Autism Spectrum Disorder in Fragile X Syndrome: Cooccurring Conditions and Current Treatment

Walter E. Kaufmann, MD, a, b Sharon A. Kidd, PhD, MPH, c Howard F. Andrews, PhD, d Dejan B. Budimirovic, MD, e Amy Esler, PhD, fl Barbara Haas-Givler, MEd, BCBA f Tracy Stackhouse, MA, OTR, h Catharine Riley, PhD, MPH, i Georgina Peacock, MD, MPH, j Stephanie L. Sherman, PhD, j W. Ted Brown, MD, PhD, k Elizabeth Berry-Kravis, MD, PhD l

abstract

BACKGROUND AND OBJECTIVE: Individuals with fragile X syndrome (FXS) are frequently codiagnosed with autism spectrum disorder (ASD). Most of our current knowledge about ASD in FXS comes from family surveys and small studies. The objective of this study was to examine the impact of the ASD diagnosis in a large clinic-based FXS population to better inform the care of people with FXS.

METHODS: The study employed a data set populated by data from individuals with FXS seen at specialty clinics across the country. The data were collected by clinicians at the patient visit and by parent report for nonclinical and behavioral outcomes from September 7, 2012 through August 31, 2014. Data analyses were performed by using $\chi^2$ tests for association, $t$ tests, and multiple logistic regression to examine the association between clinical and other factors with ASD status.

RESULTS: Half of the males and nearly 20% of females met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria for current ASD. Relative to the FXS-only group, the FXS with ASD (FXS+ASD) group had a higher prevalence of seizures (20.7% vs 7.6%, $P < .001$), persistence of sleep problems later in childhood, increased behavior problems, especially aggressive/disruptive behavior, and higher use of $\alpha$-agonists and antipsychotics. Behavioral services, including applied behavior analysis, appeared to be underused in children with FXS+ASD (only 26% and 16% in prekindergarten and school-age periods, respectively) relative to other populations with idiopathic ASD.

CONCLUSIONS: These findings confirm among individuals with FXS an association of an ASD diagnosis with important cooccurring conditions and identify gaps between expected and observed treatments among individuals with FXS+ASD.
Fragile X syndrome (FXS)\textsuperscript{1,2} is the most common known inherited form of intellectual disability (ID), with prevalence estimates of \( \sim 1/4000 \) to \( 1/5000 \) in males and \( \sim 1/6000 \) to \( 1/8000 \) in females.\textsuperscript{3–5} FXS is nearly always due to an expanded CGG repeat sequence (>200 repeats), termed a “full mutation,” in the S’ untranslated region of the \textit{FMR1} gene located at Xq27.3. Smaller CGG repeat expansions in the range of 55 to 200 (termed the “premutation”) are associated with other clinical presentations, reviewed elsewhere.\textsuperscript{6,7} The majority of males who carry the full mutation have mild to moderate ID. One-third to one-half of all females with the full mutation have normal intellectual function because of cellular mosaicism resulting from X-chromosome inactivation patterns.\textsuperscript{8,9} A high proportion of males and females with FXS display behavioral abnormalities.\textsuperscript{6} As with most aspects of the FXS phenotype, behavioral manifestations in FXS are quite variable and include attention deficits, hyperactivity/impulsivity, hyperarousal, anxiety, self-injurious behavior, and autism spectrum disorder (ASD).\textsuperscript{6}

ASD is a developmental behaviorally defined disorder with multiple etiologies. Among the genetic causes, FXS is the most common known inherited single-gene disorder, accounting for an estimated 1% to 6% of all cases of ASD.\textsuperscript{10,11} ASD is characterized by an impairment in social interaction and communication and the presence of restricted and repetitive patterns of behavior, interests, or activities.\textsuperscript{12} Other cooccurring behavioral abnormalities are often associated with these core symptoms (eg, anxiety).\textsuperscript{13} The relationship between FXS and ASD is complex and evolving, influenced in part by revised definitions of ASD\textsuperscript{12} and by a better understanding of behavioral phenotypes associated with FXS.\textsuperscript{6} Although variable in degree, a large proportion of individuals with FXS exhibit poor eye contact, difficulties with peer relationships, social withdrawal, repetitive behaviors, and need for sameness (ie, distress at apparently small changes in daily activities).\textsuperscript{5,14,15} Depending on the gold standard research criteria used for the diagnosis of autism or ASD, studies on males with FXS have reported that 30% to 54% met diagnostic criteria for autism by direct assessment\textsuperscript{16–18} and 46% by parent report.\textsuperscript{19} In addition, 30% to 43% of males met diagnostic criteria for ASD\textsuperscript{20} or pervasive developmental disorder—not otherwise specified.\textsuperscript{18} For females, 16% to 20% met diagnostic criteria for autism\textsuperscript{17} or were assigned by parent report.\textsuperscript{19–22} Several studies have attempted to delineate unique features of ASD in FXS; their findings show relatively more prominent social withdrawal, higher levels of anxiety, and less intense simple and complex repetitive and restricted behaviors as measured by ASD diagnostic instruments.\textsuperscript{6,13}

ASD is a lifelong disorder that impacts multiple aspects of the individual’s functioning. Comparisons between subjects with FXS with ASD (FXS+ASD) and subjects with FXS without ASD (FXS only) reveal that the former group is more affected in many cognitive\textsuperscript{9,20,23,24} and behavioral areas.\textsuperscript{5,7,13–15,25} Examples of areas that are more problematic in those with FXS+ASD than in those with FXS only include less developed language skills, particularly receptive skills\textsuperscript{21,23,26,27}; lower nonverbal cognition and IQ scores\textsuperscript{28,29}; lower adaptive skills\textsuperscript{21}; and, in small cohorts, more severe overall behavioral problems (eg, attention problems, hyperactivity and impulsivity, anxiety, aggressive and self-injurious behaviors).\textsuperscript{7,30,31} Idiopathic ASD is associated with a higher rate of epilepsy than seen in the general population and, likewise, data from a single survey study indicate that individuals with FXS+ASD also have a higher rate of seizures than those with FXS only.\textsuperscript{13,12} The increased frequency of neurologic and behavioral impairments in subjects with FXS+ASD appears to result in more severe educational and vocational problems,\textsuperscript{7} as well as more significant therapeutic challenges, than those present in subjects with FXS only, although data describing these outcomes are limited.

The main obstacle for determining medical and neurobehavioral cooccurring conditions exacerbated by ASD in FXS, and their impact on interventions and outcomes, is that most studies of ASD in FXS are based on small clinical research samples or family surveys. Small cohorts may not be generalizable to the entire population and although family surveys may produce accurate accounts of medical data, this type of information always needs to be confirmed in a clinical setting. The Fragile X Online Registry With Accessible Research Database (FORWARD), a registry and longitudinal database, provides a large sample size with clinical data for this rare disorder to examine the impact of ASD in FXS (see Sherman et al in this supplement). In this study, we used FORWARD to study the impact of an ASD diagnosis in children and adolescents/young adults with FXS in 4 key areas: (1) neurologic cooccurring conditions known to be associated with idiopathic ASD, including seizures and sleep disorders; (2) behavioral cooccurring conditions; (3) psychopharmacologic interventions targeting behavior; and (4) nonpharmacologic interventions. Based on past literature and clinical impressions, we hypothesized that (1) the association of an ASD codiagnosis with seizures would be confirmed, particularly by the time patients reached the adolescent/young adult ages; (2) there would be more...
METHODS

Data for this report were derived from FORWARD, a multisite, observational study that includes a registry and longitudinal database using standardized clinician- and parent-report data submitted by 25 of the 27 fragile X clinics affiliated with the Fragile X Clinic and Research Consortium. Clinics obtained institutional research board approval from their own institutions before enrolling families in FORWARD. Written informed consent was obtained at the time of a clinic visit from parents/guardians and from adult patients for whom legal guardianship was not required. Data in the longitudinal database are collected yearly from participants by clinicians, primarily during a patient’s scheduled clinic visit, and by parents/caregivers. Data are collected by using a clinician report form, a parent report form, and 3 standardized parent-report instruments, including the Social Responsiveness Scale, Second Edition (SRS-2), the Social Communication Questionnaire (SCQ), and the Aberrant Behavior Checklist, Community Edition. The SRS and SRS-2 are completed once over the 4-year period of the current study. This article only includes analyses of the SRS-2 started later in the project to accommodate the incorporation of the update of the SRS-2. Analyses presented in this article were conducted on a fixed cross-sectional data set (FORWARD Dataset, Version 1.0) by using registry data linked to clinical baseline (cross-sectional) data on 713 subjects with FXS, collected from September 7, 2012 to August 31, 2014. After excluding patients due to age considerations and availability of data on ASD status, almost 600 individuals were eligible for most of the study analyses presented in this article. Full details on the creation, enrollment, maintenance, and data quality and management for FORWARD are presented in an accompanying report in this supplement (Sherman et al).

Data related to ASD diagnosis were obtained from the FORWARD clinician report form. The diagnosis of ASD was ascertained with the question “Based on THIS clinic assessment, does the child CURRENTLY have a diagnosis of ASD?” (capitalized emphasis from the question itself). The question was answered by the clinician by using Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as required by the FORWARD data collection training (ie, by taking relevant clinical history and observation). However, during the first 6 months of enrollment, a small number of subjects were likely diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, because DSM-5 criteria were not available until the spring of 2013.

Analyses related to neurologic and behavioral problems and psychopharmacology were performed for 2 selected age groups, ages 3 to 11 (children, N = 348) and ages 12 to 21 (adolescents/young adults, N = 199), because the impact of the ASD diagnosis on certain parameters might differ by age. The upper age limit was chosen because pediatric patients transition to adult care between the ages of 18 and 21 years. The following variables were compared between groups of patients with and without a diagnosis of ASD: frequency of seizures occurring at any age, sleep problems requiring medication or treatment, cooccurring behavioral problems (including attention deficits, hyperactivity, sensory hypersensitivity/overreactivity, anxiety, obsessive compulsive disorder/perseverative behavior, mood swings/depression, and irritability/aggression); use of psychotropic medication for treatment of behavior in any of the above categories; and type of psychotropic medication used for any behavior. Parents were asked about provision of services to the patient during school years (preschool, elementary, and high school). These services are in the categories of special education, speech and language therapy, occupational therapy, sensory integration therapy, physical therapy, psychological/behavioral program, social skills therapy, or program, tutoring, and ABA.

The frequency of characteristics is presented as a number (percentage) according to diagnosis (FXS+ASD, FXS only) and age (within age group or age groups combined). The χ² statistic was used to test for association between variables. For continuous variables, means and their respective confidence intervals (CIs) were obtained. Multiple logistic
regression was used for multivariate analyses related to the use of services and ASD status. Analyses were performed by using the Statistical Package for the Social Sciences (IBM SPSS Statistics, IBM Corporation) and EpInfo, Version 7.1.5.0 (Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Briefly, there were more males (78% male vs 22% female), individuals that identify themselves as white (88.7%), and individuals <15 years of age (75%) (see Sherman et al in this supplement). The FORWARD Dataset Version 1.0 included 237 (42%) subjects who were diagnosed by the clinic physician as having ASD. The prevalence was much higher in males than in females (51% vs 18%, P < .001). The ASD group had a significantly higher mean SCQ total score than the FXS-only group (17.2 vs 11.6, P < .001), mean difference = 5.6 points (95% CI = 4.4–6.8). The prevalence of ASD in the 3 to 11 years of age group was 42.2% (N = 147) and it was 45.2% (N = 90) in the 12 to 21 years of age group.

Impact of ASD Codiagnosis on Seizures and Sleep in FXS

Across all ages and diagnostic groups, the prevalence of seizures ever occurring was 13.3%. The FXS+ASD group was more likely to have had seizures at some time in life compared with the FXS-only group (20.7% vs 7.6%, P < .001) (Table 1). This difference was driven mostly by the older age group. Sleep problems requiring treatment with behavioral methods or medications were also more common in the FXS+ASD group (all ages, 41% vs 30%, Table 1). The difference between the 2 diagnostic groups was mainly due to a higher proportion of sleep problems in the adolescent/young adult FXS+ASD group (41% vs 16%, P < .003). In the 3 to 11 years of age group, sleep problems were frequent in general, occurring in ~40% of children in both the FXS+ASD and FXS-only groups.

Table 2 illustrates that the only behavior problem more common in FXS was evaluated in 2 complementary ways: by drugs used for specific symptoms (eg, anxiety) and by categories of drugs (eg, α-adrenergic agonists). Overall, 66% of participants with FXS of any age were on some type of psychopharmacologic treatment of common behavioral problems. Table 3 illustrates that the only behavior for which there was a significantly higher occurrence of anxiety than its FXS-only counterpart (98% vs 87%). Mood swings/depression problems were less common in the data set as a whole (~18%), and no significant difference was observed between those with and without ASD.

Impact of ASD Codiagnosis on Use of Psychoactive Drugs in FXS

The use of psychoactive drugs in FXS was evaluated in 2 complementary ways: by drugs used for specific symptoms (eg, anxiety) and by categories of drugs (eg, α-adrenergic agonists). Overall, 66% of participants with FXS of any age were on some type of psychopharmacologic treatment of common behavioral problems. Table 3 illustrates that the only behavior for which there was a significantly higher use of psychopharmacology among those with FXS+ASD was aggressive/disruptive behavior. Concomitantly, there was a significantly higher use of α-agonists and antipsychotics (which are typically used to treat aggression) in the FXS+ASD group (Table 4). There were no significant differences in the use of stimulants, selective serotonin reuptake inhibitors (SSRIs), mood stabilizers, anxiolytics, or non-SSRI antidepressants between FXS participants with and without ASD.

TABLE 1 Seizures and Sleep Problems Associated With FXS+ASD and FXS Only, by Age Groups and All Ages, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th></th>
<th>Ages 3–11 y</th>
<th>Ages 12–21 y</th>
<th>All Ages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FXS+ASD</td>
<td>FXS Only</td>
<td>P</td>
</tr>
<tr>
<td>Does/did child have seizures (ever and currently)?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>85</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>12 (14.1)</td>
<td>8 (6.2)</td>
<td>&lt;.05 a</td>
</tr>
<tr>
<td>Is child currently on treatment of sleep problems (includes behavioral treatments)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total N</td>
<td>87</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>36 (41)</td>
<td>46 (36)</td>
<td>&lt;.03 a</td>
</tr>
</tbody>
</table>

FORWARD is a data set of clinician and parent-report information from specialty clinics in the FXCRC.  χ² tests for association were used to obtain P values for differences in proportions between case groups for use of services.

a Significant P value (a level of .05 was considered statistically significant).
TABLE 2 Behavioral Problems Associated With FXS+ASD and FXS Only, by Age Group, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Ages 3–11y FXS+ASD (N = 111)</th>
<th>Ages 3–11y FXS Only (N = 164)</th>
<th>P</th>
<th>Ages 12–21y FXS+ASD (N = 52)</th>
<th>Ages 12–21y FXS Only (N = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention problems</td>
<td>126 (88)</td>
<td>153 (77)</td>
<td>&lt;.01⁵</td>
<td>81 (64)</td>
<td>103 (72)</td>
<td>&lt;.01⁵</td>
</tr>
<tr>
<td>Anxiety</td>
<td>120 (83)</td>
<td>149 (78)</td>
<td>&lt;.08</td>
<td>87 (67)</td>
<td>76 (48)</td>
<td>&lt;.01³</td>
</tr>
<tr>
<td>Hypersensitivity/overreaction</td>
<td>114 (82)</td>
<td>130 (66)</td>
<td>&lt;.01³</td>
<td>74 (57)</td>
<td>60 (36)</td>
<td>&lt;.01³</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>108 (75)</td>
<td>126 (63)</td>
<td>&lt;.02²</td>
<td>57 (40)</td>
<td>44 (26)</td>
<td>&lt;.01³</td>
</tr>
<tr>
<td>Irritability/agression/</td>
<td>103 (72)</td>
<td>76 (38)</td>
<td>&lt;.01³</td>
<td>65 (37)</td>
<td>39 (27)</td>
<td>&lt;.01³</td>
</tr>
<tr>
<td>Self-injury</td>
<td>95 (67)</td>
<td>87 (44)</td>
<td>&lt;.01³</td>
<td>64 (40)</td>
<td>56 (33)</td>
<td>&lt;.01³</td>
</tr>
<tr>
<td>Mood swings/depression/</td>
<td>22 (16)</td>
<td>29 (15)</td>
<td>&lt;.51</td>
<td>22 (15)</td>
<td>22 (15)</td>
<td>&lt;.51</td>
</tr>
</tbody>
</table>

Does the Child Currently Have This Behavior? N (%)

| Treatment of Behaviors in FXS+ASD and FXS only, by Age Group, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Ages 3–11y FXS+ASD (N = 111)</th>
<th>Ages 3–11y FXS Only (N = 164)</th>
<th>P</th>
<th>Ages 12–21y FXS+ASD (N = 52)</th>
<th>Ages 12–21y FXS Only (N = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>39 (35)</td>
<td>43 (26)</td>
<td>&lt;.11</td>
<td>33 (64)</td>
<td>10 (19)</td>
<td>&lt;.77</td>
</tr>
<tr>
<td>Aggression/disruptive behavior</td>
<td>36 (32)</td>
<td>19 (11)</td>
<td>&lt;.001⁴</td>
<td>32 (62)</td>
<td>21 (36)</td>
<td>&lt;.001⁴</td>
</tr>
<tr>
<td>Attention problems</td>
<td>29 (26)</td>
<td>49 (30)</td>
<td>&lt;.50</td>
<td>24 (46)</td>
<td>33 (47)</td>
<td>&lt;.91</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (8)</td>
<td>7 (4)</td>
<td>&lt;.18</td>
<td>10 (19)</td>
<td>12 (17)</td>
<td>&lt;.77</td>
</tr>
</tbody>
</table>

Impact of ASD on Use of Services in Individuals With FXS

Use of services at school was examined in 2 groups, preschool and kindergarten to grade 12 (K-12), both in terms of total services (ie, proportion of subjects using any service, mean number of services) as well as the proportion using specific services. In the preschool group, a higher proportion of children with FXS+ASD received any service (P < .008), specifically special education (P < .003) and ABA services (P < .02), than those with FXS only (Table 5). It is of note that ABA was used less than any other service in the preschool period in either group. The average number of services among children with FXS+ASD was significantly higher than for those with FXS in the preschool period (3.1 vs 2.7, mean difference, 0.5 [95% CI = 0.1–0.8]). Given that the older the child is at the time of the clinic visit, the more likely he/she is to have had a particular service, we adjusted for age at the

TABLE 4 Psychotropic Drug Class Use by FXS+ASD and FXS Only, by Age Group, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Psychotropic Drug Class</th>
<th>Ages 3–11y FXS+ASD (N = 111)</th>
<th>Ages 3–11y FXS Only (N = 164)</th>
<th>P</th>
<th>Ages 12–21y FXS+ASD (N = 52)</th>
<th>Ages 12–21y FXS Only (N = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>31 (28)</td>
<td>21 (13)</td>
<td>&lt;.002¹</td>
<td>32 (62)</td>
<td>20 (29)</td>
<td>&lt;.001⁴</td>
</tr>
<tr>
<td>SSRIs</td>
<td>29 (26)</td>
<td>31 (19)</td>
<td>&lt;.16</td>
<td>17 (33)</td>
<td>34 (49)</td>
<td>&lt;.08</td>
</tr>
<tr>
<td>Stimulants</td>
<td>21 (19)</td>
<td>41 (25)</td>
<td>&lt;.24</td>
<td>22 (42)</td>
<td>33 (47)</td>
<td>&lt;.60</td>
</tr>
<tr>
<td>α-agonists</td>
<td>24 (22)</td>
<td>15 (9)</td>
<td>&lt;.004¹</td>
<td>19 (38)</td>
<td>9 (13)</td>
<td>&lt;.002⁵</td>
</tr>
<tr>
<td>Non-SSRI antidepressants</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>&lt;.16</td>
<td>5 (10)</td>
<td>3 (4)</td>
<td>&lt;.24</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>&lt;.07</td>
<td>2 (4)</td>
<td>4 (6)</td>
<td>&lt;.64</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>&lt;.07</td>
<td>2 (4)</td>
<td>1 (1)</td>
<td>&lt;.40</td>
</tr>
</tbody>
</table>

TABLE 5 Treatment of Behaviors in FXS+ASD and FXS only, by Age Group, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Ages 3–11y FXS+ASD (N = 111)</th>
<th>Ages 3–11y FXS Only (N = 164)</th>
<th>P</th>
<th>Ages 12–21y FXS+ASD (N = 52)</th>
<th>Ages 12–21y FXS Only (N = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>39 (35)</td>
<td>43 (26)</td>
<td>&lt;.11</td>
<td>33 (64)</td>
<td>10 (19)</td>
<td>&lt;.77</td>
</tr>
<tr>
<td>Aggression/disruptive behavior</td>
<td>36 (32)</td>
<td>19 (11)</td>
<td>&lt;.001³</td>
<td>32 (62)</td>
<td>21 (36)</td>
<td>&lt;.001³</td>
</tr>
<tr>
<td>Attention problems</td>
<td>29 (26)</td>
<td>49 (30)</td>
<td>&lt;.50</td>
<td>24 (46)</td>
<td>33 (47)</td>
<td>&lt;.91</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (8)</td>
<td>7 (4)</td>
<td>&lt;.18</td>
<td>10 (19)</td>
<td>12 (17)</td>
<td>&lt;.77</td>
</tr>
</tbody>
</table>

Ages 3–11y FXS+ASD (N = 144) FXS Only (N = 199) P | Ages 12–21y FXS+ASD (N = 70) FXS Only (N = 109) P

TABLE 3 Psychotropic Drug Class Use by FXS+ASD and FXS Only, by Age Group, in Subjects Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Psychotropic Drug Class</th>
<th>Ages 3–11y FXS+ASD (N = 111)</th>
<th>Ages 3–11y FXS Only (N = 164)</th>
<th>P</th>
<th>Ages 12–21y FXS+ASD (N = 52)</th>
<th>Ages 12–21y FXS Only (N = 70)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>31 (28)</td>
<td>21 (13)</td>
<td>&lt;.002¹</td>
<td>32 (62)</td>
<td>20 (29)</td>
<td>&lt;.001⁴</td>
</tr>
<tr>
<td>SSRIs</td>
<td>29 (26)</td>
<td>31 (19)</td>
<td>&lt;.16</td>
<td>17 (33)</td>
<td>34 (49)</td>
<td>&lt;.08</td>
</tr>
<tr>
<td>Stimulants</td>
<td>21 (19)</td>
<td>41 (25)</td>
<td>&lt;.24</td>
<td>22 (42)</td>
<td>33 (47)</td>
<td>&lt;.60</td>
</tr>
<tr>
<td>α-agonists</td>
<td>24 (22)</td>
<td>15 (9)</td>
<td>&lt;.004¹</td>
<td>19 (38)</td>
<td>9 (13)</td>
<td>&lt;.002⁵</td>
</tr>
<tr>
<td>Non-SSRI antidepressants</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>&lt;.16</td>
<td>5 (10)</td>
<td>3 (4)</td>
<td>&lt;.24</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>&lt;.07</td>
<td>2 (4)</td>
<td>4 (6)</td>
<td>&lt;.64</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>&lt;.07</td>
<td>2 (4)</td>
<td>1 (1)</td>
<td>&lt;.40</td>
</tr>
</tbody>
</table>

Ages 3–11y FXS+ASD (N = 111) FXS Only (N = 164) P | Ages 12–21y FXS+ASD (N = 52) FXS Only (N = 70) P

FORWARD is a data set of clinician and parent-report information from specialty clinics in the FXCRC. χ² tests for association were used to obtain P values for differences in proportions between case groups for use of services.

a Only subjects on investigational drugs were excluded from the analyses.

b Subjects in FXS+ASD and FXS-only groups could be treated for >1 behavior.

c Significant P value (a level of .05 was considered statistically significant).
TABLE 5 Use of Services in FXS+ASD and FXS Only, Reported for Preschool Years, in Subjects Aged 3 to 21 Years, Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Service</th>
<th>FXS+ASD (N = 181)</th>
<th>FXS Only (N = 211)</th>
<th>P</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any prekindergarten services</td>
<td>149 (81)</td>
<td>171 (81)</td>
<td>&lt;.005p</td>
<td>2.33 (1.25–4.42)</td>
<td>&lt;.01p</td>
</tr>
<tr>
<td>Speech and language therapy</td>
<td>142 (87)</td>
<td>167 (79)</td>
<td>&lt;.06</td>
<td>1.70 (0.87–2.98)</td>
<td>&lt;.06</td>
</tr>
<tr>
<td>Occupational/ sensory integration therapy</td>
<td>129 (79)</td>
<td>150 (71)</td>
<td>&lt;.10</td>
<td>1.50 (0.83–2.43)</td>
<td>&lt;.10</td>
</tr>
<tr>
<td>Special education</td>
<td>119 (73)</td>
<td>122 (58)</td>
<td>&lt;.005p</td>
<td>1.85 (1.25–5.00)</td>
<td>&lt;.003p</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>73 (44)</td>
<td>83 (59)</td>
<td>&lt;.31</td>
<td>1.24 (0.82–1.88)</td>
<td>&lt;.31</td>
</tr>
<tr>
<td>ABA/modified ABA/other behavioral</td>
<td>42 (26)</td>
<td>34 (16)</td>
<td>&lt;.02b</td>
<td>1.83 (1.09–3.06)</td>
<td>&lt;.02b</td>
</tr>
</tbody>
</table>

Parents were asked to report on all services that were used historically during the preschool period. FORWARD is a data set of clinician and parent-report information from specialty clinics in the FXCRC. χ2 tests for association were used to obtain P values for differences in proportions between case groups for use of services.

a Adjusted for age (in years) at clinic visit; odds ratio, the odds of using a service given ASD+FXS status.

b Significant P value (a level of .05 was considered statistically significant).

TABLE 6 Use of Services in FXS+ASD and FXS Only, Reported for Kindergarten Through High School Years, in Subjects Aged 5 to 21 Years, Enrolled From September 7, 2012 Through August 31, 2014, FORWARD Database

<table>
<thead>
<tr>
<th>Service</th>
<th>FXS+ASD (N = 145)</th>
<th>FXS Only (N = 181)</th>
<th>P</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any K-12 services</td>
<td>131 (92)</td>
<td>156 (86)</td>
<td>&lt;.13</td>
<td>1.73 (0.81–3.68)</td>
<td>&lt;.15</td>
</tr>
<tr>
<td>Speech and language therapy</td>
<td>125 (88)</td>
<td>132 (73)</td>
<td>&lt;.003p</td>
<td>2.51 (1.30–4.12)</td>
<td>&lt;.003p</td>
</tr>
<tr>
<td>Occupational therapy</td>
<td>114 (80)</td>
<td>124 (68)</td>
<td>&lt;.05p</td>
<td>1.84 (1.09–3.09)</td>
<td>&lt;.02b</td>
</tr>
<tr>
<td>Social skills</td>
<td>108 (75)</td>
<td>106 (59)</td>
<td>&lt;.01b</td>
<td>2.18 (1.35–3.53)</td>
<td>&lt;.002b</td>
</tr>
<tr>
<td>Sensory integration therapy</td>
<td>62 (43)</td>
<td>73 (40)</td>
<td>&lt;.59</td>
<td>1.16 (0.75–1.83)</td>
<td>&lt;.53</td>
</tr>
<tr>
<td>Psychological/ behavioral</td>
<td>44 (31)</td>
<td>32 (18)</td>
<td>&lt;.008p</td>
<td>2.08 (1.24–3.51)</td>
<td>&lt;.008p</td>
</tr>
<tr>
<td>Physical therapy</td>
<td>39 (27)</td>
<td>36 (20)</td>
<td>&lt;.12</td>
<td>1.53 (0.91–2.58)</td>
<td>&lt;.11</td>
</tr>
<tr>
<td>ABA</td>
<td>35 (24)</td>
<td>37 (20)</td>
<td>&lt;.39</td>
<td>1.26 (0.74–2.13)</td>
<td>&lt;.59</td>
</tr>
<tr>
<td>Tutoring</td>
<td>23 (16)</td>
<td>21 (12)</td>
<td>&lt;.24</td>
<td>1.46 (0.77–2.76)</td>
<td>&lt;.25</td>
</tr>
<tr>
<td>Vocational training</td>
<td>10 (7)</td>
<td>11 (6)</td>
<td>&lt;.16</td>
<td>0.59 (0.27–1.30)</td>
<td>&lt;.19</td>
</tr>
</tbody>
</table>

Parents were asked to report on all services that were used historically during the K-12 period. Only subjects 5 to 21 years of age were included. FORWARD is a data set of clinician and parent-report information from specialty clinics in the FXCRC. χ2 tests for association were used to obtain P values for differences in proportions between case groups for use of services.

a Adjusted for age (in years) at clinic visit; odds ratio, the odds of using a service given ASD+FXS status.

b Significant P value (a level of .05 was considered statistically significant).

time of baseline visit using multiple logistic regression. The total of any services (P < .01), special education (P < .003), and ABA (P < .02) were used significantly more often in the ASD+FXS group relative to the FXS-only group during the preschool period, controlling for current age. The odds ratios for these services indicate that the odds of service use among those with ASD+FXS are approximately twice as great as among those with FXS only.

By contrast, during the K-12 period, the proportion of children receiving any services, although somewhat higher in the ASD group, was not significantly greater than in the FXS-only group (Table 6). In the K-12 group, a statistically significantly higher proportion of children with FXS+ASD received special education, speech and language therapy, occupational therapy, and sensory integration therapy than those with FXS only (P values ranged from P < .03 to P < .001). Similar to the preschool period, ABA services were not used to a high degree in either group. The average number of services among children with FXS+ASD was significantly higher than among those with FXS only (4.1 vs 3.4, mean difference, 0.7 [95% CI = 0.2–1.2]). Again, as was done for the preschool period, we adjusted for age at the time of baseline visit by using multiple logistic regression. Speech and language therapy (P < .005), special education (P < .02), occupational therapy (P < .002), and sensory integration therapy (P < .006) were used significantly more often in the ASD+FXS group relative to the FXS-only group in the K-12 period regardless of current age. Similar to the preschool period, those with ASD+FXS were approximately twice as likely to use these services as those with FXS only.

DISCUSSION

ASD is a common codiagnosis for patients with FXS and is associated with increased severity of developmental and behavioral symptoms. Despite the frequency and severity of ASD in FXS, there are
still important gaps in knowledge in many areas, ranging from diagnostic accuracy to need for and response to drugs and other treatments, because most of the available literature is based on small clinical or research samples and family surveys. The FORWARD longitudinal database constitutes a unique large-scale source of clinician-acquired data for confirming and expanding our knowledge about ASD in FXS. The current study focused on determining the impact of an ASD codiagnosis in FXS, to address specific hypotheses about neurologic and behavioral cooccurring conditions and treatment approaches associated with the ASD codiagnosis. The analyses from FORWARD presented in this article are consistent with clinical experience and findings reported in the existing literature on ASD in the FXS population, but also provide new information on the magnitude of cooccurring conditions and differences in the use of services between affected groups.

**Impact of ASD Codiagnosis on Seizures and Sleep in FXS**

The frequency of seizure history in FXS+ASD in this FORWARD cohort is somewhat lower than that reported in cohorts from multiple previous studies, although it is consistent with the frequency of 16% reported from the 2005–2011 Fragile X Clinic and Research Consortium pilot database. This difference is perhaps due to ascertainment bias in previous large studies from clinics where the clinic’s physician was a neurologist, thus attracting patients with seizures. The FORWARD data set is probably less skewed because many clinics’ physicians are developmental pediatricians or psychiatrists and thus would not particularly concentrate on patients needing seizure management. Although ascertainment bias related to clinical expertise would not be present in a survey study, seizures may be overreported by parents due to confusion with other types of episodes (eg, abnormal behaviors). The clinical evaluation of seizure history by a physician allows nonepileptic episodes to be filtered out and is expected to result in more accuracy in the identification of patients with a seizure history. As hypothesized, seizure history was associated with an ASD diagnosis, with a stronger association in the adolescent/young adult group because, by that age, most individuals with FXS had manifested their seizures if they were going to do so. This result is consistent with the finding of an association between seizures and an ASD codiagnosis in survey studies and confirms this relationship in a clinically characterized population, increasing the likelihood of the association and emphasizing the concept of shared synaptopathy resulting in both epilepsy and ASD phenotypes. The overall frequency of significant sleep problems (needing therapeutic intervention) in the FORWARD data set was comparable to previous reports. The fact that similar findings were observed both in FORWARD and previous survey-based studies confirms that parents consistently report sleep problems in FXS. As expected, based on high frequencies of sleep dysfunction in idiopathic ASD, the FXS+ASD group in the FORWARD data set had a higher frequency of sleep problems. It has been hypothesized that the impact of ASD codiagnosis on sleep problems would be larger in the younger group, given the tendency for sleep problems to be worse in younger children with idiopathic ASD. In fact, sleep problems were frequent in both of the younger patient groups in the FORWARD data set, both those with and without ASD. However, whereas the FXS-only group appeared to be more likely to grow out of their sleep problems, the FXS+ASD continued to have sleep problems after early childhood into the young adult years. This possible lack of maturation of sleep in FXS+ASD has not been reported before and, if confirmed, could be a significant contributor to family stress.

**Impact of ASD Codiagnosis on Behavioral Problems in FXS**

The FORWARD cohort showed a higher prevalence of a wide range of behavioral problems in the FXS+ASD group as compared with the FXS-only group. The FXS+ASD group had the most dramatically increased frequency of irritability/aggression, perseverative/obsessive compulsive behavior, and sensory hypersensitivity/overreactivity. Although the association of behavioral problems with FXS+ASD serves to confirm previous smaller studies, the FORWARD data set contains additional information to illustrate the impact of ASD codiagnosis in FXS on multiple behaviors with a defined pattern of strength of association with specific behavioral classes. In addition, the association between ASD and anxiety in the FORWARD data set was statistically significant for the adolescent/young adult FXS+ASD group, in contrast with previous survey data indicating a link at all ages. Overall, the frequency of reported anxiety in the FXS population represented in FORWARD was substantially higher than in family surveys (~80% FORWARD vs ~50% in the National Fragile X Survey). This could be in part because of ascertainment bias resulting from recruiting participants.
in a clinic setting, where patients often go for behavioral treatment.

Impact of ASD Codiagnosis on Use of Psychoactive Drugs in FXS

In agreement with previous reports on the use of psychoactive drugs in the FXS population, a high proportion of individuals with FXS are treated with psychoactive drugs.48–50 This report, however, represents the first comparison of patterns of use of psychopharmacology in FXS+ASD versus FXS only. As hypothesized by the authors, and based on clinical experience and the extensive use of antipsychotics in idiopathic ASD, use of antipsychotics was significantly more prevalent in the FXS+ASD group as compared with the FXS-only group. Although overall rates of antipsychotic use in the younger group were lower, somewhat unexpectedly, the use of antipsychotics in the FXS+ASD group was approximately double that of the FXS-only group at both age levels. This may suggest that in FXS+ASD, behavioral issues are more difficult in childhood, possibly leading to the use of more potent medications with higher levels of side effects even at a young age. A greater use of α-adrenergic agonists was also found in the FXS+ASD group, which could be because of lower cognitive functioning and more severe hypersensitivity and hyperactivity relative to the FXS-only group. A lower frequency of stimulant use was not identified in the FXS+ASD group, in contrast with previous reports in idiopathic ASD populations.51,52 Stimulants tend to produce side effects of irritability and aggression in individuals who have ASD or other neurodevelopmental disorders and are lower functioning cognitively.13 This side effect may not be as prevalent in the FXS+ASD population, given the frequency of patients tolerating stimulant medication. Interestingly, despite the frequent occurrence of anxiety in adolescents with FXS+ASD, the use of SSRIs in this group was lower than in the FXS-only group, likely due to the common clinical experience of better effectiveness of antipsychotics for symptom combinations of anxiety and aggression/irritability often seen in those with FXS+ASD (although there is a dearth of literature on this53), or due to side effects of disinhibition from SSRIs, which may occur in FXS and other neurodevelopmental disorders.21 The only symptom specifically targeted by psychopharmacology more commonly in those with FXS+ASD than with FXS only was aggressive/disruptive behavior, a finding previously reported exclusively for those individuals with FXS and both ASD and anxiety.13

Impact of ASD Codiagnosis on Use of Services in Individuals With FXS

This study presents new data on service use in FXS with and without ASD co-diagnosis. As hypothesized and consistent with literature on idiopathic ASD,54–56 among individuals receiving services during preschool and school-time periods, the FXS+ASD group had a higher proportion of children in special education, receiving speech and language therapy, receiving ABA and other behavioral services, but not physical therapy. It would also be expected that the greater social impairment and more challenging educational and vocational situations for individuals with FXS+ASD would result in a greater use of services related to these areas. However, in the FORWARD data set, there was a comparable proportion of FXS individuals with and without ASD receiving behavioral services, social skills therapy, vocational training, and tutoring during the K-12 period. Also, contrary to expectations, despite the overall greater use of nonpharmacologic interventions in the FXS+ASD group, there was no difference in the use of behavioral services, including ABA and social skills therapies in the school-age group. In a US national survey, autism status among individuals with FXS was significantly associated with receipt of behavior management therapy among males, but not for ABA specifically.57

Because these types of therapies would be expected to address critical support needs in FXS+ASD, their underutilization in this cohort may be the result of limited availability. Indeed, families of children with idiopathic ASD are more likely to report unmet needs with respect to therapies compared with families of children with other special health care needs, including provider inability to treat the child as a barrier to obtaining therapy.58 Nonetheless, other factors may affect provision of services to individuals with FXS+ASD. It is of note that ~20% of children with FXS+ASD of all ages in FORWARD were receiving ABA, whereas 36% of children with idiopathic ASD were reported to be receiving ABA by parents in an internet survey of treatments.59

Comparison and Implications for Idiopathic ASD

The features distinguishing individuals co-diagnosed with FXS and ASD from those with FXS only were similar to features known to distinguish individuals with ASD from typically developing individuals or individuals with other forms of ID without ASD. These features include: more prevalent seizure disorder, frequent sleep problems, high frequency of behavioral cooccurring conditions, and high use of psychoactive drugs.54,60–62 Also, the need for a variety of interventions during the preschool and school years are also characteristic in idiopathic ASD.54–56,63,64 On the other hand, there is a higher frequency of treatment of aggressive/disruptive behavior in FXS+ASD. Similar neurobehavioral profiles can be found in other genetic disorders associated with ID and ASD, although
data are more limited compared with that available for FXS.\textsuperscript{28,65} Perhaps unique to individuals with FXS and ASD is the high frequency of hypersensitivity and anxiety, 2 conditions sometimes difficult to differentiate from each other that can provide a unique profile of autistic features in FXS. A few studies comparing individuals with FXS and ASD to those with idiopathic ASD indicate that, although the FXS and ASD group is relatively less impaired in social interaction and lower-order restricted and repetitive behaviors, it is clear that problem behaviors, nonverbal cognition, and adaptive behavior impairment are comparable or more severely affected.\textsuperscript{25,26,66,67} Nevertheless, these studies suggest that the data presented here have important implications for characterizing idiopathic ASD.

**Strengths and Limitations**

We believe that clinician assessment as used in FORWARD has several advantages over parent report, particularly as it applies to FXS. Parents of children with FXS will recognize similar and overlapping behaviors between the FXS behavioral phenotype and ASD, and likely do not have the knowledge base to determine *Diagnostic and Statistical Manual of Mental Disorders* criteria. Parents may also be unclear about the accuracy of the child’s diagnosis if the label of ASD was only provided for obtaining services. Parents may also not know of the ASD diagnosis given that the key diagnosis is FXS; this could be due to a delayed or absent ASD diagnosis once FXS is confirmed due to a lack of additional diagnostic diligence. Given the complexities of the behavioral phenotype of FXS, diagnostic measures that allow for greater depth in symptom evaluation may be needed to be certain of the diagnosis of ASD in individuals with FXS. We hope that in the future, diagnostic uncertainty can be additionally reduced by a multipronged effort to complement clinician assessment with the SCQ and SRS-2 instruments in FORWARD. Currently, in the absence of research gold standard instruments, such as an autism diagnostic observation schedule and Autism Diagnostic Interview-Revised, clinician assessment by using *Diagnostic and Statistical Manual of Mental Disorders* criteria would be considered the gold standard over parent report.

In addition, the data in FORWARD come from multiple clinics across the country and from different settings, and thus are less biased than data coming from any single clinic. Consequently, this study showcases the power of natural history projects, such as FORWARD, to characterize critical phenotypes, interventions, and other knowledge gaps in a rare disease population.

Although the data collected in FORWARD are extremely valuable, we recognize inherent limitations in terms of comprehensiveness and completeness. There was inconsistency in responses to some items on the clinician report form, which were identified through a comprehensive data review and process evaluation. Anchoring of responses to questions with specific instructions is being carried out to improve the consistency of future data collection for these items. In particular, as shown in Table 2, questions about the presence of problem behaviors were answered inconsistently. Data on services (Tables 5 and 6) may be prone to recall inaccuracy, because parents were asked to report on the history of services used during 2 different time periods, both of which may have occurred long ago. Despite these limitations, bias toward FXS+ASD or FXS is not that likely because the data were collected without regard to these classifications.

The number of females with FXS+ASD ($N = 23$) was too small to break out into the analytical groups we used. Therefore, our analyses, although focused on all individuals with FXS+ASD, likely reflected the disease status of males in the analyses. With future data collection, we hope to increase the overall enrollment of females in FORWARD.

Other limitations are specific to ASD; data collected were based on the clinicians’ impression based on use of DSM-5 criteria, interview with the parent, and review of records. In the earliest set of enrollments, before the release of DSM-5, DSM-IV was used. Although there were only a few months of enrollment during the period of DSM-IV use, this may have impacted the diagnosis of ASD+FXS. The current study is one of the first studies to use DSM-5 criteria to classify FXS patients as having cooccurring ASD. In fact, a recent study analyzed caregiver responses to survey questions about their child with FXS pertaining to diagnostic criteria for ASD based on DSM-IV versus DSM-5 and found that fewer individuals with FXS are likely to meet ASD criteria based on DSM-5.\textsuperscript{68} Although most individuals with FXS met repetitive behavior criteria, fewer individuals met the more stringent DSM-5 criteria for impairment in social interaction. Thus, the ASD group identified in this article may be different from ASD groups in previous studies on FXS and ASD, and the aforementioned survey work would suggest it would be a more severely affected group than previous groups classified based on DSM-IV.

It must also be recognized that the clinical setting is affected by constraints in the use of clinical services, such as medical insurance, and the skewed nature of the ascertained population (e.g., individuals at both ends of the spectrum of behavioral severity may be underrepresented). Parents of
patients with milder symptoms may not seek care from a specialty clinic, and those patients with more severe symptoms may not be able to attend a clinic due to severe behavioral cooccurring conditions (e.g., anxiety, obsessive compulsive disorder). Additional information about the limitations of FORWARD is discussed in an accompanying article by Sherman et al in this supplement.

CONCLUSIONS

The current study was focused on the impact of ASD codiagnosis in FXS in terms of neurologic and behavioral cooccurring conditions and treatment approaches, and used a larger sample than any previous study conducted on a population codiagnosed with FXS and ASD. Therefore, this study was able to provide a more robust description of the population affected by both FXS and ASD because it included a large enough sample population to be able to do analyses by age group; by specific cooccurring conditions, of which some are relatively infrequent (e.g., seizures); and by particular medications or services. Because many of the variables studied occur only in a fraction of the population in either the FXS+ASD or FXS-only group, large numbers, such as those available in FORWARD, may be needed to see significant group differences. This study confirmed earlier reports based on smaller samples or family surveys and revealed new findings, some with potential implications for clinical management and public health approaches to addressing the needs of this population. Greater frequency of seizures and certain behavioral cooccurring conditions, such as aggressive/disruptive behavior, in those with FXS+ASD have considerable impact on the management of the affected population. Underuse of behavioral services, including ABA, social training, tutoring, and vocational training, in individuals with FXS+ASD is of some concern considering the core nature of ASD and its associated cognitive and learning challenges. The data reported in this study can guide future research in the FXS and ASD fields.

ACKNOWLEDGMENTS

We thank the National Fragile X Foundation for their support, encouragement, and commitment to establish the Fragile X Clinical Research Consortium (FXCRC). We thank Don Bailey, Melissa Raspa, and Anne Wheeler for their input into FORWARD. Importantly, FORWARD could only exist with the effort of families who have FXS and the clinicians and teams who care for them. To acknowledge the work of each clinic contributing data to FORWARD, we list the clinical director, their affiliation, and the year they joined the FXCRC. The list is alphabetical by state.

ABBREVIATIONS

ABA: applied behavior analysis
ASD: autism spectrum disorder
CI: confidence interval
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FORWARD: Fragile X Online Registry With Accessible Research Database
FXCRC: Fragile X Clinical Research Consortium
FXS: fragile X syndrome
FXS+ASD: FXS with ASD
FXS only: FXS without ASD
ID: intellectual disability
K-12: kindergarten to grade 12
SCQ: Social Communication Questionnaire
SRS-2: Social Responsiveness Scale, Second Edition
SSRI: selective serotonin reuptake inhibitor

reviewed and revised the manuscript; Dr Brown contributed to data collection and critically reviewed and revised the manuscript; Dr Berry-Kravis contributed to the conception and design of the analyses, contributed to data collection and interpretation of the data, and drafted and revised the manuscript; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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.

DOI: https://doi.org/10.1542/peds.2016-1159F

Accepted for publication Jan 24, 2017

Address correspondence to Walter E. Kaufmann, MD, Center for Translational Research, Greenwood Genetic Center, 113 Gregor Mendel Cir, Greenwood, SC 29646.
E-mail: wkaufmann@ggc.org

PEDIATRICS (ISSN Numbers: Print, 0031-400S; Online, 1098-4275).

Copyright © 2017 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Kaufmann is a consultant to Neuren, Edison, Newron, EryDel, Marinus, and GW Pharmaceuticals and has received funding to his institution from Ipsen and Ellex; Dr Berry-Kravis has received funding to her institution from Seaside Therapeutics, Novartis, Roche, Alcobra, and Neuren.
Pharmaceuticals to consult on trial design and conduct clinical trials in fragile X syndrome; and from Asuragen, Inc to develop testing standards for FMR1 testing; and also has grant funding from the National Institutes of Health, the Merck Foundation, and the Centers for Disease Control and Prevention; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by cooperative agreements SU10DD000231 and SU10DD000753-02 with the Centers for Disease Control and Prevention.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES


Autism Spectrum Disorder in Fragile X Syndrome: Cooccurring Conditions and Current Treatment


*Pediatrics* 2017;139;S194
DOI: 10.1542/peds.2016-1159F
Autism Spectrum Disorder in Fragile X Syndrome: Cooccurring Conditions and Current Treatment

Pediatrics 2017;139;S194
DOI: 10.1542/peds.2016-1159F

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/139/Supplement_3/S194