

# Public Health Literature Review of Fragile X Syndrome

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abstract

**OBJECTIVES:** The purpose of this systematic literature review is to describe what is known about fragile X syndrome (FXS) and to identify research gaps. The results can be used to help inform future public health research and provide pediatricians with up-to-date information about the implications of the condition for individuals and their families.

**METHODS:** An electronic literature search was conducted, guided by a variety of key words. The search focused on 4 areas of both clinical and public health importance: (1) the full mutation phenotype, (2) developmental trajectories across the life span, (3) available interventions and treatments, and (4) impact on the family. A total of 661 articles were examined and 203 were included in the review.

**RESULTS:** The information is presented in the following categories: developmental profile (cognition, language, functional skills, and transition to adulthood), social-emotional profile (cooccurring psychiatric conditions and behavior problems), medical profile (physical features, seizures, sleep, health problems, and physiologic features), treatment and interventions (educational/behavioral, allied health services, and pharmacologic), and impact on the family (family environment and financial impact). Research gaps also are presented.

**CONCLUSIONS:** The identification and treatment of FXS remains an important public health and clinical concern. The information presented in this article provides a more robust understanding of FXS and the impact of this complex condition for pediatricians. Despite a wealth of information about the condition, much work remains to fully support affected individuals and their families.

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Fragile X syndrome (FXS) is the most common single-gene cause of inherited intellectual disability. FXS is caused by an expanded trinucleotide repeat (CGG) on the 5' untranslated region of the fragile x mental retardation 1 (*FMR1*) gene. A normal range is between 6 and 44 repeats. Individuals with 45 to 54 repeats are considered to have a gray zone or intermediate expansion. Those with 55 to 200 repeats have the premutation, which is likely to become unstable in future generations. Affected individuals with the full mutation FXS have >200 repeats. In the full mutation, methylation occurs during gestation, silencing *FMR1* transcription.<sup>1</sup> This silencing leads to a reduction or absence of fragile X mental retardation protein (FMRP), which is needed for normal brain development. In a small number of males with the full mutation, there are no methylation patterns observed, resulting in residual levels of FMRP, which results in less impaired functioning. In females, FMRP levels are related to the X activation ratio and the amount of FMRP produced.<sup>2</sup> FXS results in cognitive and adaptive limitations that impact everyday function. Given that FXS is inherited, there are numerous implications for families, ranging from carrier issues and testing to family adaptation to the condition.

Policy documents by the American Academy of Pediatrics (AAP) suggest ways to identify and treat individuals with FXS. The Committee on Genetics published a clinical report on the comprehensive genetic evaluation of children with general development delays or intellectual disabilities.<sup>3</sup> The report recommends FXS testing as a first-line test for all boys and girls with general developmental delay or intellectual disability of unknown origin. The AAP also provides clinical guidelines on health supervision of children with FXS,<sup>4</sup>

**TABLE 1** Search Terms and Inclusion/Exclusion Criteria by Topic Area

Topic Area	Search Terms	Search Dates	Other Search Criteria
Full mutation phenotype	Fragile X syndrome, fragile X-associated disorders, fragile X premutation, fragile X carrier, fragile X-associated tremor/ataxia syndrome, or fragile X-associated primary ovarian insufficiency and phenotype, clinical presentation, clinical description, neurocognitive, cognitive, behavior, social-emotional, or language, communication	2008–2014	English language Human United States only
Developmental trajectories across the life span	Fragile X syndrome or fragile X and lifespan, developmental, longitudinal, adolescent, adult, services, or transition to adulthood	1991–2014	English language Human
Available interventions and treatments	Fragile X syndrome or fragile X and treatment, intervention, pharmacological, educational, behavioral, medication, or clinical trial	1991–2014	English language Human
Impact on family	Fragile X syndrome or fragile X and family adaptation, family impact, family outcomes, burden, or cost of care	1991–2014	English language Human United States only

including information on genetic testing, recommended examinations for well-care visits, and anticipatory guidance. However, these guidelines do not provide for treatment of FXS, including the use of medications.

The purpose of this review is to describe the state of the science on FXS and research gaps to help pediatricians support patients with FXS and their families.

## METHODS

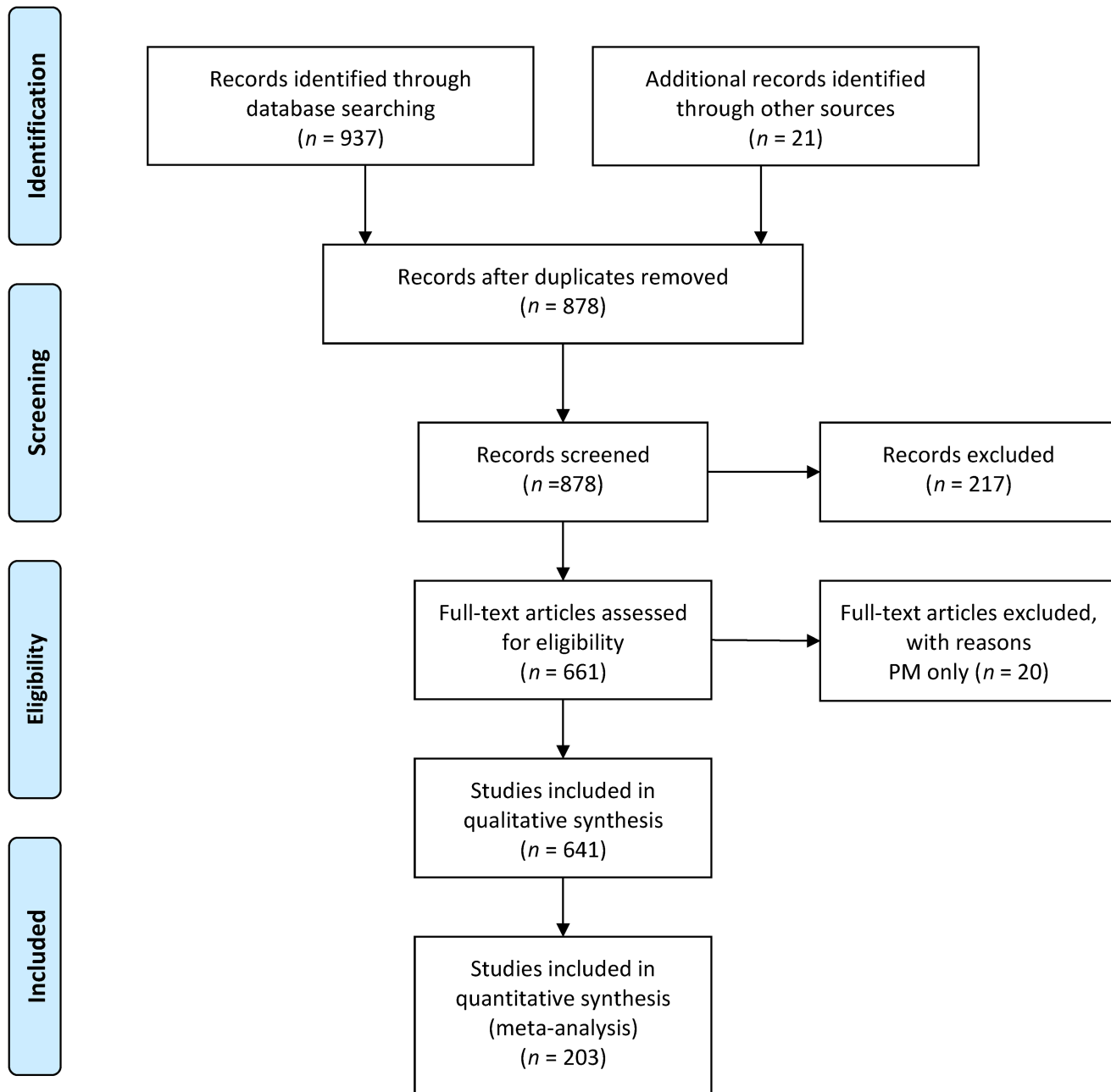
### Search Terms

Four overarching themes of both public health and clinical importance in FXS guided the systematic literature review: (1) epidemiology, (2) impact, (3) health care delivery, and (4) genetics. Of the topics included under these overarching areas, we focused the search on 4 topic areas for this manuscript: (1) the full mutation phenotype, (2) developmental trajectories across the life span, (3) available interventions and treatments, and (4) the impact

on the family. Given that there are other reviews of the FXS phenotype, we focused on literature published in the past 6 years, but also included seminal articles outside the search dates. The other areas had more inclusive search dates. Table 1 details the search terms and inclusion/exclusion criteria for all 4 areas.

### Abstract Review and Refinement

An electronic literature search was conducted by using search terms in PubMed, CINAHL, and Embase. All iterations of the search terms were combined within each topic area. For example, the interventions and treatment topic search combined either “fragile X syndrome,” or “fragile X,” with any 1 of the following: “treatment,” “intervention,” “pharmacological,” “educational,” behavioral,” “medication,” or “clinical trial.” A total of 878 unique citations matched the search criteria (Fig 1). We reviewed titles and abstracts to determine studies appropriate for inclusion. We excluded articles that



**FIGURE 1**

Articles included in the public health literature review. (Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 6(7):e1000097.)

either did not meet the inclusion criteria (Table 1), had a focus on basic rather than social science, or were not research studies (eg, letters to the editor). These exclusions resulted in a total of 661 articles that were reviewed. Of these, 20 were excluded because the content focused exclusively on the fragile X premutation. In sum, 203 are

summarized in this review. The information from the first 2 areas of focus are presented below by profile type: (1) developmental profile, (2) social-emotional profile, and (3) medical profile. The last 2 are summarized in the Treatments and Interventions section and the Impact on the Family section.

## RESULTS

The results are organized into 5 sections. The Developmental Profile section provides an overview of research on cognitive and academic skills, language ability, functional skills, and the transition to adulthood. The Social-Emotional Profile section details the behavioral phenotype of FXS, including cooccurring conditions

and other behavioral problems. The Medical Profile section describes the literature on physical features associated with FXS, seizures, sleep issues, other health issues, and physiologic characteristics. The Treatments and Interventions section summarizes research on behavioral and educational interventions, allied health services, and pharmacologic treatments. Finally, the Impact on the Family section includes research on family adaptation, such as impacts on the family environment and the financial impact of FXS.

## Developmental Profile

### *Cognitive Development and Academic Skills*

The neurocognitive profile of individuals with FXS is well described, including several recent reviews.<sup>5–11</sup> Boys typically have moderate to severe intellectual disability, with average IQ scores <55. Other areas of weakness include short-term and working memory, spatial memory, auditory and sequential processing, abstract thinking, executive function, and mathematical thinking.<sup>5–11</sup> Areas of strength for boys include receptive vocabulary, visual memory, simultaneous processing, experiential learning, and imitation.<sup>5–11</sup> This profile of cognitive challenges persists across groups of high-, mid-, and low-functioning individuals.<sup>12</sup>

Boys exhibit a unique cognitive profile compared with other types of intellectual or developmental disabilities or with typically developing peers. When compared with individuals with Down syndrome, boys with FXS have greater impairments in object discrimination learning, but better performance on object recognition memory and egocentric spatial learning tasks.<sup>13</sup> They also have significant deficits in all areas of executive function (ie, inhibition, working memory, cognitive flexibility, and planning) compared

with typically developing peers.<sup>14,15</sup> Boys with FXS show relatively stable deficits across most developmental domains, whereas boys with autism show more varying ability levels.<sup>16</sup>

Girls with FXS may demonstrate similar patterns of strengths and weaknesses to boys, but are often less severely affected.<sup>17</sup> Girls have a higher rate of learning disability in mathematics than grade-matched comparisons.<sup>18</sup> Mathematical tasks requiring a conceptual understanding of numbers or amounts are most challenging for girls,<sup>19</sup> which may be related to delays in spatial location skills.<sup>20</sup>

Several longitudinal studies have demonstrated that IQ scores are lower in adolescents and adults with FXS when compared with younger children with FXS.<sup>21–26</sup> Children make steady cognitive growth through early adolescence, at which point mental age plateaus and IQ declines.<sup>27</sup> Older children with FXS have a developmental growth rate 2.2 times slower than their non-FXS siblings.<sup>27</sup> A pattern of cognitive decline holds even when assessed by using nonverbal measures.<sup>28,29</sup> The increasing gap in IQ scores from typical development may be due to the nature of standardized tests (ie, increased importance of symbolic language in adolescence) as opposed to the loss of skills.<sup>30</sup> However, studies examining these variable rates in cognitive decline<sup>30,31</sup> have suggested that methylation level, delayed frontal lobe maturation, level of FMRP production, comorbid autistic behaviors, and maternal education may be contributing factors.<sup>28,29,32,33</sup>

More recently, other longitudinal studies starting as young as infancy have explored the earliest age of onset of decline. Roberts et al<sup>34</sup> found delays beginning as early as 9 months of age. The rate of development did not change dramatically over time; however, autistic behavior was strongly related to development. Two

other studies<sup>35,36</sup> found global delays in boys, with the rate of development being approximately half that of typically developing peers. Across these studies communication and cognition were the most affected domains of functioning.

### *Language Development*

Many areas of language development appear to be affected in FXS, and therefore this area has been studied extensively; recent reviews provide a summary of research findings to date.<sup>37–39</sup>

### *Prelinguistic*

Young children with FXS often have delays in attaining early language milestones<sup>40,41</sup> as well as delays in nonverbal communication (ie gestures and reciprocal/symbolic behavior).<sup>42</sup> Children with more autistic behaviors have a negative pattern of development; initial gesture use may be negatively associated with later rates of words used.<sup>43</sup>

### *Receptive*

Studies of receptive language have shown mixed results. Some have found receptive vocabulary in boys with FXS to be below that of typically developing peers, even after controlling for nonverbal cognitive ability.<sup>44,45</sup> However, other studies report vocabulary skills on par with mental age-matched peers.<sup>46,47</sup> Receptive language ability does appear to improve over time.<sup>48</sup>

Recent work has compared receptive language in individuals with FXS with other groups who have an intellectual or developmental disability. Receptive language is similar between individuals with FXS and those with autism.<sup>49</sup> In another set of studies, girls, but not boys, with FXS had higher receptive syntax scores than those with Down syndrome.<sup>50,51</sup> Girls with FXS also have been shown to have higher scores on receptive vocabulary than on nonverbal IQ,

indicating a relative strength in this area.<sup>52</sup>

### *Expressive*

Individuals with FXS outperform individuals with Down syndrome or autism on global measures of expressive language<sup>53</sup> and in general are more talkative and more intelligible.<sup>54</sup> When compared with mental age (MA)-matched peers, individuals with FXS often have equivalent overall expressive language skills<sup>53</sup> and numbers of communication units.<sup>55</sup> A relative strength in phonological memory may be associated with higher expressive language scores.<sup>56</sup>

Zajac et al<sup>57,58</sup> examined articulation in young boys with FXS compared with typically developing peers. In the first study, boys with FXS did not differ from MA-matched peers with regard to articulation rate. However, boys with comorbid FXS and autism had faster rates than the chronologically matched peers. Another study found that those with FXS, regardless of autism status, performed better than those with Down syndrome and did not differ from typically developing peers on phonological accuracy.<sup>59</sup> On a measure of intelligibility, those with FXS had a lower percentage of words that were understood when compared with MA-matched peers but did not differ from those with Down syndrome.

Syntax also appears to be a challenge for individuals with FXS. Boys with FXS have shorter, less complex utterances than MA-matched peers.<sup>53,57,60</sup> No differences existed between boys with and without a codiagnosis of autism, but those with FXS did perform better than individuals with Down syndrome.<sup>60,61</sup> Sterling et al<sup>62</sup> found that boys with lower receptive vocabulary scores were more likely to make grammatical tense errors (eg, “She walk home.”) than those with higher receptive vocabulary scores. Nonverbal cognition and

phonological working memory are other key factors that play a role in syntactic ability.<sup>63</sup>

### *Pragmatics*

Pragmatic development, or the ability to use language in social interactions, is an area of deficit in FXS for both boys and girls. Individuals with FXS engage in fewer conversational turns and ask fewer clarifying questions to continue the conversational topic than typically developing peers.<sup>64,65</sup> Boys with both FXS and autism also appear to struggle with pragmatics.<sup>61</sup> When narrative language is examined, however, individuals with FXS perform similarly or better than MA-matched peers, suggesting an area of strength.<sup>66,67</sup> Early and sustained levels of maternal responsivity, an interaction style characterized by warmth and sensitivity, appears to play a role in many language outcomes.<sup>68,69</sup>

### *Functional Skills*

Studies on functional skills and adaptive behavior in FXS have been limited. Using a large sample of parents of individuals with FXS, Bailey et al<sup>70</sup> reported on skill attainment in 7 areas: eating, dressing, toileting, bathing/hygiene, communication, articulation, and reading. Most adult males and females were verbal and independently used the toilet, bathed, dressed themselves, and ate. However, skills, such as using complex sentences, reading, or speaking at a typical rate, were weaknesses. Hatton et al<sup>71</sup> showed steady improvements in adaptive behavior over time for children up to age 12 years. Those with fewer autistic behaviors and higher levels of FMRP showed more improvements over time. In adolescents and adults, delays in communication, socialization, and daily living skills for both males and females have been documented.<sup>72–74</sup> Individuals codiagnosed with autism exhibit the

biggest declines in adaptive scores over time.<sup>75–77</sup>

### *Transition to Adulthood*

The majority of research on FXS to date has focused on children and adolescents, and therefore information about adults with FXS is limited. A large national survey showed that the majority of adult males (70%) lived with their parents, and even 50% of adult females still lived at home.<sup>78</sup> Many females were working full time (48%) compared with only 20% of males. More males (57%) than females (19%) needed moderate to considerable assistance with everyday life. The strongest predictor of independence was functional skill level (males) and the ability to interact appropriately (females). Adolescents and young adults with more autism symptoms had lower independent living skills, especially managing money, health and safety, and problem solving, relative to typically developing peers even after controlling for IQ.<sup>79</sup>

### **Social-Emotional Profile**

#### *Cooccurring Psychiatric Diagnoses*

Research on conditions that cooccur with FXS has focused primarily on attention, anxiety, autism, and other behavioral problems. These are now well-described features of the FXS phenotype that have broad implications for treatment and family adaptation.

#### *Attention*

In a large national survey of parents, 84% of males and 67% of females with the full mutation had attention problems.<sup>80</sup> When compared with boys with Down syndrome and typically developing peers, boys with FXS had more difficulty with attention, impulsivity and inhibition control.<sup>81,82</sup> A detailed exploration of these difficulties using a touch screen search task revealed several differences between boys with FXS and typically developing peers.

Although there were no differences in overall search speed, boys with FXS made more errors.<sup>83</sup> Boys with FXS also show overall lower levels of attention, especially auditory attention, when compared with a MA-matched peers. Using a multimodal approach of visual and auditory stimuli did not improve performance.<sup>84</sup> Boys with FXS show slight declines over time in sustained attention and larger declines in response inhibition when compared with their MA-matched peers on both visual and auditory continuous performance tests.<sup>85</sup> Auditory attention was associated with later IQ.<sup>86</sup>

Recent work has studied underlying physiologic attention processes in very young children with FXS. Infants and toddlers display lower heart rate variability and shallower heart rate decelerations during attentional tasks when compared with typically developing peers.<sup>87</sup> This finding suggests a hampered capacity to regulate arousal levels and thus attentional behavior.<sup>87</sup> Visual attention was associated with the severity of autistic behaviors.<sup>87</sup>

### Anxiety

Anxiety is a pervasive concern among providers, caregivers, and individuals living with FXS.<sup>88–90</sup> Early work found high rates of anxiety in girls with FXS compared with typically developing peers and those with other developmental disabilities.<sup>91–93</sup> In a national survey, 70% of boys and 56% of girls were reported to have been treated or diagnosed with anxiety.<sup>80</sup> Other studies have found similarly high rates.<sup>89,94</sup> A recent study described an association between negative affect, a temperament construct, and later anxiety in preschool boys with FXS providing an early diagnostic method.<sup>95</sup> A study of brain activity in the prefrontal regions found that social anxiety in FXS may be related to challenges in higher-level social

cognition.<sup>96</sup> These findings may also explain other phenotypic traits associated with anxiety in FXS, such as poor eye contact, gaze aversion, excessive shyness, hand flapping, self-injurious behaviors, aggression, and autistic symptoms.<sup>10,88,97</sup>

### Autism

FXS is the most common known inherited single-gene condition associated with autism.<sup>98</sup> Individuals with FXS can exhibit several behaviors commonly associated with autism, including difficulties with social communication, self-injurious behavior, perseverative or restricted behavior, motor stereotypies, poor eye contact, and odd or delayed speech.<sup>99,100</sup> Depending on the presentation of symptoms, individuals with FXS can be codiagnosed with autism spectrum disorder (ASD). Reports of comorbidity of ASD diagnoses range from 15% to 52%.<sup>80,101</sup> Additionally, an estimated 90% of boys with FXS exhibit at least 1 autistic behavior.<sup>102</sup>

A series of studies suggests that children with FXS without ASD share similar profiles with children diagnosed with developmental delay, whereas children with FXS and comorbid ASD (FXS+ASD) are more similar to children with idiopathic autism.<sup>100,103,104</sup> Children with FXS+ASD exhibit poorer developmental outcomes, including late-onset language milestones, weaker communication and social skills, lower adaptive behavior scores, greater behavior problems, and greater cognitive impairment than boys with FXS only or those with idiopathic autism.<sup>16,41,105</sup> In addition, individuals with FXS only have profiles of higher receptive than expressive language, whereas those with FXS+ASD do not exhibit this strength.<sup>106,107</sup>

Social impairments may be the most significant predictor differentiating individuals with FXS+ASD from individuals with FXS only.<sup>102</sup>

Specifically, social withdrawal (eg, avoidance and indifference) and adaptive socialization behaviors (eg, recognizing emotions or appropriate social interactions) are often independent predictors of ASD in individuals with FXS.<sup>105,108–110</sup> In cross-sectional<sup>105</sup> and longitudinal studies,<sup>101</sup> impaired socialization was the greatest contributor to ASD diagnosis and severity in the FXS population, more so than communication or cognition.<sup>110</sup> Per parent report, however, repetitive and stereotyped behaviors were the strongest predictors of ASD in FXS.<sup>102</sup> Boys with FXS+ASD exhibited significantly less ritualistic and compulsive behavior, but increased repetitive motor behaviors compared with boys with idiopathic autism.<sup>111</sup>

Few studies have examined the severity of ASD symptoms in individuals with FXS over time, and conflicting evidence exists. Two longitudinal studies showed that behavioral profiles did not change significantly over time, with lower levels of FMRP correlated with more ASD symptoms.<sup>99,112</sup> However, these studies did not use gold standard ASD measures, which is the use of *Diagnostic and Statistical Manual of Mental Disorders* criteria by an experienced clinician, using the Autism Diagnostic Observation Schedule with or without the Autism Diagnostic Interview-Revised. More recently, the Autism Diagnostic Interview-Revised was used to examine current versus lifetime behaviors, with current scores subtracted from lifetime scores to gauge age-related improvement. By using this method, autism symptoms improved with age, with the least improvement in the Restricted Interests and Repetitive Behaviors domain.<sup>113</sup> In this and 1 other study<sup>114</sup> once IQ was controlled for, levels of FMRP were not related to ASD.

### Other Behavioral Problems

Behavior problems, including tactile defensiveness, hand flapping, poor eye contact, hyperactivity, tantrums, perseveration, hyperarousal to sensory stimuli, and impulsivity are hallmark features of FXS.<sup>115–117</sup> Physiologic dysregulation and hyperarousal are common challenges in FXS and have been associated with avoidant behaviors.<sup>48,118,119</sup> Problem behavior is one of the strongest predictors of negative outcomes for individuals with FXS and their caregivers.<sup>120–123</sup> Many of these behaviors can be considered behavioral markers of other comorbid diagnoses, such as anxiety or autism.

One concerning behavior not well described in the literature is aggression toward others. Survey data indicate that 38% of boys with FXS have been diagnosed or treated for aggression,<sup>80</sup> and 24% of boys with FXS were taking medications for anger or aggression.<sup>124</sup> Medication use to treat anger or aggression increased significantly from early childhood through adolescence, remaining relatively constant at around 30% into the adult years. In another survey, 31% of caregivers of boys and 17% of caregivers of girls reported that they had been injured by the child (eg, knocked down or hit) at least once in the previous 12 months.<sup>124</sup> Parents of boys reporting injuries had a mean of 16 per year; on average, 2.7 of those injuries were serious enough to require medical care.

A recent study using parent-reported functions of behavior suggested escape as a primary function of aggression in FXS.<sup>125</sup> However, these reported functions are likely to be highly specific to each child, as suggested by a study of behavioral interventions in 3 children with FXS requiring considerable individualized assessment before intervention development.<sup>126</sup>

Self-injury is also common in individuals with FXS, with prevalence rates as high as 79% of boys.<sup>117</sup> Compared with other genetic conditions or intellectual and developmental disability populations, self-injury is generally mild,<sup>127</sup> however, when it occurs, it generally occurs frequently.<sup>117</sup> Approximately one-third of boys exhibit severe self-injury.<sup>117</sup> The most commonly reported self-injury in FXS is biting of hands and fingers.<sup>128</sup>

### Medical Profile

#### Physical Features

Boys often present with long, narrow faces; high-arched palates; prominent ears; macroorchidism (during and after puberty); hypermobility of joints; hypotonia; and flat feet.<sup>129–131</sup> Other conditions that are found at increased rates include cleft palates and orthopedic abnormalities, such as scoliosis or severe flat feet.<sup>5</sup> Adults with FXS have a shorter average height than that of the general population.<sup>132</sup> Girls with FXS have similar physical features to boys with FXS although at lower rates.<sup>133</sup>

#### Seizures

The incidence of epilepsy is between 10% and 20% for boys with FXS, with lower percentages for girls.<sup>134</sup> A national survey of parents found that 14% of boys and 6% of girls had experienced at least 1 seizure,<sup>135</sup> similar to earlier reports.<sup>136,137</sup> The first seizure commonly occurs between 4 and 10 years of age, and the seizures are typically focal or localized.<sup>135</sup> Most seizures occur while awake, but approximately one-third of individuals with FXS have seizures when sleeping.<sup>135</sup> A key factor associated with the occurrence of seizures is whether the individual is codiagnosed with autism.<sup>135,138</sup>

#### Sleep

Over time, providers and caregivers anecdotally reported sleep problems in the FXS population, prompting

several studies to explore sleep problems in FXS.<sup>139–141</sup> In a national survey, 32% of individuals with FXS were reported by the caregiver to experience sleep difficulties, with 85% having at least 2 problems (eg, trouble falling asleep and frequent night awakenings). Of those with problems, 47% of boys and 40% of girls were taking at least 1 medication to help with sleep. A study of sleep architecture in FXS revealed less time in bed and less time in REM sleep.<sup>141</sup>

#### Other Medical and Health Problems

Several reviews highlight the medical needs of children with FXS.<sup>4,142,143</sup> A recent review<sup>143</sup> reported higher rates of several medical conditions, including otitis media, gastrointestinal problems, and ocular disorders. However, little is known about the overall public health needs of individuals with FXS. One recent study on physical activity and obesity suggested the rate of obesity in adults with FXS is similar to the general population (30%).<sup>144</sup> Boys with FXS, however, had higher rates of obesity (31%) compared with typically developing, same-aged peers (18%). Neither children nor adults with FXS met the recommended levels of physical activity. Other researchers have documented a Prader-Willi–like phenotype in FXS, which may explain the increased rates of obesity in a subgroup of patients.<sup>145</sup>

#### Physiologic Features

Studies of brain structure using MRI have shown several enlarged regions in the brains of individuals with FXS compared with typically developing controls, including the hippocampus, amygdala, caudate nucleus, and thalamus.<sup>119</sup> These regions are critical in regulating cognitive and behavioral functions, such as memory and learning, information and sensory processing, and social and emotional behavior, all of which are known to be impaired in individuals with FXS.

However, the cerebellar vermis and the superior temporal gyrus are smaller than those in typically developing controls.<sup>119</sup> MRIs of young boys with FXS show increased caudate volume when compared with typically developing peers.<sup>146</sup> Amygdala volume in those with FXS, although larger than controls, was not as enlarged as in individuals with ASD.<sup>146</sup> However, other studies have shown no differences in amygdala volume between individuals with FXS and typically developing peers.<sup>147</sup> Functional MRIs, which predominantly have been conducted on girls, have shown different neural activity, which may help to explain the cognitive delays in the FXS population.<sup>119,148</sup>

In a review of neuroendocrinology studies,<sup>119</sup> individuals with FXS were reported to have impaired hypothalamic functioning due to decreased levels or absence of FMRP. These studies may help explain the abnormal stress responses, sleep abnormalities, and physical growth patterns commonly seen in affected individuals. Other work has examined the relationship between an individual's genetic expression, brain structure, and behavior.<sup>149,150</sup>

Other physiologic features have also been reported. Roberts et al<sup>151</sup> found that the blink rate in boys with FXS was much higher than typically developing peers during passive tasks. The blink rate was correlated with problem behaviors and physiologic arousal, indicating possible underlying pathophysiological differences in dopamine functioning in individuals with FXS.<sup>151</sup> Studies of heart rate activity and its relationship with sensory processing have shown that boys with FXS have increased cardiac reactivity to auditory stimulus compared with typically developing peers.<sup>152</sup> Studies of prepulse inhibition have shown significant deficits in individuals with FXS.<sup>153,154</sup>

Miller et al<sup>155</sup> demonstrated enhanced electrodermal reactivity to sensory stimuli in those with FXS, and this reactivity correlated inversely with the level of FMRP. Taken together, these results suggest that individuals with FXS have atypical physiologic characteristics when compared with typically developing peers and that these differences may be related to the behavioral profile of FXS.

## Treatments and Interventions

### *Behavioral Interventions*

Anecdotal reports suggest that reducing anxiety or sensory issues may reduce challenging behaviors in some children with FXS.<sup>156</sup> Several case studies suggest the use of behavioral principles, such as positive reinforcement.<sup>157,158</sup> Behavioral interventions can be effective for children with FXS through the development of individualized multicomponent intervention plans implemented by parents and supported by professionals.<sup>126</sup> Although these studies differ in approach, they suggest that behavioral techniques can be useful for reducing challenging behaviors in children with FXS.

### *Cognitive/Educational Interventions*

Few studies have examined cognitive or educational interventions for individuals with FXS. One interview study of professionals working with young children with FXS<sup>159</sup> reported that learning strategies that incorporate visually based, experiential or holistic learning were most successful. A recent case study<sup>160</sup> found a combination of early pharmacologic treatment combined with intensive educational interventions resulted in improved behavior and normal IQ in 2 young children with FXS. The intensive interventions included cognitive and memory games, visualized math tasks, and supplemental occupational

therapy, speech-language therapy, and social skills training.

The use of a self-paced computer program (Discrete Trial Trainer [DTT]) to assess learning of basic math and geography skills by using a match-to-sample teaching procedure has been tested as a possible intervention technique.<sup>161–164</sup> Results showed that basic mathematical relations could be taught and were comparable with those of the control group; however, improved outcomes were not maintained, and more complex concepts (eg, equality and congruence concepts) were not learned at a rate similar to that of the control group. Additional studies using the DTT software suggest that it may be a promising approach for outcome measurement.<sup>164,165</sup>

These studies of DTT exemplify a shift toward technological mechanisms for assessing and treating cognitive and learning impairments. Another example is the use of the Cogmed program, which can improve working memory and is being tested with individuals with FXS.<sup>166</sup> These computerized tools have the advantage of providing increased independent learning, are generally highly motivating, and reduce social pressure, which may affect learning in children whose anxiety is increased with social interactions. In addition, computerized protocols may be useful for research design with this population; they theoretically could be implemented anywhere at any time, thereby reducing geographical challenges.

### *Allied Health Services*

Given the high rates of intellectual disability and comorbidities, such as autism, anxiety, and attention-deficit/hyperactivity disorder (ADHD), individuals with FXS have significant needs for specialized therapies and services, including speech-language, occupational, and



physical therapies; special education services; and behavior management. In addition, individuals with FXS frequently require specialized medical care, such as consultations with developmental-behavioral pediatricians or neurologists.

Despite the clear need for services for individuals with FXS, the intensity and use of health or therapeutic services has not been well described. Three papers reporting on early intervention services<sup>40,99,159</sup> all suggest that children with FXS <3 years of age commonly use speech-language, occupational, and physical therapy services. More recently, allied health service use was reported based on findings from a large survey.<sup>160</sup> The use of, intensity of, and parent satisfaction with speech-language, occupational, and physical therapies, as well as behavior management therapy, were examined across sex and age groups. Almost all males and half of females were receiving at least 1 of these therapies at the time of the survey. Clear declines in service use occurred across age groups, with those no longer in school (>20 years of age) receiving few services. Parents were generally satisfied with the amount and quality of services received.

One study examined parent reports of medical services and procedures that their child with FXS received during the previous year.<sup>167</sup> This study found that most boys and girls had at least 1 visit with their primary care physician, with an average of 2.5 visits for boys and 2.1 visits for girls in the year. Although there were few emergency department visits or inpatient care, almost all individuals with FXS required some medical specialist care (97% of boys, 95% of girls). The most common specialists seen were ophthalmologists, psychiatrists, developmental-behavioral pediatricians, and neurologists. The majority of both boys and girls were taking at least

1 prescription medication for FXS-related problem.

### *Pharmacologic Treatments*

Pharmacotherapy is frequently used as a primary intervention to target specific symptoms for individuals with FXS. Guidelines for the suggested treatment of neuropsychiatric symptoms of FXS have been published suggesting that stimulants or selective serotonin reuptake inhibitors (SSRIs) typically work to decrease hyperactivity, cognitive deficits, and psychiatric symptoms.<sup>115,168</sup> A recent article reviews the treatment strategies found to be most effective for specific symptoms.<sup>169</sup>

### *Anxiety Symptoms*

SSRIs are the most common first-line treatment of anxiety in FXS, which is the most common reason parents seek medication treatment.<sup>167</sup> Case reports and survey studies suggest SSRIs are effective ~50% of the time at reducing anxiety in FXS.<sup>170–172</sup> No controlled studies on the efficacy of SSRIs for reducing anxiety in FXS have been conducted. In addition, side effects, including weight loss or gain, and behavioral activation for those on SSRIs, specifically fluoxetine, have been reported.<sup>115,172</sup>

### *Attention-Deficit/Hyperactivity Disorder Symptoms*

Impulsivity and hyperactivity are 2 common challenges for individuals with FXS, and stimulant medications are the most common type of medication prescribed to individuals with FXS.<sup>173</sup> However, only 1 controlled trial conducted years ago has been carried out demonstrating efficacy.<sup>133</sup> In addition, stimulant use for children <5 years old can often cause irritability and, according to the AAP, is not the recommended treatment for children ≤5 years of age.<sup>115,174</sup> Typical doses have been found to be effective at reducing impulsivity and hyperactivity and increasing attention in a controlled

trial of boys with FXS.<sup>175</sup> Second-line treatments, recommended for those who do not respond to stimulants, include  $\alpha$ -adrenergic receptor agonists (eg, clonidine and guanfacine).<sup>115</sup> Although surveys and case studies suggest clonidine can be effective<sup>171,176</sup> and clinical experience suggests guanfacine<sup>115</sup> can be helpful, no controlled trials have examined the efficacy of these medications for ADHD symptoms in FXS specifically. Two controlled studies of L-acetyl-carnitine<sup>177,178</sup> suggest some reduction of ADHD symptoms in FXS compared with placebo. More recently, valproic acid, the antiepileptic drug, was found to reduce ADHD symptoms in an open-label trial.<sup>179</sup>

### *Aggression and Mood Symptoms*

Aggression and irritability are behaviors of great concern to parents of individuals with FXS and are often the primary outcome of clinical trials.<sup>169</sup> Antipsychotic medications have been the first-line treatment of these behaviors and are effective at reducing irritability, aggression, mood instability, and perseverative behaviors in individuals with FXS.<sup>115</sup> In survey studies, both risperidone and aripiprazole have been reported to be effective at reducing aggression and self-injurious behaviors in FXS.<sup>170,171</sup> In a recent pilot, open-label study of aripiprazole,<sup>180</sup> 10 out of 12 participants showed improvement in irritability, hyperactivity, and social behavior. Risperidone has a positive effect on irritability symptoms in individuals with autism compared with placebo.<sup>181</sup> However, no controlled trials of antipsychotics have been completed with individuals with FXS.

### *Sleep*

Sleep issues are a significant concern for families of a subsample of individuals with FXS.<sup>140</sup> So far, melatonin is the only treatment that has been studied for individuals with FXS, with findings suggesting

efficacy for increased sleep onset and duration compared with placebo.<sup>182</sup>

### Next Generation Treatments

Recent discoveries in the pathophysiology of FXS have led to excitement in the field about the development of possible therapeutic agents. Multiple reviews summarize these discoveries and the preclinical and clinical trials that are under way to examine the efficacy of these treatments.<sup>183–187</sup>

The metabotropic glutamate receptor (mGluR) theory of FXS, first formulated by Bear et al,<sup>188</sup> suggests that the absence of FMRP in FXS leads to enhanced glutamatergic signaling via mGluR5, which subsequently results in increased protein synthesis and defects in synaptic plasticity. The resulting weakening of the synapse and increased number of longer immature dendritic spines is thought to explain the intellectual disability found in FXS.<sup>130</sup> Based on this theory, there has been a heavy focus on developing and testing agents that target mGluR5 modulation.<sup>189–193</sup>

Based on promising findings in *FMR1* knockout mice,<sup>184</sup> several agents have been or are currently being tested in human clinical trials. These agents include the following, which are in clinical development in open-label phase II or higher clinical trials<sup>183</sup>: (1) glutamatergics (ie, mavoglurant/AFQ056, RG7090/RO4917523, STX107, and fenobam/NPL-2009), (2) GABAergics (ie, arbaclofen, ganaxolone, and acamprosate), (3) atypical antipsychotics (ie, aripiprazole), (4) antidepressants/anxiolytics (ie, sertraline), (5) mood stabilizers (ie, lithium), and (6) antibiotics (ie, minocycline). Trials of mavoglurant (AFQ056), RG7090/RO4917523, and STX107 were proven ineffective in comparison with placebo and have been terminated. In addition,

given the heterogeneity of the FXS phenotype, debate is ongoing regarding the most appropriate target patients and outcome measures that will allow for valid efficacy results.

Minocycline is a targeted treatment in FXS that lowers matrix metalloproteinase 9, an important protein for synaptic development that is elevated in FXS. A controlled trial of minocycline demonstrated efficacy in young children with improvements in behavior and moodiness.<sup>194</sup> Side-effects included graying of the permanent teeth, the rare occurrence of swollen joints, rash, or a lupus-like syndrome that resolves once the minocycline is discontinued.

In a retrospective study of young children on low-dose sertraline, a commonly used SSRI, those treated demonstrated improvements on both receptive and expressive language development compared with controls.<sup>160</sup> Sertraline stimulates neurogenesis in addition to increasing brain-derived neurotrophic factor, which can improve connectivity in the developing central nervous system. The current thinking is that low-dose sertraline may also improve anxiety and sensory hyperarousal in children <5 years of age.

### Impact on the Family

#### Family Environment

The stress of raising a child with FXS on carrier mothers may have an impact on the family unit as well as the maternal-child relationship. Maternal depression, anxiety, and stress are related to both marital satisfaction and family cohesion in families affected by FXS.<sup>120,195,196</sup> Family cohesion was slightly higher than previously reported levels of families of individuals with developmental disabilities or ASD.<sup>195</sup> Research on the family environment has also examined molar levels of maternal responsiveness (ie, overall

interaction styles), including levels of warmth, positive affect, expressed emotion, and criticism. Mothers of children with FXS display high levels of warmth and positive affect with little to no negative behaviors exhibited.<sup>197,198</sup> These behaviors appear to be related to many child variables, as observed in unaffected populations as well, such as a child's rate of communication<sup>199</sup> or developmental level.<sup>200</sup> Child age and frustration or help-seeking behaviors also predicted maternal encouraging/responsive behaviors.<sup>201</sup> Mothers of younger children and those whose children had more behavior problems had higher levels of criticism of their children.<sup>197</sup>

#### Financial Impact

Results of a national survey indicated that approximately half of all families experienced at least some financial burden, with almost 60% stating that someone in the family had to change work hours or stop work as a result of having a child with FXS.<sup>202</sup> Family (ie, not having adequate health insurance or having multiple affected sons) and child (ie, higher numbers of cooccurring conditions) factors were associated with financial burden and employment. The median out-of-pocket expenditures for families were \$1900 per year, which included expenses for transportation (31%), therapy (31%), medications or other medical needs (25%), supervision (6%), recreation (4%), or other needs (3%).<sup>202</sup> A second survey examined the amount of paid and unpaid time spent in providing care to individuals with FXS.<sup>124</sup> On average, parents spent 9.2 hours per day in care or support for sons and 4.8 hours per day for daughters. The average boy with FXS also received 5.5 hours per day of paid support, and the average girl received 1.9 hours. Caregivers also had to take an average of 19.4 hours off from work each month to care for their child's needs. In a study comparing

survey responses by parents of children with FXS to those with ASD only, intellectual disability only, and ASD and intellectual disability,<sup>203</sup> a higher percentage of caregivers of children with FXS reported a negative financial and employment impact than caregivers of children with ASD only or intellectual disability only. The negative financial and employment impact of FXS was comparable to that of caring for children with ASD and intellectual disability. Greater financial and employment impact were associated with increased anxiety, seizures, irritability, and reduced thinking, reasoning, or learning ability regardless of condition.

## DISCUSSION

### Gaps in the Research Literature

Despite extensive literature on FXS, there are gaps that need to be addressed. Below we outline key remaining questions, which can be used to shape future research.

1. Are there subtypes of the FXS phenotype? There is strong evidence for the impact of FXS on cognitive and language development. Less is known about behavior problems, self-injury, and sleep issues. Research has shown differences in cognitive and behavioral profiles for individuals with FXS only and those with FXS+ASD. However, little information exists about other phenotypic subgroups within FXS. Do certain cooccurring conditions form clusters or profiles? Are there biomarkers that correlate with certain subgroups? Answering these questions is critical to additional understanding the FXS phenotype.
2. What are the needs of young adults, middle-aged adults, and seniors living with FXS? The vast majority of research on FXS has

been conducted with children and adolescents. Longitudinal studies of age-related decline in adolescence in cognition and adaptive behavior have shown mixed results. Moreover, a large evidence base is emerging on the premutation phenotype in older adults, specifically the impact of fragile X-associated tremor-ataxia syndrome and fragile X-associated primary ovarian insufficiency. However, much less is known about FXS across the life span; in particular, studies on young adults, middle-aged adults, and seniors are lacking. Although some studies include individuals with FXS in this age range, they often focus on non-age-related topics (eg, language abilities and autism symptoms). Little is known about the transition out of school, employment opportunities, daily living and functional skills of adults, caregiving demands on families who provide assistance to adult children who are living at home, and guardianship issues. Moreover, studies examining the health and social needs of these individuals are needed.

3. What are the greatest public health needs of individuals with FXS? The physical features and medical problems associated with FXS have been well documented. However, little research has been conducted on public health issues related to the fragile X population, including areas such as health disparities, health literacy, access to preventative health care, health promotion activities, and health care decision-making. The communication of important health-related information to individuals with FXS is also understudied. Finally, little is known about the prevalence of noncommunicable diseases among individuals with FXS

and how it compares to other intellectual and developmental disability groups as well as the general population.

4. What educational, behavioral, and pharmacologic treatments offer the most promise for individuals with FXS? There is a shortage of evidence regarding service use, intensity, or efficacy for school-age and preschool children with FXS, including special education eligibility and the types of educational services most commonly provided. More detailed descriptive information would lead to the development of targeted treatment options. The ability to conduct a high-quality intervention study targeting specific behaviors or learning issues in FXS is challenging given the wide range of locations of individuals with FXS. However, promising interventions targeting similar issues in populations that share symptomology (eg, ASD), as well as increasing use of technological options, suggest some directions for future intervention research. In addition, little is known regarding the efficacy of treatments. Pharmacological treatments for symptoms have been reported to be beneficial for reducing some of the core features of FXS, including impulsivity, hyperactivity, anxiety, and irritability. However, few randomized controlled trials have been conducted to prove efficacy of these medications in the FXS population. Recent work has focused on pharmacologic treatments that target the core mechanism in FXS. Much work remains not only for basic scientists but also for social scientists before FXS-specific medications are commonplace. Finally, there is a need to examine the use of medications and/or behavioral interventions in the first year of life. The efficacy of

earlier treatment will need to be described if large-scale screening, like newborn screening, is to be considered. Most importantly, it has been hypothesized that the benefit of combining educational interventions with targeted psychopharmacologic interventions may prove to be more efficacious. Research on the combination of these interventions is needed.

5. What are the core risk and protective factors for families of individuals with FXS? What are the combinations of factors that lead to positive or negative adaptation in families of individuals with FXS? Although the field has begun to explore the economic burden of behavioral/educational and medical services, it is not well characterized for a representational sample of families affected by FXS. In addition, the cost associated with FXS has not been studied relative to other conditions. Finally, the cumulative health and financial consequences of multiple family members being affected by *FMR1* mutations have not been studied. Although mental and physical health in carrier mothers is fairly well documented, it is difficult to tease apart variance caused by parenting a child with FXS versus premutation carrier status. In addition, factors such as family cohesion and marital satisfaction have not been well studied and could provide more information on possible mediating variables that may contribute to or lessen the impact on maternal outcomes. Likewise, knowledge about how FXS affects fathers and siblings, both carriers and noncarriers, is lacking. Finally, no research has been conducted on family-focused interventions that aim to improve both family and child functioning.

### Implications for Pediatricians

The identification and treatment of FXS remains an important concern for pediatricians. In addition to the AAP clinical reports and recommendations already referenced, pediatricians can find clinical practice recommendations for individuals with FXS and their families developed by the Fragile X Clinical and Research Consortium ([www.fragilex.org/treatment-intervention/consensus-on-clinical-practices/](http://www.fragilex.org/treatment-intervention/consensus-on-clinical-practices/)). The consensus documents are based on expert opinions of fragile X researchers and clinicians. The documents cover a variety of topics, such as educational guidelines, the diagnosis and treatment of associated medical conditions, and information about genetic testing. This review of the research as well as the consensus documents and AAP publications provide a wealth of information for pediatricians to help better understand and treat FXS and its associated conditions. Pediatricians can help coordinate care/therapies, provide psychopharmacologic interventions, and identify those with FXS by ordering a fragile X DNA test. In addition, pediatricians may be called on to support the larger family system, because a diagnosis of 1 individual can impact many other family members.<sup>204</sup> These basics are reviewed in this article, although if the pediatrician feels uncomfortable regarding these points, they can refer to a specialist, such as a developmental-behavioral pediatrician or psychiatrist, for psychopharmacologic intervention or a genetic counselor to discuss extended family involvement and reproductive options.

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### ABBREVIATIONS

AAP:	American Academy of Pediatrics
ADHD:	attention-deficit/hyperactivity disorder
ASD:	autism spectrum disorder
DTT:	Discrete Trial Trainer
<i>FMR1</i> :	fragile X mental retardation 1
FMRP:	fragile X mental retardation protein
FXS:	fragile X syndrome
FXS+ASD:	fragile X syndrome with comorbid autism spectrum disorder
MA:	mental age
mGluR:	metabotropic glutamate receptor
SSRI:	selective serotonin reuptake inhibitors

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