Consensus of the Fragile X Clinical & Research Consortium on Clinical Practices

Medications for Individuals with Fragile X Syndrome

First Issued: May 2012
Last Updated: October 2012
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Introduction:
Maladaptive behaviors and social deficits in fragile X syndrome (FXS) are common, and they significantly impact academic and daily functioning. Hence, medications are often necessary to decrease disruptive, anxiety, or aggressive behaviors and prevent dangerous consequences or dysfunction. Furthermore, medications may facilitate the individual’s ability to attain optimal life skills, and allow for better integration into educational and social environments.

Psychopharmacological (medication) treatment in FXS is recommended in appropriate individuals, as adjunctive treatment in conjunction with additional therapeutic services, including behavioral intervention, speech and language therapy, occupational therapy, and individualized educational support.

There are common symptoms and psychiatric conditions in individuals with FXS who are treated with the same medications that are used for these issues in the general population and in individuals with other developmental disabilities (Amaria 2001, Berry-Kravis 2004, Hagerman 2009, Valdovinos 2009, Berry-Kravis 2012). These medications have been reported to be effective for patients with FXS in retrospective clinical series and survey studies. However there is limited formal research or clinical trial data to demonstrate the best approach to the use of medication in the FXS population. There is an assumption that data from studies of medication use in autism can be applied to treatment of FXS but whether this is valid remains unclear. It is important to remember that individuals with FXS may be more sensitive to psychotropic medications and may respond to smaller doses than the general population, or may have side effects at relatively low doses, thus an important general principle with all medication treatment in FXS is to start at low doses and raise the dose gradually and systematically until the desired benefit is achieved or side effects occur. If side effects occur prior to achieving significant therapeutic benefit, the medication should be discontinued.

The following discussion includes available data wherever possible, but much of the current approach to treatment relies on expert opinion. The core behavior problems discussed below are commonly seen in FXS; and individuals with FXS may have one or more than one behavior core problems. The parent or caregiver can rank the severity of these symptoms to help prioritize treatment choices (see Symptom Rating Scale).

1. Anxiety
Many patients with FXS begin to show signs of anxiety at a very early age, often by 2-4 years. Serotonin is one of the most important neurotransmitters in the brain involved in regulating mood and affect. The selective serotonin re-uptake inhibitors (SSRIs) can be very effective in treating these symptoms. They have been used on an empirical basis in affected patients as young as 4 years old. SSRIs are the treatment of choice for symptoms of anxiety and depression. In the FXS population, antidepressants, particularly SSRIs are somewhat helpful
more than 50% of the time in helping with anxiety and behavioral/emotional symptoms when these symptoms are sufficiently severe to produce dysfunction (Hagerman 1994; Hagerman 1999, Berry-Kravis 2004, Berry-Kravis 2012). Side effects of SSRIs may include behavioral activation, which includes sleep difficulties. Activation is an increase in activity level that does not include any real change in mood, impulse control, or a change in the child’s demeanor or other behaviors. It is relatively easily managed by dose reduction or medication discontinuation. However, at times it is difficult to get the dose low enough to actually get rid of the activation and keep the clinical benefit. Activation tends to parallel the pharmacokinetics of a particular agent. As one might expect, after SSRI discontinuation activation abates more quickly for the shorter-acting ones (i.e., citalopram, escitalopram) than for the longer acting ones (i.e., fluoxetine). Other common side effects of SSRIs may include nausea, diarrhea, dizziness, and reduced sexual desire.

Other classes of antidepressants (e.g. trazodone, bupropion, tricyclic antidepressants) may be considered in instances in which SSRIs are not tolerated due to side effects such as when there is behavioral activation that could not be managed by dose reduction. Bupropion can lower the seizure threshold and it should not be used when there is an active seizure disorder. Clonidine and guanfacine have also been used to treat anxiety-like symptoms, particularly the ones related to hypersensitivity to environmental sensory stimuli (Hagerman 1995), but are probably not meaningfully effective for other forms of anxiety. Buspirone may in some cases reduce anxiety either alone or in combination with an SSRI.

Benzodiazepines can be a treatment of choice in an emotional crisis accompanied by high level of anxiety/anxiety attacks but should be avoided for long-term treatment as they can interfere with memory, increase confusion and/or cause paradoxical excitation with a significant increase in hyperactivity and disinhibition. They can also be addictive, meaning difficult to be weaned off, induce tolerance - ever increasing doses are needed to attain the desired effects, and must not be discontinued abruptly after a long-term use (i.e., risk of withdrawal seizure). However, benzodiazepines may be used in single doses to assess for paradoxical excitation, and if absent may be used on an as-needed basis to help with high-stress situations such as dental visits or airplane rides.

2. Aggression and self-injurious behavior
Aggression and/or self-injurious behavior (SIB) in FXS can present at an early age, often closely associated with intense anxiety and generalized irritability. Features of autonomic arousal, including tachycardia and diaphoresis (sweating), may indicate an underlying anxiety or panic attack and, if present, provide an added indication for treatment. Selective serotonin reuptake inhibitors (SSRIs) can be effective agents in treating children with FXS as young as three years of age who have aggressive outbursts or SIB, if the symptoms are due to anxiety. Antipsychotic medications, including risperidone and aripiprazole, have been used in children, adolescents and adults exhibiting severe behavioral disturbances that interfere with functioning or pose a
significant threat to the affected individual or others. These medications have FDA approval for use in treating irritable and aggressive behaviors in autism spectrum disorders (ASDs) from age 6 and up. However, with extreme behavior dysfunction these medications have been employed as young as age 3 years, with successful responses and with tolerable levels of side effects.

Aripiprazole (Abilify™) is reported to have response rates of ~70% in FXS (Berry-Kravis 2004, Hagerman 2009, Erickson 2011, Berry-Kravis 2012). In an open-label study aripiprazole targeted distractibility, anxiety, mood instability, aggression, and aberrant social deficits (Erickson, 2011). Some individuals cannot tolerate aripiprazole because it has dopamine agonist activity and its side effects can be similar those seen with stimulants; including exacerbation of agitation or aggravation of aggressive, irritable, and perseverative behaviors (Berry-Kravis, 2012).

At any age, antipsychotic medications can cause significant side effects including very early (i.e., dystonic or oculogyric reaction is rare but can occur within days of initiation of the treatment), early (i.e., akathisia within 1-2 weeks), extrapyramidal movement disorders (i.e., upper extremity stiffness within several weeks unless the dosage continues to be increased), and late (i.e., tardive dyskinesia) side effects. Metabolic issues such as weight gain can develop within weeks, especially with 2nd generation antipsychotics (i.e., olanzapine, risperidone) and is potentially associated with glucose intolerance due to increased insulin resistance due to the weight gain. There can also be problems with lethargy and worsening of coordination. Longer term treatments with antipsychotics may run the risk of irreversible movement disorders such as tardive dyskinesia, and withdrawal emergent problems. Therefore, careful clinical monitoring is therefore required consisting of blood tests as indicated for glucose, liver function, electrolytes, and lipid profiles, particularly in individuals with substantial weight gain.

Anticonvulsants used to target mood instability such as carbamazepine, lamotrigine and valproic acid can occasionally be effective for aggressive behavior/SIB, and thus should be considered as second-line therapy.

3. Irritability, mood disorders and mania
Irritability is frequently seen in FXS and the reasons for this can be difficult to elucidate. Irritability may include negative reactions to interruption of perseverative behaviors or obsessions, work refusals, or generally oppositional interactions. SSRI's can be helpful in managing these irritable symptoms in higher functioning FXS if they appear to relate mostly to social anxiety, rigid behaviors, obsessions or to some extent perseverative behaviors. Start-low-go-very slow approach is associated with the fewest side effects, especially in lower functioning individuals with FXS. If SSRIs are not helpful or irritable behavior does not seem specifically related to anxiety or perseverative behavior, antipsychotics such as aripiprazole or risperidone can work well. Indeed, they are FDA-approved for irritability/severe temper symptoms in ASDs.
Irritability may also be a result of an underlying mood disorder, such as major depression or bipolar disorder, and can be a symptom of mania. A manic episode, according to the DSM IV-TR, is characterized by a persistent elevation of mood, or irritability with at least three of the following symptoms present persistently for at least a week: inflated self-esteem or grandiosity, physical agitation or increased goal-oriented activity, increased impulsivity, distractibility, decreased need for sleep, racing thoughts, and pressured speech. There can be associated psychotic features such as hallucinations or delusions. In individuals with FXS, mania and psychosis are very difficult to diagnose specifically, given difficulty defining symptoms such as grandiosity, goal-directed activity, hallucinations and delusions in patients with cognitive impairment. Further, many of the symptoms of mania may be chronically present at baseline in males with FXS. Mania is probably not mediated by any single neurotransmitter, but more likely involves several interacting alterations in neuronal activity. When true mania is suspected in a patient with FXS, or if the patient shows increased disinhibition and impulsivity on SSRIs, in a setting of unstable mood, treatment with mood stabilizers may be beneficial. It is noteworthy that bipolar switching on SSRIs includes not only a change in activity level as in the behavioral activation, but should also include a prominent change in mood, behavior, and impulse control. A prototype mood stabilizer is lithium carbonate, but anticonvulsants such as carbamazepine, lamotrigine, and valproic acid are used to target mood instability in bipolar disorder. All require careful monitoring of serum drug levels, blood indices, blood chemistries (i.e., thyroid and urine panel for lithium use, especially long term). Manic symptoms can also be treated with variety of 2nd [quetiapine (Seroquel ™), risperidone (Risperdal)], and 3rd [aripiprazole (Abilify ™)] generation antipsychotics. Nevertheless, there is no superiority of one over the other antipsychotic in terms of efficacy, which makes side effect profile/tolerance the reason for choosing a particular antipsychotic. It is currently unclear what proportion of individuals with FXS experience manic episodes or psychosis because may be difficult to distinguish between mania, impulsivity and severe hyperactivity. Absent a clear diagnosis, trials of different medications may be required to achieve adequate control of symptoms, especially when it is confusing as to the category into which symptoms fall. SSRIs usually aggravate symptoms of mood instability, especially mania (its most severe form), and SSRIs should not be used until mania symptoms have been stabilized for at least 6 months in patients with anxiety co-existing with mania. Some antidepressants (i.e., bupropion) might have less propensity to destabilize mood, but controlled clinical trials are lacking. Regardless, a manic reaction does not necessarily decrease with medication discontinuation, as activation does. Instead, it can linger longer or perhaps not go away at all unless treated aggressively with mood stabilizing medications. As it takes a while for the manic reaction to occur, it may take a while for it to go away.

4. Attention-Deficit/Hyperactivity Disorder
Attention-deficit and hyperactivity symptoms are the most prevalent problem behaviors in individuals with FXS. Individuals with FXS, especially males, have challenges in shifting and sustaining attention. Attention problems and response inhibition defects such as impulsivity
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are thought to be mediated by reduced dopamine activity in frontal cortical regions. The
mainstay of treatment for these problems is psychostimulant medication which exerts its
effects primarily by increasing dopamine transporter activity and dopamine levels in the brain.
Many different preparations of these medications exist, such as methylphenidate (MPH) family
(Ritalin™) or dextroamphetamine-based family (Dexedrine™ and Adderall™), which allows the
ability to tailor the optimal dosing regimen to the individual. The amphetamine family on
average carries a double potency over the MPH family (1:2 ratio when calculating the
equivalent dosage). Long-acting modified-release preparations typically are preferable as they
tend to minimize “peaks and valleys” in blood levels of the medications which can aggravate
mood lability in sensitive FXS individuals. Long-acting preparations also alleviate the disruption
to the school day associated with a visit to the nurse’s office for a midday dose. MPH and
dextroamphetamine-based stimulant families have slight differences in effects on brain
neurotransmitters and thus some patients do very well on MPH but have poor efficacy or
develop intolerable side effects on dextroamphetamines., and vice versa. Thus, it is generally
worth doing trials of both classes of medications before concluding that psychostimulant
treatment is not helpful.

The short-term efficacy of stimulant medications such as MPH is well established in children
with ADHD. In a single small placebo-controlled study in FXS (Hagerman 1988) results suggested
that methylphenidate was effective for attention span and improved social functioning in about
2/3 of 15 treated patients. About 70% of males with FXS treated with stimulants may have
improved attention and reduction in hyperactivity (Berry-Kravis 2004, Berry-Kravis. 2012);
however mood may become unstable at higher doses with increased irritability and agitation.
Patients may experience appetite reduction (sometimes a desirable side effect), or sleep
disruption. Some patients cannot tolerate stimulants at all due to aggravation of irritability,
aggression, or perseveration, or even induction of a depressive withdrawn state.

Atomoxetine (Strattera™), a selective norepinephrine reuptake inhibitor, may be tried for
attention problems in FXS. It can cause substantial aggravation of irritable behavior and
aggression in FXS and must be monitored carefully and discontinued if these side effects start
to occur.

Alpha-agonists including clonidine and guanfacine (and long-acting preparations Kapvay and
Intuniv, respectively) may also be useful where features of ADHD coexist with sleep disturbance
and anxiety states (Ingrassia 2005). These medications have been shown to be helpful for
hyperactivity in ADHD, and can also be quite helpful for hyperactivity, hyperarousal,
hypersensitivity to sensory stimuli, or ADHD comorbid with tics in individuals with FXS,
especially in younger children, and those with severe cognitive impairment, as well as those
who have had agitation or develop tics on stimulants.

Alternative pharmacological treatment of ADHD symptoms is sometimes considered. Folic or
folic acid may have a mild stimulant effect in very young children. There have been anecdotal
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reports and testimonials from parents saying that some children may benefit from its use in ADHD and FXS, but controlled trials in FXS have produced conflicting results (Hagerman 1986, Strom 1992).

L-acetylcarnitine (LAC), a nutritional supplement, was shown to have an apparent beneficial effect on hyperactive-impulsive behavior in boys with FXS and ADHD without side effects in a placebo-controlled trial. Specifically, a reduction of hyperactivity and improvement in social behavior were observed in patients with FXS treated with LAC, as determined by the Conners' Global Index Parents and the Vineland Adaptive Behavior Scale. Results from a single study suggest that LAC (20-50 mg/kg/day) may represent a safe alternative to the use of stimulant drugs for the treatment of ADHD in some cases for boys with FXS (Torrioli 2008).

Hyperactivity develops in about 75% of boys with FXS in the 4-10 year old age range, and often decreases with puberty. Hyperactivity often responds to psychostimulants as well. Hyperactivity may be partially mediated by the neurotransmitter norepinephrine, and can be treated with clonidine which may provide the added benefit of treating symptoms of aggression, anxiety, and insomnia (Hagerman 1995, Berry-Kravis 2004, Berry-Kravis 2012).

5. Repetitive and perseverative behaviors
Perseverative speech and actions, ritualistic behavior, constant chewing of clothing or other objects, hair-pulling, and a general love of routine and repetition are frequently seen in patients with FXS. Although obsessive-compulsive behaviors may be mediated predominantly by the serotonin system, perseverative repetitive behaviors and stereotypies may be more closely linked to dopamine systems. Thus, either SSRI's or antipsychotics (especially if associated with irritable behaviors) may be helpful for this category of behaviors. However, perseverative behaviors and stereotypies can be difficult to eliminate.

6. Sleep problems
Sleep problems are a frequent complication of FXS (Kronk 2010) and are most commonly caused by hyperarousal and inability to settle down either when trying to fall asleep in the evening or after awakening in the middle of the night (Turk, 2010). The first step in managing sleep problems should be implementation of behavioral strategies such as consistent bedtimes and sleep schedules, bedtime routines, and calming strategies for bedtime and middle night awakenings, however these strategies may be insufficient and may need to be combined with medication treatment. Melatonin has been successfully used to treat sleep problems in a subgroup of children with FXS and represents the most benign treatment. It is particularly useful for difficulties settling to sleep (sleep induction problems). There are extended-release forms available that may be more helpful if the problem is predominantly middle night awakenings. If melatonin is unsuccessful, alpha-2 agonists such as clonidine and guanfacine, trazodone, and quetiapine can all help with induction and maintenance of sleep. Of these
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options, clonidine has the fewest side effects and is usually tried first. It is noteworthy that the alpha-2 agonists can be associated with middle insomnia. In some instances, sleep problems are a symptom of underlying anxiety, which requires adequate non-pharmacological and/or pharmacological (i.e., SSRIs) treatment.

### Symptom Rating Scale

<table>
<thead>
<tr>
<th>Target Symptoms</th>
<th>Not a Problem</th>
<th>Is a Problem</th>
</tr>
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<tbody>
<tr>
<td>1. Anxiety</td>
<td></td>
<td></td>
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<tr>
<td>2a. Aggression</td>
<td></td>
<td></td>
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<tr>
<td>2b. Self-Injurious behavior (<em>e.g.</em> hand-biting, hair-pulling)</td>
<td></td>
<td></td>
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<tr>
<td>3a. Irritability</td>
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<td></td>
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<tr>
<td>3b. Mania (<em>persistently elevated mood or disinhibited behavior</em>)</td>
<td></td>
<td></td>
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<tr>
<td>4a. Attention Problems</td>
<td></td>
<td></td>
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<tr>
<td>4b. Hyperactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5a. Perseverative and stereotyped behavior (<em>rituals/insistence on routines/difficulty with minor changes in schedule or other things</em>)</td>
<td></td>
<td></td>
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<tr>
<td>5b. Repetitive motor or sensory activities (<em>e.g.</em> hand flapping or other motor stereotypies)</td>
<td></td>
<td></td>
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<tr>
<td>6. Sleep problems (insomnia or middle night awakenings)</td>
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</tbody>
</table>

Which symptom(s) is/are the biggest problem for your child/family: ____________________________


References:


Author note: This guideline was authored by Gudrun Aubertin, MD, Jeremy Turk, MD, Andrew Levitas, MD, Jeannie Visootsak, MD, Carol Delahunty, MD, and Elizabeth Berry-Kravis, MD, PhD, and was reviewed and edited by consortium members both within and external to its Clinical Practices Committee. It has been approved by and represents the current consensus of the members of the Fragile X Clinical & Research Consortium.

Funding: This project was made possible by Cooperative Agreement U01DD000231 from the Centers for Disease Control and Prevention to the Association of University Centers on Disabilities (AUCD) and RTOI 2008-999-03 from AUCD to W.T. Brown in support of the National Fragile X Clinical and Research Consortium. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The Fragile X Clinical & Research Consortium was founded in 2006 and exists to improve the delivery of clinical services to families impacted by any fragile X-associated Disorder and to develop a research infrastructure for advancing the development and implementation of new and improved treatments. Please contact the National Fragile X Foundation for more information. (800-688-8765 or www.fragilex.org)