Advances in the Treatment of Fragile X Syndrome
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Pediatrics 2009;123:378-390
DOI: 10.1542/peds.2008-0317

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Fragile X Syndrome (FXS) is associated with an array of intellectual and emotional disabilities, ranging from mental retardation (hereafter referred to as intellectual disability) to learning problems, autism, and anxiety. The cause of FXS is decreased or absent levels of fragile X mental retardation protein (FMRP). Decreased levels of FMRP typically are caused by the full mutation (200 CGG repeats), which usually is methylated, in the proximal regulatory region of FMR1 (fragile X mental retardation 1 gene).4,5 FXS occasionally occurs because of a point mutation or deletion in FMR1 or even a smaller expansion in the CGG repeat, which leads to lower levels of FMRP and intellectual disability.6 Intellectual disability linked to FXS occurs in ~1 per 3600 individuals in the general population,7,8 whereas milder cognitive and behavioral problems (eg, math and language deficits, social phobia, and attention-deficit/hyperactivity disorder [ADHD]) associated with FXS may be more common. A more-frequent (1 of 130–250 female individuals and 1 of 250–800 male individuals) but smaller expansion (55–200 CGG repeats) of FMR1 is termed a premutation.9–12 In contrast to the full mutation, the premutation usually does not cause decreased FMRP levels but leads to enhanced production of FMR1 mRNA (2–8 times normal levels)13,14 (Fig 1). The enhanced mRNA production can lead to clinical features in premutation carriers that do not occur in full mutation carriers, including primary ovarian insufficiency and the fragile X-associated tremor/ataxia syndrome (FXTAS).

In general terms, the severity of the FXS physical phenotype and intellectual impairment is correlated with the magnitude of the FMRP deficit.1,2,11 Male individuals with incomplete methylation of a full mutation (methyloma mosaicism) or a mixture of the premutation and full mutation alleles (allele size mosaicism) and female individuals with a favorable activation ratio (proportion of cells that have the normal X chromosome as the active X chromosome) generally have the highest levels of FMRP and the highest IQs.1,2,11,12,15,16 Male individuals with a completely methylated full mutation commonly display mild to moderate intellectual disability. Female individuals with the full mutation typically present with learning disabilities, although ~25% have intellectual disability.17 Most individuals with the premutation have a normal IQ, although mild cognitive and behavioral problems (eg, executive dysfunction, social deficits, anxiety, and obsessive-compulsive behavior) have been reported, particularly for male individuals.18,19 Children with the premutation occasionally present with physical or behavioral features of FXS, including large ears, hand flapping, poor eye contact, and social deficits consistent with autism spectrum disorder (ASD); this...
presumably is related to mild deficits in FMRP. The premutation also can cause clinical involvement that is related to RNA toxicity resulting from elevated mRNA levels, which is not seen with the full mutation. Approximately 20% of female individuals with the premutation have primary ovarian insufficiency, and ~40% of aging male individuals and 4% to 8% of aging female individuals with the premutation develop FXTAS. FXTAS includes intention tremor, ataxia, neuropathy, autonomic dysfunction, brain atrophy, and cognitive decline. Recent research also demonstrated an increased frequency of autoimmune disorders, including hypothyroidism and fibromyalgia, in female individuals with the premutation, compared with control female subjects. Both premutation involvement and full mutation involvement make FXS a family affair, with an array of disorders seen throughout multiple generations (Fig 2). Once a proband is diagnosed, the clinician should address issues regarding treatment, referral, and genetic counseling for multiple family members.

This review addresses treatment issues related to behavioral problems for individuals affected by FXS. Information on treatment regarding medical complications of FXS, primary ovarian insufficiency, and FXTAS can be found elsewhere. The few controlled and open trials of medication use in FXS are reviewed. Most FXS medication studies are surveys of clinical populations, as described below, and additional controlled studies are needed. The input of clinicians from the Fragile X Research and Clinical Consortium, an international network of FXS clinics established by the National Fragile X Foundation in 2006, was used to complete this report.

**BEHAVIORAL FEATURES AND TREATMENT**

**Behavioral Phenotype**

The behavioral phenotype of FXS involves poor eye contact, excessive shyness, anxiety, hand flapping, hand biting, aggression, tactile defensiveness, attention deficits, hyperactivity, impulsivity, hyperarousal to sensory stimuli, and ASD. In female individuals with FXS, the behavioral phenotype is characterized by relatively milder cognitive and behavioral problems than those observed for male individuals, including shyness, social anxiety, features of ADHD combined with language and other learning deficits (eg, math disability), and mood lability. Female individuals typically are less affected than male individuals because their normal X chromosome yields some FMRP (related to the X activation ratio). Only ~25% of female individuals with the full mutation have an IQ of <70, although the majority present with the aforementioned learning and/or behavioral problems.

Similar to avoidant and anxious behavior, most boys with FXS display autistic behavior, and ~30% meet formal Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for autistic disorder. Autism is a major concern in FXS because it is associated with more-severe impairment of social interactions, in addition to lower cognitive ability, academic achievement, adaptive behavior, and language ability than seen in individuals with FXS without autism.
Treatment of ADHD

Relative to individuals with other genetic conditions or individuals with nonspecific intellectual disability, the prevalence of ADHD symptoms in children with FXS is higher.49,69,71 In addition to behavioral intervention and individualized therapies, stimulants were shown to improve symptoms of ADHD in FXS in 1 controlled trial,72 in surveys of medication use in FXS,73,74 and in 1 psychophysiologic study of FXS.75 Those studies indicated that stimulants, at usual doses, were the most frequently used class of medication for boys with FXS72–74 and they were thought to help in ~70% of cases, on the basis of clinical evaluations.

Treatment of ADHD symptoms in younger children (< 5 years of age) is particularly challenging. Stimulants may induce irritability and other behavioral problems in children < 5 years of age; therefore, nonstimulant medications may be helpful.37 α-Adrenergic receptor agonists, including clonidine and guanfacine, seem to be the best option for younger children or neurologically more affected children who do not fare well with stimulants. In a survey of clonidine use among 35 children with FXS, 63% of parents thought that clonidine was very helpful for their child, whereas 20% found clonidine to be a little helpful, 11% thought that behavior was worse, and 6% thought that there was no effect.76 The average dose was 0.15 mg/day. Clonidine was prescribed most often to treat hyperactivity, overstimulation, and attention/concentration problems. Clonidine was used as monotherapy for preschool-aged children and was used in conjunction with another medication for the majority of older children.76 The results of that study were similar to the 70% response rate for α-adrenergic receptor agonists from clinic-based evaluations of 27 treated patients.74 Clonidine can be beneficial for children with ADHD who have sleep disturbances, and sleep problems often are present among children with FXS.77,77

Guanfacine can improve ADHD symptoms, including hyperactivity and frustration intolerance, as well as hyperarousal in children without FXS.78–80 Our clinical experience has demonstrated guanfacine to be helpful in FXS because it generally is less sedating than clonidine and it has a longer half-life; therefore, twice-daily dosing usually is sufficient. A dose of 0.1 mg of clonidine is equivalent to a dose of 1 mg of guanfacine, and abrupt withdrawal should be avoided for both drugs.81

Two controlled trials of the nonstimulant L-acetyl-carnitine, at dosages of 20 to 50 mg/kg per day, for treatment of ADHD in boys with FXS have been reported.82,83 Both studies demonstrated efficacy of L-acetyl-carnitine in the treatment of ADHD symptoms, but the effects were more remarkable in the parent reports than in the teacher reports. These trials of L-acetyl-carnitine were conducted in European countries where the use of stimulant medications either is not allowed or is discouraged, and L-acetyl-carnitine seems to be a reasonable alternative.

Treatment of Anxiety

Selective serotonin reuptake inhibitors (SSRIs) at typical doses were helpful > 50% of the time in relieving anxiety and related problems, in surveys of patients with FXS.74,84 Selective mutism is a form of anxiety in some female individuals with FXS; it is rare among male individuals with FXS. Fluoxetine can be beneficial for this problem, as reported for 1 family with FXS.85 As reported for idiopathic autism,86–91 SSRIs can be helpful for individuals with FXS, on the basis of survey reports and clinical series.73,74,84

Genotypic differences in gene polymorphisms regulating serotonin seem to modify the expression of aggressive and stereotypic behaviors in male individuals with FXS and may be related to SSRI treatment responses.92 Specifically, male individuals with FXS who were homozygous for the high-transcribing, long serotonin transporter-linked polymorphic region genotype had the most aggressive and destructive behavior and individuals who were homozygous for the short genotype had the least aggressive behavior. There was no effect of the monoamine oxidase A polymorphism on behavior; however, individuals with the high-activity, 4-repeat genotype were more likely to be taking SSRI or serotonin/norepinephrine reuptake inhibitor medication.

Activation with SSRIs occurred for ~20% of individuals with FXS who were surveyed.84 Activation may be manifested as restlessness, mood changes, and disinhibited behaviors, including aggression. Fluoxetine may be the most activating and is not the SSRI of choice for very hyperactive patients with FXS, but it may be useful for individuals with social anxiety, autism, or selective mutism.74 SSRIs may lead to suicidal ideation among depressed patients (although this has never been reported for FXS), and careful monitoring of patients for mood changes is justified. To date, no completed suicides have been attributed to SSRI use among youths with or without FXS, according to the Food and Drug Administration.93

Treatment of Aggression and Mood Instability

Antipsychotic drugs generally are helpful in clinical settings to target irritability, aggression, mood instability, and perseverative behaviors in both male individuals and female individuals with FXS. In a study of a large FXS clinic population, ~ 80% of individuals with FXS responded to ≥ 1 antipsychotic drug, without adverse effects requiring withdrawal.74 Risperidone (Risperdal [Janssen Pharmaceutica Products, LP, Titusville, NJ]) was the most frequently used antipsychotic drug in the past and was effective clinically, with high response rates for aggressive behavior in older male individuals with FXS and other irritable, aberrant, and undesired behaviors in young boys with FXS and autistic traits.74 These results are consistent with the finding that risperidone was safe and effective for aggressive and aberrant behaviors in a double-blind, placebo-controlled trial with individuals with autism who did not have FXS.95 The typical risperidone dose range for children with FXS is 1 to 2.5 mg/day.

Aripiprazole (Abilify [Bristol-Myers Squibb Co, Princeton, NJ]) was the second most frequently used atypical antipsychotic agent in a FXS clinic survey,96 with the highest overall response rate (~ 71%) for an individual...
antipsychotic and the lowest concern about weight gain.

Because of its unique pharmacologic profile, aripiprazole targets multiple behavior difficulties in FXS, including distractibility, anxiety, mood instability, aggression, and aberrant social behaviors. Typically, low doses of aripiprazole (2.5–5.0 mg for adolescents and even lower doses for younger children, eg, ≤1 mg at bedtime) work best for patients with FXS, because agitation is a common finding at higher doses. If agitation occurs, then the dose should be decreased. Most of our information on medication use in FXS is from medication surveys and clinical experience, and there is a tremendous need for controlled trials to confirm this information and to document efficacy and safety, particularly for long-term use.

**Treatment of the Prader-Willi Phenotype**

A subgroup of male individuals with FXS have hyperphagia and obesity that develop in early to middle childhood, with a physical phenotype similar to that of Prader-Willi syndrome but with negative results of molecular testing for 15q11 abnormalities. This was first described as the Prader-Willi phenotype (PWP) of FXS in 1987; since then, ~25 additional cases have been described. Symptoms of autism are more common with the PWP, with a recent study showing 54% of patients with autism, compared with ~30% of patients with FXS without the PWP.

Recent molecular research showed that expression of cytoplasmic FMR1-interacting protein 1 (CYFIP1) was decreased in individuals with the PWP, compared with both control subjects without FXS and patients with FXS without the PWP. This finding is especially interesting because the CYFIP1 gene is located in the Prader-Willi critical region of 15q, and CYFIP1 interacts with FMRP in neurons during synaptic development and plasticity. Recently, a study of lymphoid cells from boys with either FXS and autism or autism associated with chromosome 15 duplication demonstrated that both groups had abnormal expression of GP155 (G protein-coupled receptor 155), a gene regulated by CYFIP1. This finding of one of the first abnormalities seen in >1 autistic disorder may explain the high frequency of autism in PWP.

Treatment considerations for children with the PWP include early implementation of strategies developed for Prader-Willi syndrome, to address the weight gain associated with the onset of hyperphagia. These strategies include consultation and follow-up monitoring with a dietician, regular physical exercise, environmental modifications (eg, locking the kitchen or cupboards), and programs such as the Food Security and Red, Yellow, Green dietary programs developed for Prader-Willi syndrome.

**Seizures and Treatment**

Individuals with FXS have increased risk for seizures, with rates of 13% to 18% for boys and ~5% for girls. In general, the risk of epilepsy onset seems to be highest in childhood; one study suggested that the peak incidence was between the ages of 6 months and 4 years, with a mean age of onset of 2 years. In addition, many individuals have abnormal electroencephalographic findings without overt epileptic seizures. More than 50% of electroencephalographic abnormalities seem to resemble those observed in childhood epilepsy (benign focal epilepsy of childhood and benign Rolandic epilepsy), with centrotemporal spikes. However, a wide range of seizure types have been reported in FXS. The most common seizure type is complex partial seizures, although simple partial febrile convulsions and generalized tonic-clonic seizures may occur. Status epilepticus has been reported but is relatively rare in FXS.

The majority of individuals with FXS experience resolution of their epilepsy during childhood. Although the type of seizures (partial or generalized) does not seem to predict seizure remission, the centrotemporal spike pattern on electroencephalograms seems to be an excellent prognostic factor for remission of epilepsy, as in benign focal epilepsy of childhood. Poor seizure control and a focal, frontal, rhythmic, slowing pattern on electroencephalograms may be risk factors for the persistence of epilepsy into adulthood. Recurrent seizures may be an indicator of increased risk for autism in FXS, because individuals with FXS and autism have seizure rates 3 times those of individuals with FXS alone.

Seizures in FXS generally are easily controlled with a single anticonvulsant. Treatment involves the use of the range of anticonvulsant medications; however, because FXS is associated with hypotonia, loose connective tissue, and cognitive and behavioral problems, these issues should be taken into account when the choice of medication is being considered. Adverse effects that exacerbate hypotonia, clumsiness, cognitive dulling, and daytime sedation are particularly undesirable. Historically, most individuals with FXS have experienced good control with carbamazepine or valproic acid, with fairly limited adverse effects. More recently, lamotrigine (Lamictal [GlaxoSmithKline, Research Triangle Park, NC]), oxcarbazepine (Trileptal [Novartis Pharmaceuticals Corporation, Saffron, NJ]), zonisamide (Zonegran [Evan Biopharmaceuticals, Inc, San Diego, CA]), and levetiracetam (Keppra [UCB Pharma, Inc, Smyrna, GA]) have proven to be effective potential additions to the anticonvulsant regimen for patients with seizures that are difficult to control, with the advantage of minimal cognitive adverse effects. Phenytoin generally is avoided, if possible, for children with FXS because of the adverse effects of gum hypertrophy and tissue overgrowth, coupled with the difficulty of managing dental problems in these oversensitive children. Phenytoin and gabapentin also should be avoided, because they exacerbate behavioral problems, including hyperactivity, in individuals with FXS. Levetiracetam occasionally worsens irritability and aggressive be-
havior, although some individuals with FXS have positive behavioral and anticonvulsant responses, in our clinical experience. Because a wide range of anticonvulsants with good safety profiles are now available, individuals who are not attaining control or who are experiencing significant adverse effects should be switched to reasonable alternative preparations.

In the future, direct effects on the biological deficits resulting from deficient FMRP may offer more-targeted treatments, such as treatment directed at normalization of decreased inhibitory signaling through γ-aminobutyric acid (GABA) pathways, attributable to decreased GABA_A 6 receptor activity in FXS. Treatment with neurosteroidal GABA receptor agonist anticonvulsants such as ganaxolone, which is used to treat infantile spasms, may be useful for epilepsy, anxiety, and aspects of cognition in FXS. Other potential target mechanisms of epileptogenesis operating in the absence of FMRP, such as overactivity of metabotropic glutamate receptor (mGluR)-mediated translation (see below) and indirect effects of altered α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor levels on N-methyl-D-aspartate receptor-evoked epileptiform potentials, may offer alternative therapeutic options in the future.

After the choice of anticonvulsant, drug-specific blood and general health monitoring should be as indicated for any child taking these medications. It should be noted that, although immunization may be a time of risk for individuals predisposed to seizures, the epilepsy and autism risks in FXS are not contraindications to a standard immunization schedule.

**NEUROBIOLOGICAL FEATURES AND TARGETED TREATMENTS**

**Neurobiological Findings**

FMRP is a RNA-binding protein that modulates dendritic maturation and synaptic plasticity through a mechanism involving particularly the inhibition of group 1 mGluR-mediated dendritic protein synthesis. This concept is based in part on the finding that hippocampal and cerebellar long-term depression (ie, weakening of synaptic connections), mediated by mGluR5 and mGluR1, respectively, is enhanced in the *fmr1*-knockout mouse model of FXS (Fig 3). Furthermore, these forms of synaptic plasticity are not dependent on protein synthesis in knockout mice, which results in excessive translation of mRNAs normally bound by FMRP. Numerous additional hypothesized consequences of excessive activity of mGluR-mediated processes are found in knockout mice, including reduced synaptic AMPA receptor levels and long-term potentiation deficits in the cortex and hippocampus, excessive internalization of AMPA receptors in cultured knockout mouse neurons, immature-appearing, elongated dendritic processes, and abnormal epileptiform discharges. Furthermore, on the basis of known locations and activities of group 1 mGluR receptors in the nervous system, many phenotypic features of FXS, including seizures, electrical excitability on electroencephalograms, hypersensitivity to tactile stimuli, cognitive difficulties, strabismus, enhanced anxiety, coordination problems, and even loose stools, have been proposed to occur through enhancement of mGluR-mediated processes that normally would be inhibited by FMRP.

**mGluR5 Antagonists**

Many aspects of the phenotype in FXS animal models, including the behavioral abnormalities, cognitive deficits, and dendritic spine changes, are thought to be attributable to excessive mGluR5 signaling and can be rescued through genetic downregulation of mGluR5 expression, through crossing of *fmr1*-knockout mice with heterozygous mGluR5-knockout mice. The only phenotypic aspect in knockout mice that is not rescued through this crossing is macroorchidism, in which the mGluR5 pathway likely is not involved.

It has been suggested that mGluR5 antagonists would be an effective treatment for FXS (Fig 3). Selective mGluR5 antagonists have been available as research tools for nearly a decade, and the prototype of the class, 2-methyl-6-(phenylethynyl)pyridine, has been tested extensively in animal models of FXS. 2-Methyl-6-(phenylethynyl)pyridine rescues the most robust central nervous system phenotypes in knockout mice, namely, hyperactivity and audiogenic seizure susceptibility. It also has been shown to rescue cognitive and neuroanatomical phenotypes in a *Drosophila* (fruit fly) model of FXS, as well as neurite branching and craniofacial abnormalities in zebrafish.

Although no mGluR5 antagonist has ever been marketed in any country, there has been some published human experience with fenobam, a drug that was developed originally as an anxiolytic agent and was found to be a selective mGluR5 antagonist. Investigational trials of fenobam (in non-FXS populations) showed it to be a very safe drug and a modestly effective anxiolytic agent. Fenobam is under development as an orphan drug for the treatment of FXS, with initial human FXS trials in 2008. Other mGluR5 antagonists are in development for a FXS indication, with clinical trials anticipated in the near future.

Because the pharmacologic spectrum of mGluR5 antagonists in animal models, that is, anxiolytic, antidepressant, and anticonvulsant, is remarkably close to the neurobehavioral phenotype of FXS, these drugs have great potential for reversing or ameliorating many core features of the disorder. It is possible that some other developmental disorders, including other ASDs that may share pathophysiologic elements with FXS, also may respond to treatment with this emerging drug class.

**Lithium**

Lithium is an alternative agent, currently available for use in humans, that downregulates the phospholipase C signaling pathway by inhibiting inositol phosphate turnover, thus attenuating phospholipase C enzyme activity. Because this pathway is used by mGluRs and other receptors to activate dendritic translation, its inhibition by lithium theoretically may correct excessive dendritic protein synthesis in FXS (Fig 3). Furthermore, lithium inhibits glycogen synthase kinase 3β, which may
downregulate mGluR-mediated translation of at least some proteins through additional pathways.\textsuperscript{149} In fact, lithium was shown to improve defects in naive courtship behavior, as well as immediate recall and short-term memory, in the \textit{Drosophila} model of FXS.\textsuperscript{136} Lithium and other agents that block glycogen synthase kinase 3β (GSK3β) were shown to improve seizures in the knockout mouse model.\textsuperscript{149} Berry-Kravis et al.\textsuperscript{150} conducted an add-on trial of lithium with 15 young male individuals (6–23 years of age) with FXS and found significant improvement in behavioral functioning, adaptive behavior, and verbal memory. The extracellular signal-regulated kinase activation rate, a potential biomarker for modulation of translational signaling through the phospholipase C cascade that is reduced in knockout mice and in patients with FXS, was normalized significantly with 2 months of lithium treatment. Results from that study suggested that lithium is well tolerated and may provide some functional benefits in FXS.

**Ampakines**

Although there has been much focus on the mGluR pathway as a treatment target in FXS, reduced AMPA receptor signaling and impaired cortical and hippocam-
pal long-term potentiation\textsuperscript{126,127} represent other potential targets for pharmacologic intervention. A placebo-controlled clinical trial of the AMPA receptor positive modulator (ampakine) CX516 did not show improvements in behavioral or cognitive functioning in a cohort of subjects with FXS,\textsuperscript{151} although there was a suggestion of improvement for the small number of subjects treated with antipsychotic agents (which potentiate the effects of ampakines) and active drug, compared with placebo. This finding, combined with emerging data from other trials and pharmacologic work, suggested that CX516 is an agent with low potency that does not induce synaptic changes (increases in brain-derived neurotrophic factor [BDNF] levels) as effectively as other ampakine compounds and was likely being used at subtherapeutic doses. Lauterborn et al\textsuperscript{127} showed recently that BDNF fully rescued hippocampal long-term potentiation deficits in \textit{fmr1}-knockout mice; therefore, an appropriately therapeutic ampakine with good capability for induction of endogenous BDNF production\textsuperscript{152} would be a good candidate to target at least part of the underlying mechanism of abnormal synaptic plasticity in FXS.

BEHAVIORAL INTERVENTIONS

Despite the wealth of knowledge regarding the behavioral phenotype of FXS, there are almost no empirical studies on the effectiveness of behavioral treatments among patients with FXS.\textsuperscript{153} Obviously, the lack of treatment studies severely restricts the empirically validated behavioral treatment recommendations that can be made to patients with FXS and their families. Providers generally have relied on their own clinical experience and an understanding of the aforementioned factors shown to be associated with behavioral problems in phenotype studies to guide treatment approaches. The lack of empirical treatment studies in the FXS field is ironic, given that several research projects have highlighted the fact that challenging behaviors of these individuals seem to have the greatest impact on parents and families, greater than that of cognitive impairment.\textsuperscript{154}

Both animal and human studies have shown that variations in the environment have an impact on behavior.\textsuperscript{155} For example, a higher-quality home environment is associated with fewer autistic behaviors, better adaptive behavior, and higher IQ scores in children with FXS.\textsuperscript{156,157} Effectiveness of educational services, as reported by parents, also has been associated with better behavioral outcomes and fewer autistic behaviors.\textsuperscript{158} Those studies suggest that modifications in the home environment and more-tailored behavioral interventions and classroom environments should lead to better outcomes for children with FXS, but this overly general suggestion has not been tested with specific interventions. Similarly, the findings that children with FXS have heightened electrodermal responses to sensory stimuli\textsuperscript{12} and elevated stress hormone levels, which are related to the severity of behavioral and social problems,\textsuperscript{159,160} suggest that interventions aimed at reduction of and better coping with stress and sensory input should result in better outcomes, but no treatment studies have been performed to document this. Reiss and Hall,\textsuperscript{153} in their review of the assessment and treatment of FXS, provided examples of novel behavior modification interventions aimed at improving social eye contact and stress reduction and supported treatment models that combine behavioral interventions with experimental pharmacologic or hormonal treatments that are supported by laboratory data. Studies comparing behavioral, targeted pharmacologic, and combined approaches are needed.

Although large behavioral treatment studies of individuals with FXS are difficult, well-designed, multiple-baseline, individual-subject studies are quite feasible and can yield convincing accounts of efficacy with relatively few participants. Weiskop et al,\textsuperscript{161} in the only empirical FXS behavioral treatment study in the literature, used such a design to investigate a parent training program to reduce sleep problems in children with autism ($N = 6$) or FXS ($N = 5$). Although the study was small, the program seemed generally successful; the study provides a good model for other multiple-baseline studies that could be performed, focusing on aggression, self-injury, and other maladaptive behaviors.

A detailed review and recommendations for behavioral treatment of individuals with FXS were provided by Hills-Epstein et al.\textsuperscript{162} Those recommendations, which generally follow principles of functional behavioral analysis and the antecedent-behavior-consequence model, are based on sound principles of how maladaptive behaviors are maintained and rewarded and how they can be replaced through positive reinforcement of appropriate or adaptive behaviors.

The state of the science in psychosocial treatment through behavioral interventions in ASDs was reviewed comprehensively by a National Institutes of Health-sponsored panel of national experts on autism.\textsuperscript{163} That review offers important insights and recommendations that are applicable to behavioral treatment of individuals with FXS, because of the very high rates of autism and autistic behaviors. The authors emphasized that the traditional 1-hour/week treatments for language, social skills, or behavior that are used in the US mental health and educational systems are rarely sufficient to lead to generalized improvements for children with autism. This statement probably also reflects the needs of children with FXS, with or without autism. The unique factors likely to be contributing to maladaptive behaviors in FXS (ie, anxiety, sensory overload, and inattention/impulsivity) would need to be fully appreciated by an equivalently trained behavioral intervention team. There are several treatment models, including the Treatment and Education of Autistic and Related Communication-Handicapped Children model,\textsuperscript{164} the Denver model,\textsuperscript{165} pivotal response training,\textsuperscript{166} and applied behavior analysis,\textsuperscript{167} that are well established in autism treatment. These models, or aspects of these models, should be applied to groups of individuals with FXS or with FXS and autism, to test their efficacy. In our clinical experience, these treatment programs have been helpful for many children with FXS and ASD.

Higher-functioning individuals with FXS can benefit from psychotherapy or counseling.\textsuperscript{162,168} This work can focus on anxiety reduction through desensitization, sexuality
issues, management of depression (usually through structured cognitive behavioral approaches), and socialization issues. Many individuals with FXS who have autistic symptoms and social anxiety also can benefit from social skills-oriented group therapy. A program to address behavioral problems and sexuality issues in adolescence and young adulthood was developed recently by the National Fragile X Foundation, to guide professionals and family members.

GENETIC COUNSELING
When an individual is identified as being at risk for FXS, it is imperative that the clinician explains to the family the indications for testing. If the testing results are positive, then referral to a geneticist and/or a genetic counselor is recommended, so that the appropriate clinician can interpret the results for the family according to the guidelines for FXS established by the National Society of Genetic Counselors and the American Society of Human Genetics. The genetic counselor will review the inheritance pattern for FXS, which should enable identification of individuals at risk for carrying FMR1 mutations and should help the family in developing an appropriate strategy regarding how information is conveyed to other family members. This may involve personal contact between family members or an informational letter, or the family may choose to have the genetic counselor, geneticist, or pediatrician meet with members of the extended family, to discuss the diagnosis of FXS and FX-associated conditions and to facilitate testing for family members who are at risk.

The counselor also can review reproductive options for future pregnancies, including egg donation, prenatal diagnosis, adoption, and preimplantation genetic diagnosis through polar body analysis. Emotional, endocrinologic, and neurologic problems need to be reviewed for all extended family members at risk for either the premutation or the full mutation. Individuals who have symptoms of involvement should be tested, as well as their siblings. Positive test results for siblings often help to mobilize treatment even for mild problems (e.g., ADHD or anxiety). Newly diagnosed families should be connected to local parent support groups, which can be found with the advocacy groups listed in the Appendix.

SCREENING FOR FXS
High-risk testing for FXS is recommended for individuals with autism, ASD, or intellectual disability. In addition, screening is recommended for individuals with features of FXS and learning disabilities, women with primary ovarian insufficiency, and aging adults with ataxia or tremor combined with other features of FXTAS or a family history consistent with FXS. Several studies have assessed broader population screening, including prenatal screening and screening of populations with neurologic conditions. Newborn screening for FXS is currently being researched in multiple locations in the United States, in line with the broadening of newborn screening criteria to include neurodevelopmental disorders that would benefit from early intervention. Many children with FXS receive late diagnoses, and as many as 50% of parents have had another child or pregnancy before the diagnosis, without the opportunity for counseling and informed decision-making before the subsequent pregnancy. One impediment to widespread screening has been the cost of the FMR1 DNA test. Less-expensive screening methods have been developed. The blood spot test described by Tassone et al substantially reduces the cost of screening, to less than $5 per test, and screens for the full mutation and the premutation in both genders. If screening test results are positive, then follow-up definitive DNA testing for FXS, including Southern blotting, is recommended. The availability of this test, and perhaps other tests in the future, will likely facilitate expansion of newborn screening and the screening of high-risk populations.

CONCLUSIONS
We are entering a new age of targeted treatments for FXS and more-widespread screening for this disorder. Therefore, it is likely that most pediatricians or medical providers will encounter 1 patient affected by FXS or the premutation in their practices. Multidisciplinary treatment, including speech and language therapy, occupational therapy, physical therapy, special education, behavioral interventions, and genetic counseling, can be coordinated by the pediatrician, who also adds the medical interventions reviewed here. As newborn screening develops, early intervention for infants can be coordinated by the pediatrician or family care provider, working with an early intervention team. New targeted treatments for FXS are emerging, and older treatments (such as lithium) also can target the mGluR5 pathway abnormalities in FXS. Extended involvement in multiple family members is common, because several medical problems affect premutation carriers, in addition to a broad spectrum of involvement in individuals with the full mutation. Therefore, pediatricians should consider extended family DNA testing, with the help of a genetic counselor or geneticist, and follow-up care with a multidisciplinary treatment team.

APPENDIX: FXS RESOURCES

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<td>National Fragile X Foundation, PO Box 37, Walnut Creek, CA, 94597.</td>
<td>Telephone: 800-688-8765, 925-938-9300; fax: 925-938-9315</td>
<td>e-mail: <a href="mailto:natlfx@fragilex.org">natlfx@fragilex.org</a></td>
<td>Internet: <a href="http://www.fragilex.org">www.fragilex.org</a></td>
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<td>FRAXA Research Foundation, 45 Pleasant St, Newburyport, MA 01950.</td>
<td>Telephone: 978-462-1866; fax: 978-463-9985</td>
<td>e-mail: <a href="mailto:info@fraxa.org">info@fraxa.org</a></td>
<td>Internet: <a href="http://www.fraxa.org">www.fraxa.org</a></td>
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<tr>
<td>National Institute of Child Health and Human Development, PO Box 3006, Rockville, MD 20847.</td>
<td>Telephone: 1-800-370-2943; fax: 866-760-5947</td>
<td>e-mail: níchidinformati on researc <a href="mailto:hcenter@mail.nih.gov">hcenter@mail.nih.gov</a></td>
<td>Internet: <a href="http://www.nichd.nih.gov">www.nichd.nih.gov</a></td>
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<td>Dolan DNA Learning Center: Your Genes Your Health.</td>
<td>Internet: <a href="http://www.ygyh.org">www.ygyh.org</a></td>
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<td>GeneTests.</td>
<td>Internet: <a href="http://www.geneclinics.org">www.geneclinics.org</a></td>
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