chaudhuri A, Cornish K. Associating neural alterations and genotype in autism and fragile X syndrome: incorporating perceptual phenotypes in causal modeling. *J Autism Dev Disord.* 2010; 40(12):1541–8. [PubMed: 20872060]
30. Tsiouris JA, Brown WT. Neuropsychiatric symptoms of fragile X syndrome: pathophysiology and pharmacotherapy. *CNS drugs.* 2004; 18(11):687–703. [PubMed: 15330685]
31. Fletcher, R.; Loschen, E.; Stavrakaki, C.; First, M., editors. *Diagnostic Manual - Intellectual Disability (DM-ID): A Clinical Guide for Diagnosis of Mental Disorders in Persons with Intellectual Disability.* Kingston, NY: NADD Press; 2007.

32. Fletcher, R.; Loschen, E.; Stavrakaki, C.; First, M., editors. Diagnostic Manual - Intellectual Disability (DM-ID): A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability. Kingston, NY: NADD Press; 2007.
33. Silverman, WK.; Albano, AM. Anxiety Disorders Interview Schedule (ADIS-IV) Child/Parent Clinician Manual. New York: Oxford University Press; 2004.
34. Esbensen AJ, Rojahn J, Aman MG, Ruedrich S. Reliability and validity of an assessment instrument for anxiety, depression, and mood among individuals with mental retardation. *J Autism Dev Disord.* 2003; 33(6):617–29. [PubMed: 14714931]
35. Aman MG, Burrow WH, Wolford PL. The Aberrant Behavior Checklist-Community: factor validity and effect of subject variables for adults in group homes. *Am J Ment Retard.* 1995; 100(3):283–92. [PubMed: 8554775]
36. Sansone SM, Widaman KF, Hall SS, et al. Psychometric study of the Aberrant Behavior Checklist in fragile X syndrome and implications for targeted treatment. *J Autism Dev Disord.* 2011 Oct 5. Epub ahead of print.
37. Lord, C.; Rutter, M.; DiLavore, PC.; Risi, S. Autism Diagnostic Observation Schedule. Los Angeles, CA: Western Psychological Services; 1999.
38. Hessl D, Dyer-Friedman J, Glaser B, et al. The influence of environmental and genetic factors on behavior problems and autistic symptoms in boys and girls with fragile X syndrome. *Pediatrics.* 2001; 108(5):E88. [PubMed: 11694672]
39. Hessl D, Tassone F, Cordeiro L, et al. Brief report: aggression and stereotypic behavior in males with fragile X syndrome--moderating secondary genes in a "single gene" disorder. *J Autism Dev Disord.* 2008; 38(1):184–9. [PubMed: 17340199]
40. Berry-Kravis E, Potanos K. Psychopharmacology in fragile X syndrome-present and future. *Ment Retard Dev Disabil Res Rev.* 2004; 10(1):42–8. [PubMed: 14994287]
41. Hagerman RJMM, Wittenberger MD. A controlled trial of stimulant medication in children with the fragile X syndrome. *Am J Med Genet.* 1988; 30:377–92. [PubMed: 3052064]
42. Hagerman RJ, Riddle JE, Roberts LS, Brease K, Fulton M. A survey of the efficacy of clonidine in fragile X syndrome. *Dev Brain Dysf.* 1995; 8:336–44.
43. Amaria RN, Billeisen LL, Hagerman RJ. Medication use in fragile X syndrome. *Mental Health Asp Dev Dis.* 2001; 4(4):143–7.
44. Hagerman RJ, Fulton MJ, Leaman A, Riddle J, Hagerman K, Sobesky W. A survey of fluoxetine therapy in fragile X syndrome. *Dev Brain Dysf.* 1994; 7:155–64.
45. Erickson CA, Stigler KA, Wink LK, et al. A prospective open-label study of aripiprazole in fragile X syndrome. *Psychopharmacology (Berl).* 2011; 216(1):85–90. [PubMed: 21318565]
46. Torrioli M, Vernacotola S, Setini C, et al. Treatment with valproic acid ameliorates ADHD symptoms in fragile X syndrome boys. *Am J Med Genet.* 2010; 152A:1420–7. [PubMed: 20503316]
47. Berry-Kravis ESA, Hervey C, Nelson M, et al. Open-label treatment trial of lithium to target the underlying defect in fragile X syndrome. *J Dev Behav Pediatr.* 2008; 29:293–302. [PubMed: 18698192]
48. Torrioli MG, Vernacotola S, Peruzzi L, et al. A double-blind, parallel, multicenter comparison of L-acetylcarnitine with placebo on the attention deficit hyperactivity disorder in fragile X syndrome boys. *Am J Med Genet.* 2008; 146(7):803–12. [PubMed: 18286595]
49. Hagerman RJ, Berry-Kravis E, Kaufmann WE, et al. Advances in the treatment of fragile X syndrome. *Pediatrics.* 2009; 123(1):378–90. [PubMed: 19117905]
50. Winarni RI, Chonchaiya W, Au J, et al. Sertraline improves language development trajectory in young children with fragile X syndrome. *J Dev Behav Pediatr.* 2012 submitted.
51. Muddashetty RS, Nalavadi VC, Gross C, et al. Reversible inhibition of PSD-95 mRNA translation by miR-125a, FMRP phosphorylation, and mGluR signaling. *Mol Cell.* 2011; 42(5):673–88. [PubMed: 21658607]
52. Gross C, Yao X, Pong DL, Jeromin A, Bassell GJ. Fragile X mental retardation protein regulates protein expression and mRNA translation of the potassium channel Kv4. 2. *J Neurosci.* 2011; 31(15):5693–8. [PubMed: 21490210]

53. Bear MF, Huber KM, Warren ST. The mGluR theory of fragile X mental retardation. *Trends Neurosci.* 2004; 27(7):370–7. [PubMed: 15219735]
54. Kooy, F.; Heulens, I.; D'Hulst, C., et al. The GABAA receptor as a potential target for therapy of the fragile X syndrome [Abstract]. Presented at NFXF 12th International Conference; 2010; Detroit, MI.
55. Levenga J, de Vrij FM, Oostra BA, Willemsen R. Potential therapeutic interventions for fragile X syndrome. *Trends Mol Med.* 2010; 16(11):516–27. [PubMed: 20864408]
56. Berry-Kravis E, Hessel D, Coffey S, et al. A pilot open label, single dose trial of fenobam in adults with fragile X syndrome. *J Med Genet.* 2009; 46(4):266–71. [PubMed: 19126569]
57. Jacquemont S, Curie A, des Portes V, et al. Epigenetic modification of the FMR1 gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056. *Sci Transl Med.* 2011; 3(64):64ra1.
58. Hagerman R, Lauterborn J, Au J, Berry-Kravis E. Fragile X syndrome and targeted treatment trials. *Results Probl Cell Differ.* 2012; 54:297–335. [PubMed: 22009360]
59. Qin M, Kang J, Burlin TV, Jiang C, Smith CB. Postadolescent changes in regional cerebral protein synthesis: an in vivo study in the FMR1 null mouse. *J Neurosci.* 2005; 25(20):5087–95. [PubMed: 15901791]
60. Berry-Kravis, E.; Cherubini, M.; Zarevics, P., et al. Arbaclofen for the treatment of children and adults with fragile X syndrome: Results of a phase 2, randomized, double-blind, placebo-controlled, crossover study [Abstract]. Presented at International Meeting for Autism Research; 2010; Philadelphia, PA.
61. Bilousova TV, Dansie L, Ngo M, et al. Minocycline promotes dendritic spine maturation and improves behavioural performance in the fragile X mouse model. *J Med Genet.* 2009; 46(2):94–102. [PubMed: 18835858]
62. Utari A, Chonchaiya W, Rivera SM, et al. Side effects of minocycline treatment in patients with fragile X syndrome and exploration of outcome measures. *Am J Intellect Dev Disabil.* 2010; 115(5):433–43. [PubMed: 20687826]
63. Paribello C, Tao L, Folino A, et al. Open-label add-on treatment trial of minocycline in fragile X syndrome. *BMC Neurol.* 2010; 10:91. [PubMed: 20937127]

Table 1

Summary of Evidence for Psychotropic Medication Use in FXS [40–48].

Medication (dose)	Response	Evidence
Stimulants		
Stimulants	75% response rate	Chicago FXS cohort, clinical survey of 83 children [40]
Methylphenidate (0.3 mg/kg bid)	Statistically significant improvement in attention and social functioning	3-week double blind crossover study, 15 children [41]
Dextroamphetamine (0.2 mg/kg qam)	Improved behavior, not statistically significant	
Alpha 2 agonists		
Alpha 2 agonists	70% response rate with reduction in hyperactivity, hyperarousal, hyper-sensitivity, impulsivity, and aggressive behaviors	Chicago FXS cohort, clinical survey of 27 boys [42]
Clonidine	63% response rate (per parent report)	Parent survey, 35 children [42]
Antidepressants		
SSRIs	Reduced anxiety (50% of time)	Clinical surveys [40, 43]
Fluoxetine*	83% response rate with reduction in depression, mood lability, panic attacks, outburst behavior, obsessive-compulsive symptoms, and anxiety	Clinical survey, 18 adult females [44]
Fluoxetine*	70% response rate with reduction in aggression, verbal outbursts, mood lability, obsessive-compulsive symptoms, hyperactivity, depression, and anxiety	Clinical survey, 17 males [44]
Antipsychotics		
Antipsychotics	80% response rate, reduced aggression	Chicago FXS cohort, clinical survey of 28 individuals [40]
Aripiprazole (mean dose 10 mg/day)	Decreased irritability	Prospective open label study, 12 individuals [45]
Mood stabilizers		
Valproic acid	Significant reduction in hyperactivity	6-month open label trial, 10 boys [46]
Lithium	Decreased irritability, not statistically significant	2-month open label study, 15 individuals [47]
Other agents		
L-acetyl-carnitine (20–50 mg/kg/day)	Reduced ADHD symptoms	Double blind placebo controlled study, 63 males [48]

* About 20% of participants had activation, including restlessness, mood changes, and disinhibition.