

# Managing maladaptive behaviors in fragile X patients

Psychotropics can improve hyperactivity, anxiety, and aggression



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**P** psychotropics<sup>1,2</sup> are used to manage maladaptive and interfering behaviors in 70% of patients with fragile X syndrome (FXS), the leading cause of hereditary mental retardation. Treatment tends to follow a developmental course:

- In children, stimulants and alpha-2 agonists are used for attention-deficit/hyperactivity disorder (ADHD)-like symptoms.
- In adolescents and adults, selective serotonin reuptake inhibitors (SSRIs) are used for anxiety/repetitive phenomena and second-generation antipsychotics (SGAs) for irritability.

This course—which is often effective—is based primarily on anecdotal descriptions and on rationales borrowed from studies of ADHD, obsessive-compulsive disorder (OCD), and autistic disorder/related pervasive developmental disorders (PDDs).<sup>3</sup> Disease-modifying agents to target the underlying brain dysregulation inherent in FXS (*Box*)<sup>1,4-10</sup> are being investigated. For now, psychotropics can help you manage three common FXS symptom clusters: inattention and hyperactivity, anxiety, and aggression and self-injurious behavior (SIB).

### INATTENTION AND HYPERACTIVITY

Mike, age 6, has fragile X syndrome. He has been attending first grade for 4 months, and his teacher reports he does not sit still, runs throughout the classroom, and cannot focus on class work. Mike's hyperactivity has been evident for 2 years but did not cause problems until first grade, his parents report.

**Psychostimulants** are the most frequently prescribed agents for inattention and hyperactivity in FXS, particularly in boys and male adolescents.<sup>1</sup> Among FXS patients prescribed  $\geq 1$  psychotropic, approximately 70% are taking a stimulant.<sup>1,2</sup>

**Efficacy.** A clinical chart review found a 75% response rate in FXS children and adolescents who were given a stimulant for inattention and/or hyperactivity.<sup>1</sup> This is higher than the 25% to 49% stimulant response rate reported in patients with PDDs.<sup>11,12</sup>

A 3-week, placebo-controlled, crossover trial of methylphenidate and dextroamphetamine noted a statistically significant response only to methylphenidate, with a positive response reported in 10 of 15 children (67%).<sup>13</sup>

**Side effects.** To date, limited information has described the rate of intolerable side effects associated with stimulant use in FXS,<sup>14</sup> but in patients with PDD:

#### Box

### Fragile X syndrome's genetic and behavioral features

**The term “fragile X”** describes how the X chromosome of affected individuals fractures in a folate-deprived medium. This most common form of inherited mental retardation affects 1 in 2,000 to 4,000 males and 1 in 4,000 to 8,000 females.<sup>4</sup> One in four individuals with fragile X syndrome (FXS) also meets diagnostic criteria for autistic disorder (*Table 1, page 82*), with social skill and communication delays and interfering repetitive behaviors.<sup>5</sup>

**Genetic profile.** FXS results from a triplet repeat expansion in the fragile X mental retardation-1 gene.<sup>6</sup> This mutation causes underproduction of fragile X mental retardation protein (FMRP), an inhibitor of the metabotropic glutamate receptor (mGluR). In theory, insufficient FMRP allows exaggerated group 1 mGluR activity and leads to the FXS neurobehavioral phenotype: mental retardation, increased seizure risk, behavioral symptoms, and stereotypic movements.<sup>7,8</sup>

**Behavioral difficulties** cluster in three categories: attention-deficit/hyperactivity disorder-like symptoms, anxiety symptoms, and aggression and self-injurious behaviors.<sup>1,4,9</sup> These are thought to be more prevalent in persons with FXS than would be expected from the degree of cognitive delay alone.<sup>1</sup> Potential differences in the behavioral phenotypes of FXS patients with and without comorbid autism continue to be defined.<sup>10</sup>

- 154 of 268 (57.5%) patient trials in a retrospective naturalistic study showed significant adverse effects with stimulant use.<sup>11</sup>

continued



Table 1

### Clinical characteristics of patients with fragile X syndrome

<b>Physical features (seen in some males)</b>	Long, narrow face High, arched palate Narrow inter-eye distance Enlarged ears Macro-orchidism
<b>Behavioral symptoms</b>	Inattention Hyperactivity Anxiety Repetitive behaviors Aggression and self-injurious behaviors (increased in adolescence and adulthood)
<b>Comorbidities</b>	Mental retardation (mean IQ for affected males in moderate range) Comorbid autism (25% of affected individuals) Frequent seizures (10% to 20% of affected males) Hypersensitivity to sensory stimuli

- 13 of 72 (18%) subjects in a controlled trial discontinued methylphenidate because of adverse events (most commonly irritability).<sup>12</sup>

Based on these observations, possible side effects that deserve close monitoring include mood lability, exacerbation of anxiety, increased social withdrawal, irritability, insomnia, decreased appetite, and increased repetitive movements.

**Antiadrenergics.** The alpha-2 agonists clonidine and guanfacine are the second most-used class of agents for inattention and hyperactivity in FXS. As with stimulants, boys and male adolescents are most likely to receive alpha-2 agonists, with administration rates of 10% to 20%.<sup>1,2</sup>

**Efficacy.** In one survey, nearly two-thirds (63%) of parents described clonidine as “very ben-

eficial” to 35 children (mean age 6.6) with FXS.<sup>15</sup> This is similar to a 70% response rate described for these alpha-2 agonists in a chart review.<sup>1</sup> These rates are much higher than the 24% response rate reported with guanfacine in a retrospective chart review of 80 children and adolescents with a PDD.<sup>16</sup> In that review, guanfacine use was associated with reduced hyperactivity, insomnia, and tics, and increased attention.<sup>15</sup>

**Side effects** associated with alpha-2 agonists include lowered blood pressure and sedation.

**L-acetylcarnitine**—a carnitine derivative required for neuronal use and transport of fatty acids—is being investigated to treat hyperactivity in FXS. Hyperactive symptoms improved significantly with L-acetylcarnitine, as measured by the Conners’ Abbreviated Parent-Teacher Questionnaire, in a 1-year, placebo-controlled trial of 20 boys (mean age 9.2) with FXS.<sup>17</sup>

**Discussion.** Supporting evidence is limited, but clinicians are treating ADHD-like symptoms with stimulants and alpha-2 agonists in many FXS patients. Preliminary data indicate that stimulants may be more effective and better tolerated in individuals with FXS than in those with PDD.

Trying a stimulant or alpha-2 agonist for inattention or hyperactivity symptoms in a child or adolescent with FXS appears clinically appropriate, given the available evidence. Additional data based on placebo-controlled and standardized measures of treatment response are needed to help guide treatment.

We start Mike on methylphenidate, 5 mg in the morning, for inattention and hyperactivity. He tolerates

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Table 2

**Target symptoms and treatment options for fragile X syndrome**

Medication class	Target symptom cluster	Evidence for use of drug class in FXS
<b>Stimulants</b>	Inattention, hyperactivity	One placebo-controlled trial, two large clinic surveys
<b>Alpha-2 agonists</b>	Inattention, hyperactivity	One parent-interview report, two large clinic surveys
<b>SSRIs</b>	Anxiety-related symptoms	One mailed survey, two large clinic surveys
<b>Atypical antipsychotics</b>	Aggression, self-injury	Two large clinic surveys, several controlled trials in PDDs

FXS: fragile X syndrome

SSRIs: selective serotonin reuptake inhibitors

PDDs: pervasive developmental disorders.

this well, and after 2 weeks we increase the dosage to 5 mg bid. Several weeks into treatment, his teacher comments that he is beginning to stay in his seat and attends to some assigned tasks in the classroom.

Mike continued to tolerate methylphenidate over the next 4 years. We gradually increased the dosage as he grew and when he periodically developed breakthrough interfering symptoms in the classroom.

**ANXIETY SYMPTOMS**

In grade school, Mike became increasingly nervous around schoolmates, teachers, and friends. His teachers commented that he repeated phrases when he appeared anxious. Other children in his special education class began to shun him; they found his perseveration odd and sometimes threatening.

Now that Mike is age 10 and in fifth grade, his parents decide that his anxiety, particularly in social settings, is interfering with his life.

Anxiety symptoms—including generalized nervousness and OCD-like obsessions and perseverations—are common psychotropic targets in FXS. Boys may be the FXS patients most often prescribed drugs for inattention and hyperactivity, but they are the least likely to receive antidepressants for anxiety symptoms.<sup>1,2</sup>

**Efficacy.** More than 50% of female patients and men with FXS are prescribed SSRIs for anxiety (*Table 2*), and the reported response rate of 50% to 60%<sup>1</sup> is similar to that seen with SSRIs in autism and related disorders.<sup>18</sup> In autism, a developmental approach is warranted, as SSRIs tend to be less effective and cause more side effects in children and adolescents than in adults.<sup>18</sup>

**Adverse effects** reported with SSRIs in FXS include behavioral activation, appetite changes, insomnia, and nausea.<sup>1</sup> In a study of fluoxetine for FXS symptoms, 10 of 35 patients (29%) had persistent side effects, most commonly weight

Stimulants may be more effective, better tolerated in fragile X patients than in those with PDD

Table 3

### Medication side effects and recommended monitoring

Medication class	Side effects	Medication monitoring
<b>Stimulants</b>	Anorexia, insomnia, agitation, exacerbation of tics	Observe closely when starting treatment and increasing dosage
<b>Alpha-2 agonists</b>	Lowered blood pressure, sedation, dizziness	Observe closely when starting treatment and increasing dosage  Check blood pressure with all dosage changes and at all clinic visits
<b>SSRIs</b>	Irritability, mood lability, nausea, sleep and appetite disturbances, suicidality	Observe closely when starting treatment and increasing dosage
<b>Atypical antipsychotics</b>	Sedation, weight gain, hyperglycemia, hyperlipidemia, hyperprolactinemia, EPS, NMS, tardive dyskinesia	Obtain metabolic profile, including fasting lipids, glucose, and prolactin levels  Monitor for weight gain and signs of EPS

EPS: extrapyramidal symptoms  
NMS: neuroleptic malignant syndrome  
SSRIs: selective serotonin reuptake inhibitors

loss and weight gain.<sup>19</sup> One patient with pre-existing suicidal ideation worsened.

Watch for emergence or worsening of suicidal thoughts in all children and adolescents receiving antidepressants, whatever their target symptoms.

Mike is taking methylphenidate, 15 mg bid, for comorbid ADHD, and we add fluoxetine, 10 mg/d, for anxiety. This regimen is well-tolerated, so we increase fluoxetine to 20 mg/d at his 4-week follow-up appointment. After about 8 weeks, Mike's parents report that his anxiety-associated symptoms are less severe.

Mike still appears nervous sometimes, but he uses markedly fewer perseverative phrases. This allows him to interact more meaningfully with peers and contributes to his social development.

### AGGRESSION AND SELF-INJURY

Mike, now age 20 and participating daily in a vocational workshop, begins yelling profanities at coworkers. At his group home, he has been hitting staff at least twice a week when redirected.

He is no longer taking stimulants, having been weaned from methylphenidate several years ago, but he continues to take fluoxetine, 40 mg/d.

Fluoxetine<sup>19</sup> and clonidine<sup>15</sup> can decrease irritability in FXS, but atypical antipsychotics are most commonly used for aggression and SIB.<sup>1,2</sup> SGAs are prescribed to 10% to 20% of FXS patients who are taking medication<sup>1,2</sup>—particularly to men—and have produced response rates of 60% to 100% when used for aggression and SIB.<sup>1</sup>

continued





## Fragile X

**Risperidone.** No published reports have addressed using specific SGAs in FXS. In the PDD literature, most controlled data concerns risperidone.<sup>20</sup>

The largest randomized, placebo-controlled trial enrolled 101 children ages 5 to 17 with autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior. Among the 49 children taking risperidone, 0.5 to 3.5 mg/d for 8 weeks, 34 (69%) were judged as treatment responders with significantly reduced irritable behavior, compared with 6 of 52 (12%) taking placebo.<sup>21</sup> Risperidone therapy was associated with average weight gain of  $2.7 \pm 2.9$  kg, compared with  $0.8 \pm 2.2$  kg with placebo.

Besides weight gain, other significant side effects associated with risperidone include sedation and elevated serum prolactin. These effects often are more pronounced in children and adolescents than in adults with PDDs.<sup>20</sup>

**Other antipsychotics.** Future use of SGAs in FXS will likely mirror the pattern seen in PDDs, where clinicians are moving towards weight-neutral antipsychotics such as ziprasidone and aripiprazole. In a preliminary report, aripiprazole reduced

irritability in 5 youths with PDD.<sup>22</sup> Our group is conducting a double-blind, placebo-controlled trial of aripiprazole in autism, targeting aggression, SIB, and irritability.

**Discussion.** SGAs are used most often in FXS to treat aggression and SIB, based on data from studies on treating similar symptoms in PDDs. Closely monitor patients for sedation, weight gain, and lipid, glucose, and prolactin elevations when using SGAs (*Table 3, page 87*). Be especially vigilant when children gain weight rapidly or show hyperprolactinemia signs while taking these drugs.

Be especially vigilant when children gain weight rapidly or show increased prolactin with SGAs

After being suspended from the vocational workshop, Mike is treated at a local mental health center for aggressive behaviors. He tolerates an initial dosage of aripiprazole, 2.5 mg/d, which is titrated in 2.5-mg increments biweekly to 10 mg/d. At this dosage, he stops hitting staff members and his yelling of profanities is greatly reduced. Over several months, Mike returns to his vocational workshop and maintains residence at his group home.

## GENETIC-RELATED TREATMENTS

Studies are needed to investigate the use of stimulants, SSRIs, and antipsychotics in patients with FXS unaccompanied by generalized anxiety disorder, OCD, ADHD, or PDDs. How FXS patients without those comorbidities will respond to drug treatment is unknown. Also, little also is known about possible side effects associated with combining drug treatments in individuals with FXS.

**Future drug treatment** in FXS will likely focus on agents that target the underlying neurochemical dysregulation associated with the FXS genotype. This approach might reduce interfering behaviors and alter the course of cognitive dysfunction—including mental retardation—associated with FXS.

For patients with fragile X syndrome, consider a stimulant or alpha-2 agonist for ADHD-like symptoms, an SSRI for anxiety, and a second-generation antipsychotic for aggression/self-injury. Efficacy and side effects vary by the patient's developmental stage. Watch for sedation, weight gain, and lipid, glucose, and prolactin elevations when using antipsychotics.

BottomLine

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Past attempts to correct FXS' neurochemical abnormalities focused on using folic acid. The term "fragile X" describes how the X chromosome of individuals with FXS fractures in a folate-deprived medium. Many controlled trials of folic acid in FXS did not support earlier positive reports, however.<sup>4</sup>

Greater understanding of fragile X mental retardation protein (FMRP) function has led to the metabotropic glutamate receptor (mGluR) theory.<sup>7</sup> It holds that FMRP underproduction allows exaggerated group 1 mGluR activity and leads to the FXS neurobehavioral phenotype. Researchers now are attempting to reverse the neurochemical impact of insufficient FMRP with two medication classes:

• **selective group 1 mGluR receptor antagonists** (mGluR5 antagonists, in particular). The mGluR5 receptor antagonist MPEP has shown the ability to rescue normal behaviors in animal models of FXS. MPEP and lithium have reversed behaviors associated with FXS and—at the microscopic level—rescued synaptic plasticity.<sup>23,24</sup> In the drosophila fly model of FXS, lithium reduced activity in the mGluR cascade, thus compensating for lack of FMRP.<sup>23</sup>

• **positive AMPA receptor modulators (ampakines)** that promote activity of  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.<sup>9</sup> Excessive mGluR activity appears to impair AMPA receptors' ability to promote cortical development, memory, and learning.<sup>7</sup> Reduced AMPA receptors have been shown in the FXS mouse model,<sup>25</sup> and an ampakine is being investigated in a study of men with FXS and autism.<sup>1</sup>

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## Related resources

- FRAXA: The Fragile X Research Foundation. Founded by parents of children with fragile X syndrome to increase funding for research toward effective treatments. [www.fraxa.org](http://www.fraxa.org).
- The National Fragile X Foundation. Provides educational and emotional support for fragile X families and promotes public and professional awareness. [www.fragilex.org](http://www.fragilex.org).
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## DRUG BRAND NAMES

Aripiprazole • Abilify  
Clonidine • Catapres  
Dextroamphetamine • Dexedrine  
Fluoxetine • Prozac  
Guanfacine • Tenex

Lithium • Eskalith, Lithobid  
Methylphenidate • Ritalin  
Risperidone • Risperdal  
Ziprasidone • Geodon

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