Published in final edited form as:

J Autism Dev Disord. 2019 November ; 49(11): 4595–4602. doi:10.1007/s10803-019-04173-z.

Pharmacologic Interventions for Irritability, Aggression, Agitation and Self-Injurious Behavior in Fragile X Syndrome: An Initial Cross-Sectional Analysis

Eleanor M. Eckert[1], **Kelli C. Dominick**[2,3], **Ernest V. Pedapati**[2,3], **Logan K. Wink**[2,3], **Rebecca C. Shaffer**[4,5], **Howard Andrews**[6], **Tse-Hwei Choo**[7], **Chen Chen**[7], **Walter E. Kaufmann**[8,9], **Nicole Tartaglia**[10], **Elizabeth M. Berry-Kravis**[11], **Craig A. Erickson**[2,3,4]

[1]University of Cincinnati College of Medicine, Cincinnati, OH, USA

[2]Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[3]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[4]Division of Developmental and Behavioral Pediatrics, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue MLC 4002, Cincinnati, OH 45229, USA

[5]Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[6]Departments of Psychiatry and Biostatistics, Columbia University Irving Medical Center, New York, NY, USA

[7]Division of Mental Health Data Science, New York State Psychiatric Institute, New York, NY, USA

[8]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA, USA

[9]Department of Neurology, UC Davis School of Medicine/MIND Institute, Sacramento, CA, USA

[10]Developmental Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA

[11]Departments of Pediatrics, Neurological Sciences, Biochemistry, Rush University Medical Center, Chicago, IL, USA

Abstract

Using a dataset involving 415 individuals with irritability, aggression, agitation and self-injury (IAAS) behaviors from the fragile X syndrome (FXS) FORWARD database, we describe the psychopharmacologic management of IAAS and features of the population of persons with FXS treated with drug therapy for IAAS. Among those with FXS exhibiting IAAS, individuals with FXS receiving drug treatment of IAAS were older, more predominantly male, have more significant intellectual disability, more like to have comorbid autism, hyperarousal, and social

✉Craig A. Erickson, craig.erickson@cchmc.org.

Author Contributions EME was the primary writer of the manuscript. KCD, EVP, LKW, RCS, and WEK participated in manuscript preparation and edited the manuscript. HA, TWC, and CC conducted the data analysis, participated in manuscript development and edited the manuscript. NT, EMB-K, and CAE participated in manuscript preparation, edited the document, and conceptualized the experiments in the manuscript.

impairments. The most commonly utilized medications for IAAS in FXS are antipsychotic medications, specifically aripiprazole and risperidone (37% and 27%, respectively). The majority of subjects (63%) experienced no side effects noted from the use of their psychopharmacologic medications.

Keywords

Fragile X syndrome; Irritability; Pharmacotherapy

Introduction

Fragile X Syndrome (FXS) is the most common form of inherited neurodevelopmental disability, affecting nearly 1 of 4000 males and 1/6000–1/8000 females in the United States (Hagerman and Hagerman 2008). FXS results from a trinucleotide expansion of the CGG repeat in the 5′ untranslated region of *FMR1* on the X chromosome, resulting in atypical gene methylation and transcriptional silencing with consequent reduction or lack of production of the fragile X mental retardation protein (FMRP). Affected individuals are at increased risk for marked cognitive impairment, characteristic physical features, and behavioral abnormalities such as anxiety, hyperarousal, impulsivity, self-injurious behavior, aggression and irritability (Hagerman and Polussa 2015). Among co-occurring features, lifelong treatment-resistant anxiety is a feature of FXS likely more prominent than in other forms of neurodevelopmental disability. Levels of FMRP correlate with the overall severity of the phenotype of FXS, with males being more severely affected due to the X-linked pattern of inheritance of the single gene mutation (Bailey et al. 2001b; Kaufmann et al. 1999; Loesch et al. 2004). Additionally, FXS demonstrates significant clinical overlap with autism spectrum disorder (ASD) such that FXS accounts for 1–6% of all cases of ASD and often exhibits behavioral symptoms consistent with the autism phenotype (Budimirovic and Kaufmann 2011; Hernandez et al. 2009; Kaufmann et al. 2017).

Behavioral dysregulation is a key manifestation of the FXS phenotype, often presenting out-of-proportion to the individual's cognitive level (Sansone et al. 2012; Tsiouris and Brown 2004; Bailey et al. 2008; Symons et al. 2010; Wheeler et al. 2016). One common behavioral cluster noted in individuals with FXS, particularly males, is irritability, agitation, aggression and self-injurious (IAAS) behaviors estimated to occur in at least 50% of individuals (Bailey et al. 2008; Berry-Kravis and Potanos 2004). These behaviors, principally aggression and self-injury, have been shown to increase in prevalence and severity as patients grow older, and researchers propose they may similarly be intensified secondary to increased hyperarousal to sensory stimuli and can be associated with anxiety and/or the diagnosis of ASD (Erickson et al. 2017; Tsiouris and Brown 2004; Cordeiro et al. 2011a; Bailey et al. 2012a). IAAS behaviors have also been reported to place a significant burden on both patient and caregiver quality of life (Chevreul et al. 2015, 2016; Haessler et al. 2016; Bailey et al. 2012a). Previous studies have indicated that interfering agitated and aggressive behaviors associated with FXS can lead to heightened levels of parental stress, decreased parental well-being and caregiver injury (Bailey et al. 2012a, b), and are often a primary concern for family members and clinicians (Lewis et al. 2006). Despite this significant level

of patient and caregiver burden attributable to IAAS behaviors and the relatively high proportion of individuals with FXS who exhibit these traits, there remains limited large-scale information concerning the psychopharmacologic management of IAAS to help guide future treatment.

There are currently no approved drugs for the treatment of FXS itself or behaviors associated specifically with FXS, thus clinical pharmacologic interventions are off label and generally aimed at interfering behavior. Site-specific clinical care reviews and expert reports have noted frequent use of atypical antipsychotic in FXS (Berry-Kravis and Potanos 2004; Berry-Kravis et al. 2012). This is likely a result of studies of atypical antipsychotics demonstrating efficacy in targeting irritability and aggressive behaviors in ASD and other behavioral disorders (Erickson et al. 2005, 2010; McDougle et al. 2008; Posey et al. 2008). Although findings from studies assessing similar symptomatic treatments in various developmental disorders have supported clinical interventions for IAAS in FXS, evidence regarding the specific use of these medications in FXS is limited.

Much of the current data supporting specific pharmacologic treatments of IAAS behaviors is derived from retrospective analyses of clinical samples of FXS populations. In one such study, Berry-Kravis and Potanos (2004) conducted an analysis of a large FXS clinic population and found roughly a 80% response rate in both female and male individuals with FXS treated for aggressive and other more extreme aberrant behaviors with an antipsychotic drugs (Berry-Kravis and Potanos 2004). A more recent single-site retrospective FXS study reiterated findings that risperidone and aripiprazole are the most commonly utilized antipsychotics with overall high response rates (50% and 70%, respectively), supporting their clinical use to target irritability, aggression and other perseverative behaviors (Berry-Kravis et al. 2012). Only one prospective trial of atypical antipsychotic use in FXS is available. In this 12-week prospective open-label study, 12 individuals with FXS (age range 6–25 years; mean age, 14.3 years) were treated with aripiprazole monotherapy (mean dose = 9.8 mg/day) targeting irritability with 10 of 12 (87%) of patients exhibiting clinical improvement as measured by the Clinical Global Impressions-Improvement (CGI-I) (Guy 1976) scale and the Irritability subscale of the Aberrant Behavior Checklist-Community (Aman et al. 1985; Erickson et al. 2011). Two subjects (13%) discontinued aripiprazole due to adverse effects including tiredness, drooling, and akathisia.

Based on previous literature and current clinical understanding of IAAS in FXS, we hypothesized that among individuals with FXS exhibiting IAAS, those taking medication targeting IAAS would be older, more likely male, more developmentally delayed and with more limited communication skills, and more likely with comorbid ASD, than those not requiring drug treatment of IAAS.

Methods

Data analyzed for this report were derived from Fragile X Online Registry with Accessible Research Database (FORWARD). As described in Sherman et al. (2017), FORWARD is a multisite observational study initiated in 2012 (Sherman et al. 2017). Our evaluation of drug treatment of IAAS in FXS consisted of a descriptive cross-sectional analysis of data derived

from the FORWARD baseline visit (first visit in FORWARD) Clinician Report forms (forms described in Sherman et al. 2017). Of the 828 participants with Clinician Report form data in FORWARD Version 2, 415 (50.1%) were indicated as having IAAS, and of these 415, 180 (43.5%) were being treated with medication for IAAS. Data included in this report were collected at 25 FXS clinics associated with the FORWARD project, all of which had obtained local Institutional Review Board (IRB) approval from their respective institutions covering all FORWARD-associated human subjects research. Additional data analyzed included several parent-reported questionnaires. These included the Aberrant Behavior Checklist-Community Edition (ABC-C) (Aman et al. 1985), scored according to an algorithm based on a factor analysis of the scale for FXS populations, termed ABC-C_{FX}; the Social Communication Questionnaire (SCQ) (Witwer and Lecavalier 2007); and the Social Responsiveness Scale, Second Edition (SRS-2) (Constantino et al. 2003). The analyses were conducted on a dataset representing cross-sectional baseline data from 415 subjects with FXS, indicated as having current IAAS on their Clinician Report form. This overall IAAS sample represents 50% of the 828 subjects with FXS with data from this project at time of analysis, who had a completed Clinician Report form. Full details regarding the FORWARD database collection and management can be found in the report by Sherman and colleagues (Sherman et al. 2017).

To explore potential factors associated with drug treatment for IAAS in FXS, demographic and clinical variables were compared between treated and non-treated groups. Variables taken from the FORWARD Clinician Report forms and parent-report questionnaires included: age, sex, level of intellectual disability, verbal ability, concomitant clinical ASD diagnosis, history of seizures, Body Mass Index (BMI), level of hypersensitivity to sensory stimuli, presence of anxiety, ABC-C_{FX} scores on its six subscales (irritability, socially unresponsive/lethargic, stereotypy hyperactivity, inappropriate speech, and social avoidance), SRS, and SCQ total scores. For evaluation of verbal ability, clinician responses were dichotomized as describing subjects with “phrases/sentences of 3 words or more” and those who were not. Hypersensitivity to stimuli was assessed by the question “Does the child respond too strongly to sensory information in his/her environment?” and clinician responses grouped as “often/always” indicating hyperarousal and “never/sometimes” indicating a lack of this behavior. For level of intellectual disability, this was clinician rated based on clinician knowledge of the patient and review of available medical/testing records at time of documentation.

The frequencies of each clinical characteristic were collected according to treatment regimen (medication use vs. non-use), and variables were analyzed for comparison using Chi squared tests. Means and confidence intervals were calculated for BMI, age and other continuous variables and analyzed for comparison using paired two-tailed t-tests. Given the pilot and descriptive nature of this work, significant group differences are reported at $p < 0.05$ without correction for multiple comparisons.

Within the group of subjects with FXS receiving drug treatment for IAAS, data regarding individual medications used was also collected. The latter information was then grouped by drug class, and specific medication frequencies and proportions were presented. The frequencies and overall proportions of medication-associated adverse effects reported on the

Clinician Report Form experienced by these participants (i.e., sedation, weight gain, headache, etc.) are also presented.

Results

The FORWARD dataset comprised 415 FXS individuals exhibiting current behaviors of IAAS, 180 (43.4%) of whom were described as treated with medication targeting these behaviors and 235 (56.6%) reported as not receiving drug therapy for IAAS (see Table 1 for summary of comparisons between these groups). Within this group of 415 subjects with FXS, in 343 cases clinicians answered whether current IAAS was a limiting problem for the child/family. Within this subgroup with available data describing the limiting impact of IAAS, 233 subjects (67.9%) answered that IAAS was a limiting problem. Among the 233 subjects who answered that IAAS was a limiting problem, 126 (54.1%) reported that IAAS was currently treated with medication.

Among all subjects with current IAAS, individuals treated with medication were found to be significantly older compared to those not on medication, with a mean age of 14.4 (N = 176) compared to 10.4 (N = 228) respectively ($p < 0.0001$). Significantly more males ($p = 0.0082$) were found to be taking medication for IAAS, as 90.6% of participants on medication were male, compared to 81.2% of non-medicated patients. Patients treated with psychopharmacologic interventions for IAAS were also found to have significantly more severe intellectual disability ($p < 0.0001$) and significantly lower IQ scores (45.4 vs. 54.6, $p < 0.0001$) than the non-treated population. A greater proportion of patients receiving drug treatment were also reported to have a concomitant diagnosis of ASD, with 65.9% (N = 108) and 50.2% (N = 108), $p = 0.0023$, of treatment versus non-treatment subjects. Similarly, the proportion of subjects with IAAS and anxiety was higher in those on drug treatment. The group of subjects with FXS receiving drug treatment specifically for IAAS exhibited current anxiety (92.6% vs. 83.7% $p = 0.0068$) and hypersensitivity to sensory stimuli (54.9% vs. 40.9%, $p = 0.0055$) more frequently than those with IAAS not receiving drug treatment. Additionally, those receiving drug treatment had significantly higher mean scores on the ABC-C_{FX} Irritability subscale (41.1 vs. 37.1, $p = 0.0049$). Those receiving drug treatment also had greater social deficits illustrated by higher mean SCQ total scores (17.0 vs. 14.8, $p = 0.0020$) and SRS-2 scaled T-scores (77.1 vs. 74.2, $p = 0.0246$). No significant group differences were noted in BMI, verbal ability, or *FMR1* gene methylation status.

A total of 29 individual medications from 8 different drug classes representing 216 total drug usages were reported as being prescribed for IAAS in 180 subjects with FXS (see Table 2 for summary; mean 1.2 drug usages per person). Of these 216 drug usages targeting IAAS, antipsychotic medications were the most commonly utilized drug class (136 drug usages; 63.0% of all individual medication trials). Overall, 128 of 180 subjects (71%) were taking at least one antipsychotic for IAAS. The most frequently prescribed medications among all subjects with FXS were aripiprazole, with 65 instances of use (30.1% of all drug trials targeting IAAS), and risperidone with 50 instances of use (23.15%). Selective serotonin reuptake inhibitors (SSRIs) was the next most commonly utilized drug class, used 29 times (13.4% of all drug usages), with sertraline the most commonly used SSRI for IAAS (15

uses; 6.94% of all drug usages). Other classes of psychopharmacologic medications included stimulants, non-SSRI antidepressants, alpha-agonists, mood-stabilizers, and anxiolytics.

Among those with FXS receiving drug treatment for IAAS (n = 180), drug-associated adverse effects were reported by clinicians in 67 subjects with FXS (37.2%). This means that the majority of subjects with FXS receiving drug treatment for IAAS (n = 113; 62.8%) did not have reported drug-associated side-effects (see Table 3 for summary of drug side-effects). The most commonly reported side effects were weight gain (26 Subjects, 14.4%), sedation (15 subjects, 8.33%) and other symptoms as specified by clinician (11 subjects, 6.1%). Other noted side effects were reported in less than 5% of participants and included impulsivity, agitation/irritability/anxiety, GI symptoms, weight loss, tremors, headache, dizziness, and sleep issues/insomnia.

Discussion

In this cross-sectional pilot analysis, among all subjects with FXS described by their treating clinician as exhibiting IAAS, the group receiving drug treatment targeting IAAS was older, higher proportion male, with more severe intellectual disability, and with greater social and behavioral impairment than those not receiving drug treatment for IAAS. Among those who received drug treatment for these behavioral abnormalities, antipsychotic medications were the most frequently prescribed, with aripiprazole and risperidone use being the most common by a large margin. Interestingly, the frequency of side effects with these medications in those with FXS and IAAS was lower than in other groups with neurodevelopmental disorders.

The features noted among subjects with FXS receiving pharmacologic management for IAAS are in line with clinical experience of managing severe irritability and aggressive behavior. As hypothesized, the treatment group was found to be significantly older and with a higher proportion of males, likely due to increase in symptoms of aggression and self-injury behaviors as subjects age and the X-linked nature of FXS (Bailey et al. 1998; Hatton et al. 1999, 2003; Bailey et al. 2001a; Symons et al. 2003). Increased use of psychoactive drugs in older youth with IAAS may also indicate increased reliance on medication use versus behavioral and other non-pharmacological interventions with age; may be a reflection of potential family reluctance to medicate young children; and may relate to concern that, as children grow, the significance and impact of aggressive behavior may be more concerning. Those receiving drug treatment were also found to more likely have reported hyperarousal to sensory stimuli or current anxiety, which may account for more intensified symptoms as many of the interfering behaviors exhibited in FXS, including IAAS, have been suggested to be secondary to hyperarousal or a manifestation of anxiety (Tsiouris and Brown 2004). In line with our recent published analysis of FORWARD data, demonstrating association between diagnosis of ASD, more severe intellectual disability, and more severe IAAS (Kaufmann et al. 2017), subjects using medications for IAAS were more likely to have been diagnosed with ASD and had greater intellectual impairment. In evaluating intellectual disability in this report, the use of “severe/profound” intellectual disability as a clinical characterization may overstate the degree of participant impairment as by represented by the high rate of subjects with 3+ words, the actual impairment of those rated in the severe/

profound range may be more specific to severe, but not profound, impairment. Standardized questionnaires supported the above-mentioned relationships, with the pharmacologically-treated group having higher scores on the ABC-C_{FX} Irritability subscale, SCQ, and SRS-2. Thus, co-morbid ASD may be an overall risk factor for more severe behavioral dysregulation in FXS.

Anxiety is considered a core feature of FXS with a higher prevalence than in other common forms of inherited intellectual disability, autism, and the general population (Cordeiro et al. 2011b). Despite the high prevalence of anxiety within FXS, we identified an even higher frequency of clinically significant anxiety present in subjects receiving drug treatment for IAAS. Following antipsychotics, SSRIs and sedative hypnotic anxiolytics were found in a plurality of FXS subjects treated for IAAS. In meta-analysis, SSRIs have limited evidence for use in ASD for irritability, repetitive behaviors, and core symptoms with emerging evidence of potential harm marked by behavioral disinhibition (Williams et al. 2013) but with more positive results in individuals affected by FXS (McClellan et al. 2016). This difference in response across neurodevelopmental disorders may be due to specific differences in pathophysiology or may relate to specific targets of SSRI treatment such as targeting repetitive behavior in ASD versus more targeting of anxiety in FXS. Thus, our data may reflect prescribing patterns that SSRI use in FXS may mitigate co-occurring anxiety symptoms in FXS which may be associated with IAAS behaviors and should be considered as a potential modifiable factor in treatment planning.

The findings regarding specific medication use in this analysis mirrored that of previous single site retrospective analyses of drug treatment in FXS (Berry-Kravis et al. 2012). The frequent use of aripiprazole and risperidone targeting IAAS in FXS indicates potential effectiveness of these drugs in the disorder, but also the fact that these drugs are FDA-approved for treating irritability associated with ASD points to likely effectiveness, given that FXS is one cause of ASD.

Overall reported drug-associated side effects, in those receiving drug therapy for IAAS, were relatively low in comparison to other reports of antipsychotic use in subjects with developmental disability (McDougle et al. 2008; Posey et al. 2008) indicating overall the drug treatments were well tolerated as clinician reported. As expected, given the frequent use of antipsychotics in this population, weight gain was the most commonly reported concern (n = 26 subjects; 14.4% of all subjects receiving drug treatment for IAAS). Weight gain has been previously noted as a reason for cessation of treatment with risperidone in FXS (Bailey et al. 2012b), and an indistinguishable significant weight gain has also been noted with long-term clinical use of aripiprazole or risperidone in subjects with ASD. The low rate of reported adverse effects in this cohort could be due to a lack of information regarding duration of drug treatment meaning that short periods of follow-up or even rating of adverse effects at treatment initiation could confound the side effect reporting in the FORWARD project. Also FORWARD only reports medications used at the time of clinic visits so if a patient started a medication at their previous visit but stopped it before the annual follow up visit because of a side effect, FORWARD would not capture that data, resulting in underreporting of side effects for a given medication, as patients are more likely to stay on a medication and be on it when they have their annual follow up if there are not

major side effects. Given these caveats, it may be that no reported adverse effects at time of clinician documentation may not indicate that medication use has been historically, or will be in the future, adverse effect free. Future work describing drug-associated side effects over time in subjects with FXS should address this concern with the cross-sectional data reported here. Another weakness of the side effect reporting is that there is no specific link between a reported side effect and a specific drug(s). This is important given potential polypharmacy in this population. In the FORWARD dataset an individual could receive drug treatment with various drug classes, targeting multiple target symptoms. However, the clinician side-effect reporting does not allow for parsing out side-effect by specific drug.

In addition to lack of information on duration of drug trials employed, and on drug trials that were done between visits, drug dosing is not reported in the FORWARD project and the data does not allow for precise analysis of drug combinations, both regarding effectiveness and tolerability. Inherent with survey data, there is also a degree of data missingness that may impact interpretation of study results. For example, the range of data missing in Table 1 extends from age data missing in 11 (2.6%) subjects to 221 (53%) missing IQ values. Future comprehensive analyses should include looking patterns of missingness that could confound data interpretation. While the FORWARD project draws broadly from FXS-specific clinics across the United States, factors inherent in this sampling method—clinics tend to be in major metropolitan areas, families must “self-select” to seek and find a tertiary care program for their child—may create a sampling bias whereby this sample may not be completely representative of FXS presentation and experience. Another shortcoming of the present analysis is the inability to evaluate the potential impact of behavioral therapy on medication use rates. Given behavioral interventions and medication management may be used together targeting IAAS, looking at this concomitant treatment in this context will be important in the future.

Future work using the longitudinal natural history of the FORWARD project should allow for analysis of long-term drug treatment of various target symptoms, more specific evaluation of each behavior within the IAAS symptom category, and more extensive analysis of drug tolerability over time.

Funding

The FORWARD project is supported by the Cooperative Agreement Numbers 5U01DD000231, 5U19DD000753, and 1U01DD001189 funded by the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. No authors have a conflict financially or otherwise related to the content of this manuscript. The FORWARD database project was local IRB approved at all participating sites. The data reviewed in preparation of this manuscript was deidentified data.

The FORWARD project is supported by the Cooperative Agreement Numbers 5U01DD000231, 5U19DD000753, and 1U01DD001189 funded by the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. No authors have a conflict financially or otherwise related to the content of this manuscript. The FORWARD database project was local IRB approved at all participating sites. The data reviewed in preparation of this manuscript was deidentified data.

References

Aman MG, Singh NN, Stewart AW, & Field CJ (1985). The aberrant behavior checklist: A behavior rating scale for the assessment of treatment effects. American Journal of Mental Deficiency, 5, 485–491.

Bailey DB Jr., Hatton DD, Skinner M, & Mesibov G (2001a). Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. Journal of Autism and Developmental Disorders, 31(2), 165–174. [PubMed: 11450815]

Bailey DB Jr., Hatton DD, Tassone F, Skinner M, & Taylor AK (2001b). Variability in FMRP and early development in males with fragile X syndrome. American Journal of Mental Retardation, 106(1), 16–27. 10.1352/0895-8017(2001)106<0016:VIFAED>2.0.CO;2. [PubMed: 11246709]

Bailey DB Jr., Mesibov GB, Hatton DD, Clark RD, Roberts JE, & Mayhew L (1998). Autistic behavior in young boys with fragile X syndrome. Journal of Autism and Developmental Disorders, 28(6), 499–508. [PubMed: 9932236]

Bailey DB Jr., Raspa M, Bishop E, Mitra D, Martin S, Wheeler A, et al. (2012a). Health and economic consequences of fragile X syndrome for caregivers. Journal of Developmental and Behavioral Pediatrics, 33(9), 705–712. 10.1097/DBP.0b013e318272dcbc. [PubMed: 23117595]

Bailey DB Jr., Raspa M, Bishop E, Olmsted M, Mallya UG, & Berry-Kravis E (2012b). Medication utilization for targeted symptoms in children and adults with fragile X syndrome: US survey. Journal of Developmental and Behavioral Pediatrics, 33(1), 62–69. 10.1097/DBP.0b013e318236c0e1. [PubMed: 22064563]

Bailey DB Jr., Raspa M, Olmsted M, & Holiday DB (2008). Co-occurring conditions associated with FMR1 gene variations: Findings from a national parent survey. American Journal of Medical Genetics Part A, 146A(16), 2060–2069. 10.1002/ajmg.a.32439. [PubMed: 18570292]

Berry-Kravis E, & Potanos K (2004). Psychopharmacology in fragile X syndrome—Present and future. Mental Retardation and Developmental Disabilities Research Reviews, 10(1), 42–48. 10.1002/mrdd.20007. [PubMed: 14994287]

Berry-Kravis E, Sumis A, Hervey C, & Mathur S (2012). Clinic-based retrospective analysis of psychopharmacology for behavior in fragile X syndrome. International Journal of Pediatrics, 2012, 843016. 10.1155/2012/843016. [PubMed: 22899942]

Budimirovic DB, & Kaufmann WE (2011). What can we learn about autism from studying fragile X syndrome? Developmental Neuroscience, 33(5), 379–394. 10.1159/000330213. [PubMed: 21893949]

Chevreul K, Berg Brigham K, Brunn M, des Portes V, & Network B-RR (2015). Fragile X syndrome: Economic burden and health-related quality of life of patients and caregivers in France. Journal of Intellectual Disability Research, 59(12), 1108–1120. 10.1111/jir.12215. [PubMed: 26369667]

Chevreul K, Gandre C, Brigham KB, Lopez-Bastida J, Linertova R, Oliva-Moreno J, et al. (2016). Social/economic costs and health-related quality of life in patients with fragile X syndrome in Europe. The European Journal of Health Economics, 17(Suppl 1), 43–52. 10.1007/s10198-016-0784-3. [PubMed: 27072054]

Constantino JN, Davis SA, Todd RD, Schindler MK, Gross MM, Brophy SL, et al. (2003). Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the autism diagnostic interview-revised. Journal of Autism and Developmental Disorders, 33(4), 427–433. [PubMed: 12959421]

Cordeiro L, Ballinger E, Hagerman R, & Hessl D (2011a). Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: Prevalence and characterization. Journal of Neurodevelopmental Disorders, 3(1), 57–67. 10.1007/s11689-010-9067-y. [PubMed: 21475730]

Cordeiro L, Ballinger E, Hagerman R, & Hessl D (2011b). Clinical assessment of DSM-IV anxiety disorders in fragile X syndrome: Prevalence and characterization. Journal of Neurodevelopmental Disorders, 3(1), 57–67. 10.1007/s11689-010-9067-y. [PubMed: 21475730]

Erickson CA, Davenport MH, Schaefer TL, Wink LK, Pedapati EV, Sweeney JA, et al. (2017). Fragile X targeted pharmacotherapy: Lessons learned and future directions. Journal of Neurodevelopmental Disorders, 9, 7. 10.1186/s11689-017-9186-9. [PubMed: 28616096]

Erickson CA, Stigler KA, Posey DJ, & McDougle CJ (2005). Risperidone in pervasive developmental disorders. Expert Review of Neurotherapeutics, 5(6), 713–719. 10.1586/14737175.5.6.713. [PubMed: 16274329]

Erickson CA, Stigler KA, Posey DJ, & McDougle CJ (2010). Aripiprazole in autism spectrum disorders and fragile X syndrome. Neurotherapeutics, 7(3), 258–263. 10.1016/j.nurt.2010.04.001. [PubMed: 20643378]

Erickson CA, Stigler KA, Wink LK, Mullett JE, Kohn A, Posey DJ, et al. (2011). A prospective open-label study of aripiprazole in fragile X syndrome. Psychopharmacology (Berl), 216(1), 85–90. 10.1007/s00213-011-2194-7. [PubMed: 21318565]

Guy W (1976). ECDEU assessment manual for psychopharmacology. Publication no. 76-338. Washington, DC: U.S. DHEW, NIMH.

Haessler F, Gaese F, Huss M, Kretschmar C, Brinkman M, Peters H, et al. (2016). Characterization, treatment patterns, and patient-related outcomes of patients with Fragile X syndrome in Germany: Final results of the observational EXPLAIN-FXS study. BMC Psychiatry, 16(1), 318. 10.1186/s12888-016-1020-5. [PubMed: 27612457]

Hagerman RJ, & Hagerman PJ (2008). Testing for fragile X gene mutations throughout the life span. JAMA, 300(20), 2419–2421. 10.1001/jama.2008.684. [PubMed: 19033593]

Hagerman RJ, & Polussa J (2015). Treatment of the psychiatric problems associated with fragile X syndrome. Current Opinion in Psychiatry, 28(2), 107–112. 10.1097/YCO.0000000000000131. [PubMed: 25602250]

Hatton DD, Bailey DB Jr., Hargett-Beck MQ, Skinner M, & Clark RD (1999). Behavioral style of young boys with fragile X syndrome. Developmental Medicine and Child Neurology, 41(9), 625–632. [PubMed: 10503921]

Hatton DD, Wheeler AC, Skinner ML, Bailey DB, Sullivan KM, Roberts JE, et al. (2003). Adaptive behavior in children with fragile X syndrome. American Journal of Mental Retardation, 108(6), 373–390. 10.1352/0895-8017(2003)108<373:ABICWF>2.0.CO;2. [PubMed: 14561110]

Hernandez RN, Feinberg RL, Vaurio R, Passanante NM, Thompson RE, & Kaufmann WE (2009). Autism spectrum disorder in fragile X syndrome: A longitudinal evaluation. American Journal of Medical Genetics Part A, 149A(6), 1125–1137. 10.1002/ajmg.a.32848. [PubMed: 19441123]

Kaufmann WE, Abrams MT, Chen W, & Reiss AL (1999). Genotype, molecular phenotype, and cognitive phenotype: Correlations in fragile X syndrome. American Journal of Medical Genetics, 83(4), 286–295. [PubMed: 10208163]

Kaufmann WE, Kidd SA, Andrews HF, Budimirovic DB, Esler A, Haas-Givler B, et al. (2017). Autism spectrum disorder in fragile X syndrome: Cooccurring conditions and current treatment. Pediatrics, 139(Suppl 3), S194–S206. 10.1542/peds.2016-1159F. [PubMed: 28814540]

Lewis P, Abbeduto L, Murphy M, Richmond E, Giles N, Bruno L, et al. (2006). Cognitive, language and social-cognitive skills of individuals with fragile X syndrome with and without autism. Journal of Intellectual Disability Research, 50(Pt 7), 532–545. 10.1111/j.1365-2788.2006.00803.x. [PubMed: 16774638]

Loesch DZ, Huggins RM, & Hagerman RJ (2004). Phenotypic variation and FMRP levels in fragile X. Mental Retardation and Developmental Disabilities, 10(1), 31–41. 10.1002/mrdd.20006.

McClellan L, Pedapati E, Wink L, & Erickson C (2016). Evidence-based pharmacotherapy for autism spectrum disorders. Current Treatment Options in Psychiatry, 3(2), 161–181. 10.1007/s40501-016-0077-6.

McDougle CJ, Stigler KA, Erickson CA, & Posey DJ (2008). Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. Journal of Clinical Psychiatry, 69(Suppl 4), 15–20.

Posey DJ, Stigler KA, Erickson CA, & McDougle CJ (2008). Antipsychotics in the treatment of autism. Journal of Clinical Investigation, 118(1), 6–14. 10.1172/JCI32483.

Sansone SM, Widaman KF, Hall SS, Reiss AL, Lightbody A, Kaufmann WE, et al. (2012). Psychometric study of the aberrant behavior checklist in fragile X syndrome and implications for targeted treatment. Journal of Autism and Developmental Disorders, 42(7), 1377–1392. 10.1007/s10803-011-1370-2. [PubMed: 21972117]

Sherman SL, Kidd SA, Riley C, Berry-Kravis E, Andrews HF, Miller RM, et al. (2017). FORWARD: A registry and longitudinal clinical database to study fragile X syndrome. Pediatrics, 139(Suppl 3), S183–S193. 10.1542/peds.2016-1159E. [PubMed: 28814539]

Symons FJ, Byiers BJ, Raspa M, Bishop E, & Bailey DB (2010). Self-injurious behavior and fragile X syndrome: Findings from the national fragile X survey. American Journal on Intellectual and Developmental Disabilities, 115(6), 473–481. 10.1352/1944-7558-115.6.473. [PubMed: 20946000]

Symons FJ, Clark RD, Hatton DD, Skinner M, & Bailey DB Jr. (2003). Self-injurious behavior in young boys with fragile X syndrome. American Journal of Medical Genetics Part A, 118A (2), 115–121. 10.1002/ajmg.a.10078. [PubMed: 12655491]

Tsiouris JA, & Brown WT (2004). Neuropsychiatric symptoms of fragile X syndrome: Pathophysiology and pharmacotherapy. CNS Drugs, 18(11), 687–703. [PubMed: 15330685]

Wheeler AC, Raspa M, Bishop E, & Bailey DB Jr. (2016). Aggression in fragile X syndrome. Journal of Intellectual Disability Research, 60(2), 113–125. 10.1111/jir.12238. [PubMed: 26628097]

Williams K, Brignell A, Randall M, Silove N, & Hazell P (2013). Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). Cochrane Database Systematic Review, 8, CD004677. 10.1002/14651858.cd004677.pub3.

Witwer AN, & Lecavalier L (2007). Autism screening tools: An evaluation of the Social Communication Questionnaire and the Developmental Behaviour Checklist-Autism Screening Algorithm. Journal of Intellectual Developmental Disability, 32(3), 179–187. 10.1080/13668250701604776. [PubMed: 17885895]

Table 1

Comparisons among those with IAAS—drug-treated versus not drug treated

Measure	No medication for IAAS (total N = 235)		Medication for IAAS (total N = 180)		*p* value
	N with evaluable data	Frequency (%) mean (± SD)	N with evaluable data	Frequency (%) mean (± SD)	
Age (mean years; range)	228	10.4 (±8; 1–49 years))	176	14.4 (±8; 2–57 years)	< 0.0001 *
Male	235	191 (81.3%)	180	163 (90.6%)	0.0082 *
History of seizure	228	24 (10.5%)	178	36 (20.2%)	0.0063 *
Full scale IQ	116	54.6 (± 15.5)	78	45.4 (± 11.8)	< 0.0001 *
Verbal ability—capable of 3+ words	232	141 (60.8%)	180	104 (57.8%)	0.5387
Severe/profound intellectual disability	186	110 (59.1%)	169	135 (79.9%)	< 0.0001 *
ASD diagnosis	215	108 (50.2%)	164	108 (65.9%)	0.0023 *
Hypersensitivity to sensory stimuli	225	92 (40.9%)	175	96 (54.9%)	0.0055 *
Presence of anxiety	233	195 (83.7%)	176	163 (92.6%)	0.0068 *
Indication of anxiety as a limiting factor	235	107 (46%)	180	126 (70%)	< 0.0001
Fully methylated FMR1	164	101 (61.6%)	130	93 (71.5%)	0.0736
Body Mass Index (BMI)—Z-score for age	201	0.4 (± 3.6)	145	0.4 (± 7.2)	0.9492
Full scale IQ	116	54.6 (± 15.5)	78	45.4 (± 11.8)	< 0.0001 *
ABC-C_{FX} irritability subscale	182	37 (± 12.4)	131	41.1 (± 12.6)	0.0049 *
ABC-C_{FX}ABC socially unresponsive/lethargic subscale	182	20.3 (± 6.4)	131	19.9 (± 5.6)	0.5997
ABC stereotypy subscale	182	12.2 (± 5)	131	12.4 (± 4.9)	0.6926
ABC hyperactivity subscale	182	22.6 (± 7.7)	131	23.4 (± 7.7)	0.3571
ABC-C_{FX} inappropriate speech subscale	182	8.3 (± 3.3)	131	9.1 (± 3.5)	0.0416 *
ABC social avoidance subscale	182	7.09 (± 3.3)	131	7.8 (± 3.2)	0.0646
SCQ total score	169	14.82 (± 6)	127	17 (± 5.9)	0.0020 *
SRS T score (total calculated)	158	74.15 (± 10.8)	116	77.1 (± 10.2)	0.0246 *

Statistically significant at *p < 0.05; all continuous variables are presented as means with standard deviations. Categorical variables are presented as frequencies with correlating proportion of sample

SD standard deviation

Table 2

Medications utilized for IAAS (N = 180 total subjects; N = 216 total drug trials)

Class	Medication	n (% of subjects)	n (% of all drug trials)
Stimulant	Methylphenidate	3 (1.7)	3 (1.4)
SSRI	Fluoxetine	5 (2.8)	5 (2.3)
	Sertraline	15 (8.3)	15 (6.9)
	Paroxetine	1 (0.6)	1 (0.5)
	Citalopram	3 (1.7)	3 (1.4)
	Escitalopram	5 (2.8)	5 (2.3)
Non-SSRI antidepressant	Trazodone	2 (1.1)	2 (0.9)
	Bupropion	1 (0.6)	1 (0.5)
Alpha-agonist	Clonidine	9 (5.0)	9 (4.2)
	Guanfacine	8 (4.4)	8 (3.7
Antipsychotic	Haloperidol	3 (1.7)	3 (1.4)
	Risperidone	50 (27.8)	50 (23.2)
	Aripiprazole	65 (36.1)	65 (30.1
	Quetiapine	8 (4.4)	8 (3.7)
	Olanzapine	4 (2.2)	4 (1.9)
	Thioridazine	5 (2.8)	5 (2.3)
	Trifluoperazine	1 (0.6)	1 (0.5)
Mood-stabilizer	Topiramate	1 (0.6)	1 (0.5)
	Lithium	2 (1.1)	2 (0.9)
	Valproic Acid	6 (3.3)	6 (2.8)
	Oxcarbazepine	5 (2.8)	5 (2.3)
Anxiolytic	Clonazepam	2 (1.1)	2 (0.9)
	Diazepam	2 (1.1)	2 (0.9)
	Alprazolam	3 (1.7)	3 (1.4)
	Buspirone	1 (0.6)	1 (0.5)
	Other (lithium)	1 (0.6)	1 (0.5)
Other	Other (baclofen (2), naltrexone (2), hydroxyzine)	5 (2.8)	5 (2.3)

J Autism Dev Disord. Author manuscript; available in PMC 2021 June 17.

Table 3

Reported adverse effects experienced by those on medication for IAAS

Adverse effect	n (% of subjects receiving drug treatment)
No side effects reported	113 (62.8)
Weight gain	26 (14.4)
Sedation	15 (8.3)
Activation/impulsivity/disinhibition	2 (1.1)
Agitation/irritability/anxiety	9 (5.0)
Weight loss/appetite suppression	9 (5.0)
GI (nausea/constipation/diarrhea)	5 (2.8)
Sleep issues/insomnia	4 (2.2)
Tremor	4 (2.2)
Headache	2 (1.1)
Dizziness	2 (1.1)
Other (very thirsty, drooling, increased non-compliance, mild activation, blank (7))	11 (6.1)