A Medication Guide for Fragile X Syndrome

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This guide is intended as a resource for individuals, families, and clinicians navigating treatment options for Fragile X syndrome.

About this Guide

This guide is not a medical textbook and cannot take the place of a qualified physician. It is intended to serve as background information to help parents, caregivers and others to communicate with their physicians regarding medications. The medications described in this guide are to be used only under the supervision of a qualified physician; almost all are available only by prescription.

About the Author

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About FRAXA Research Foundation

FRAXA Research Foundation is a national nonprofit organization which supports medical research aimed at finding enhanced treatments and an eventual cure for Fragile X syndrome. FRAXA was founded in 1994 by Dr. Michael Tranfaglia, Katie Clapp, and Kathy May. FRAXA funds grants and fellowships for Fragile X research, publishes a newsletter and other informational materials, and organizes events around the country to raise funds and awareness. For more information, please visit www.fraxa.org.

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Introduction: Yesterday, Today, and Tomorrow

Since the first version of this Medication Guide was published, our understanding of Fragile X syndrome and neurodevelopmental disorders has expanded dramatically. In the 1990s and early 2000s, the field was in a period of explosive growth, as new psychiatric medications and neuroscience discoveries flooded into clinical practice. By 2009 (previous edition), we were already seeing the promise of research beginning to translate into real hope for individuals and families affected by Fragile X.

Today, that progress continues, but it has not been a straight line.

While the pharmaceutical pipeline for novel psychiatric medications slowed significantly in the 2010s, basic neuroscience research has accelerated at an unprecedented pace. We now have a much deeper understanding of how Fragile X syndrome alters brain development at the molecular and synaptic levels. Specific abnormalities, like excessive activation of mGluR5 pathways and dysregulated protein synthesis, have been clearly identified, offering new therapeutic targets. Research into the endocannabinoid system, the Ras-MAPK pathway, and GABAergic dysfunction has opened new doors for potential treatments.

Yet despite these breakthroughs, new medications for Fragile X have been slow to reach the market. Drug development remains costly, complex, and heavily regulated. Large-scale Fragile X-specific clinical trials remain relatively rare. Many promising compounds have struggled to cross the finish line to FDA approval, leaving families and physicians to make difficult choices about off-label medication use.

The past 15 years have also seen a revolution in the way we think about treatment goals. Rather than simply managing the most disruptive behaviors, there is now growing recognition that early intervention, targeted therapy, and even disease-modifying approaches are possible. New medications are being developed to improve not only behavior but also cognition, language, and overall development.

At the same time, experience with available medications has expanded. We know more today about which treatments truly help, which have hidden risks, and how to tailor interventions to the specific needs of individuals with Fragile X syndrome. Newer formulations of older drugs, such as extended-release alpha agonists, offer better tolerability and flexibility. Emerging therapies, including cannabidiol-based treatments, GABA-B agonists, and even repurposed statins, show real promise for addressing the underlying biology of Fragile X.

This 2025 edition of the Medication Guide aims to provide a clear, up-to-date, and practical reference for families, caregivers, and clinicians. It includes many newly available treatments, updates on older medications, and practical insights based on decades of clinical experience. The style remains intentionally conversational and opinionated: real-world treatment is never black and white, and understanding both the pros and cons of each option is essential.

We stand at the threshold of an exciting era. Treatments that modify the course of Fragile X syndrome, rather than just managing symptoms, are within reach. But even today, with the

medications we have, thoughtful, individualized treatment can make an enormous difference in the lives of people affected by Fragile X.

Knowledge is power. The more we understand, the better we can navigate this often-confusing world of behavioral medicine.

Trends in Psychiatry

Psychiatric medication use has gone through waves of enthusiasm, skepticism, and refinement over the past several decades. In the early 2000s, we saw an explosion in the prescription of atypical antipsychotics, SSRIs, and stimulants for a wide range of pediatric and developmental conditions, often without strong data to support their use in Fragile X syndrome.

In 2025, we find ourselves in a much more nuanced place. There is greater recognition that while psychiatric medications can be life-changing for some individuals, they are not a cure-all. Medication is best viewed as one part of a comprehensive treatment plan that includes education, behavioral therapy, speech and occupational therapies, and robust social support.

One ongoing challenge in psychiatry is what we might call "herd prescribing" where certain medications become popular based more on marketing, anecdotal success, or general clinical trends rather than strong scientific evidence. For example, we saw SSRIs prescribed to nearly every anxious child at one point, or Abilify given broadly for irritability despite major concerns about side effects.

However, progress has been made. There is now more demand for real data, especially in the Fragile X and autism communities, and more awareness of the risks of overmedication, especially in children and young adults. Clinicians are becoming more cautious, more personalized in their approaches, and more interested in the underlying neurobiology of disorders rather than just masking symptoms.

Another trend in 2025 is the return to older drugs with newer delivery systems or formulations. For example, extended-release versions of clonidine and guanfacine (Kapvay and Intuniv) offer much better tolerability and adherence than their older counterparts. Even SSRIs and stimulants are now being re-engineered for smoother dosing and fewer side effects.

We also see increasing off-label exploration of treatments rooted in newer neuroscience: cannabidiol-based therapies, GABA agonists, and anti-inflammatory or metabolic agents are being repurposed for neurodevelopmental use. This shift reflects the maturing of the field from treating behaviors in isolation to treating the biology underneath them.

All of this is good news for families navigating Fragile X. The field is moving away from "one size fits all" medication use, and toward thoughtful, flexible strategies grounded in both data and deep clinical experience.

Who Should Be Treated?

Of course, this is a matter of clinical judgment in each individual case. However, since parents often ask this question, it's worth outlining a few general guidelines.

The presence of symptoms likely to respond to currently available medications is usually considered a prerequisite. The *severity* of these symptoms is not always the most important factor; many symptoms respond to treatment whether mild, moderate, or severe. In practice, however, medications are often viewed as a "last resort" and are considered only after other strategies (such as behavioral or educational interventions) have been tried. As a result, we typically see more serious cases by the time medication is considered, even though treatment might be equally effective earlier.

If a medication existed that directly addressed the root causes of Fragile X, we would likely recommend it for all children with the condition, similar to the way insulin is prescribed for all children with type 1 diabetes. However, since no such definitive treatment yet exists, we must treat the symptoms we *can* address — much like treating the lung infections of cystic fibrosis with antibiotics. In psychopharmacology, we refer to these treatable symptoms as "target symptoms," and understanding this concept is vital for families who want to be active partners in care.

Age also plays a significant role. Most physicians are cautious about prescribing psychotropic medications to preschool-aged children, and it's rare for children under 3 to receive them. This is partly because research on very young children is limited, and physicians lack firm data about safety and effectiveness in this group. It's also more difficult to assess impairment concretely until a child enters school and is expected to function in social and educational settings.

The symptoms of Fragile X often change with age and sometimes even with the seasons. For example, anxiety is commonly seen in boys ages 2–4; hyperactivity typically emerges in the 4–10 range and may ease during adolescence. Aggression and severe emotional outbursts can appear at any age, though they may escalate in adolescence. These changes require flexible, individualized treatment plans, not a one-size-fits-all or lifelong medication regimen.

Parents often prefer to try non-medication approaches first, which is entirely reasonable. Techniques like behavior modification or sensory integration may be effective. Unfortunately, there are no robust outcome studies to determine how well or how long these therapies must be applied to succeed. Importantly, these approaches are not mutually exclusive with medication — indeed, in many psychiatric conditions, combining therapies with medication yields the best results.

A practical rule of thumb: if symptoms persist after six months of active therapy (e.g., PT, OT, or sensory integration), it may be time to consider medication.

The reality is that most males with Fragile X will be prescribed psychotropic medications at some point. Many females with Fragile X may benefit from them as well. This should not be viewed as a failure or a last resort. Psychotropic medication is not a substitute for love, therapy,

education, or family, but if used thoughtfully it can make all of those things more effective. Withholding treatment can sometimes be as harmful as overmedicating. The best results come from open minds, informed decisions, and experienced providers.

Who Should Treat?

What kind of specialist should families consult? Ideally, a neuropsychiatrist — someone trained in child psychiatry and experienced in treating developmental disabilities — is best suited for these cases. Neuropsychiatrists often have deep expertise in psychopharmacology, but they are quite rare and usually found only at major medical centers.

(Important note: Neuropsychiatrists are not the same as neuropsychologists, who are non-medical professionals with doctoral degrees in psychology. Neuropsychologists do not prescribe medication, though they may provide diagnostic testing.)

Child psychiatrists are somewhat easier to find (there are roughly 3,000 in the U.S.), but their training and focus can vary widely. Some specialize in psychotherapy and may not have experience treating developmental conditions. Others are very experienced with Fragile X and psychopharmacology. It's essential to ask specific questions ahead of time to gauge their comfort and expertise.

Developmental pediatricians specialize in the care of children with developmental disabilities and are often excellent at evaluating and managing behavioral challenges. However, not all prescribe psychiatric medications. Some refer to a psychiatrist or neurologist for medication decisions. Still, developmental pediatricians often serve as the main provider coordinating care, which can be especially valuable for families.

Pediatric neurologists are frequently asked to manage behavior in Fragile X and may bring useful insights, especially if seizures are present. Some are comfortable using a wide array of behavioral medications, while others stick to simpler regimens or focus on seizure management.

If none of these specialists are accessible locally, a consultation with a more experienced provider — perhaps in another city — may still be helpful. Your child's primary care provider can then handle follow-up and medication management, under the guidance of a consulting specialist.

Ultimately, the right provider is someone with experience in Fragile X (or closely related conditions), a willingness to listen and collaborate, and the humility to ask for support when needed.

Target Symptoms

The following discussion helps to describe the symptoms of interest to a treating physician and the general strategies for managing each medically in Fragile X. It is an old maxim in medicine that "we treat the patient, not the illness," and, keeping this in mind, you should remember that it is vital to view any patient as a whole. Parents and caretakers reading this information will recognize many of the symptoms described here; but when contemplating treatment, it is at least as important to know what a patient does *not* have, the so-called "pertinent negatives" of a case.

Each patient will have a profile of symptoms present and absent which will define his needs. The job of the treating physician is to select psychopharmacologic agents with a profile of activity that most closely matches the patient's needs. Parents can assist greatly in this process by carefully noting the exact symptomatology over time in a way that no doctor can do in a brief examination. This requires some knowledge of the kinds of symptoms doctors are interested in, how they are categorized, what causes them, and the many variations on the basic themes. The goal of this section is to help parents and non-medical caretakers do this essential job better.

Families and providers should define 2–3 core target symptoms before starting any new medication. This helps ensure that progress is measurable and that treatment goals are clearly understood.

Additionally, target symptoms should be evaluated over time. What is urgent at age 4 may not be relevant at age 14. Regular re-evaluation ensures that treatment remains appropriate as the child grows and changes. Remember, the goal of medication is not to "normalize" behavior but to improve comfort, function, and quality of life in meaningful ways.

Anxiety

Most Fragile X boys begin to show signs of intense and abnormal anxiety at a very early age, often in infancy. Sometimes this presents as excessive separation anxiety, young children becoming hysterical and inconsolable when a parent leaves even briefly. Almost all Fragile X boys have intense anxiety (although it sometimes presents as a tantrum) when they go somewhere unfamiliar or their routine changes significantly. It is important for parents to know that this is not "just the kind of anxiety everyone has now and then" and it is by no means produced voluntarily. This "difficulty with transitions" is very much a primal form of panic, a physiologic kind of anxiety which can be disabling for anyone, especially someone who also suffers from some cognitive impairment.

Some Fragile X girls display significant social anxiety, and this may or may not present with discrete panic attacks or depression. Keep in mind that anxiety disorders and depression are tremendously common in the general population; Fragile X in girls almost certainly increases the chance of developing these conditions, but fortunately these are among the most treatable of psychiatric disorders.

In either case, medications play an important part in the treatment of anxiety disorders occurring in Fragile X individuals. Many people ask whether medication is really necessary, whether some people might do as well with cognitive or behavioral therapies: while a minority of developmentally normal individuals with anxiety disorders can obtain long-term remission of symptom with these techniques, they clearly do not work as well as medications for the majority. People with severe or recurrent anxiety disorders virtually always require pharmacologic intervention to control symptoms, and Fragile X boys certainly fall into this category. In addition, the people who do best in cognitive/behavioral psychotherapy protocols tend to be the more intelligent, more motivated individuals with greater resources: a profile which does not fit the average Fragile X child.

This is not to imply that many non-medical techniques are not useful, but rather that they are often not enough. Remember that medications and non-medical therapies work together well. Medication will not interfere with psychotherapy, sensory integration, or speech therapy; it should help them to work better. The skillful combination of behavioral techniques, psychotherapy, and medication will virtually always yield the best result.

What causes anxiety in Fragile X syndrome? While no one fully understands the neural mechanisms underlying anxiety, psychiatric researchers have made great advances over the past 10-15 years, so that now we can at least have a working knowledge of the neurobiology of anxiety. Starting again with the evolutionary perspective, we can easily see the importance of fear in nature: the world can be a dangerous place, and we must, for our own survival, know this instinctually right from the start of life. All animals are innately capable of experiencing fear; generally speaking, fear emanates from the more evolutionarily primitive parts of the brain, the parts that look more or less alike in mice or men. The higher parts, like the cortex, seem to suppress this activity. You could even argue that one of the great benefits of our developing this huge, complex brain of ours is that it allows us to overcome our instinctual fears so we can evolve culturally, not just genetically.

We have already mentioned that the brain has a built-in alarm system, the *locus ceruleus*, and that we already know that directly stimulating this formation will produce a classic panic attack. We theorize that this is essentially preparing the brain and body for conflict. So what is the difference between this primal fear and what we call anxiety? Probably not much. Most people think of anxiety as an intrapsychic phenomenon: the result of internal conflict, not a genuine external threat. This concept has been heavily influenced by generations of psychoanalysts who focused primarily on intrapsychic conflict as the primary origin of psychopathology. However, it has more recently been found that anxiety disorders are not related to the sort of everyday anxiety most of us experience. Anxiety disorders are most likely the result of this primal fear surfacing at inappropriate or unexpected times. Much of the anxiety that Fragile X children experience is understandable in these terms. Additionally, one of the core features of Fragile X (and most autism spectrum disorders) is **cognitive rigidity**: the inability to shift from one mental activity to another. This makes it harder for people with Fragile X to adapt to changes in the environment; when things do not go as expected, the individual can feel anxious or upset.

Most Fragile X parents first notice an abnormal amount of anxiety in their children early on, sometimes in infancy. Typically, this is seen as exaggerated separation anxiety, with the child

becoming panicked whenever the parent gets too far away. These children can be inconsolable and upset beyond all reason; yet, it is tempting to say that they are "spoiled" or somehow trying to "manipulate" the parent. All amateur psychoanalysis aside, this kind of behavior is most certainly not voluntary, nor even controllable. This is primal fear uninhibited by the usual cortical input that would tell most children, "Mommy is coming right back" or "Daddy is just going to get your bottle". Because the Fragile X child is slower to develop the advanced circuitry of the cortex, the "thinking" part of the brain, he has fewer resources to draw on in a difficult situation, and separating from a parent can be a difficult situation for any child.

Likewise, most children experience stranger anxiety at a certain stage of development, instinctively fearing people they do not know, regardless of how dangerous they really are. Eventually, most children learn from family members how to judge other, unfamiliar people. The higher areas of the brain override instinctual fear through learning and conditioning. However, if this is slow to occur or incomplete, persistent social anxiety can result.

This is also a type of anxiety frequently seen in Fragile X children, one that can cause great social impairment and difficulty with reciprocal interactions. Not only new faces, but also new situations can cause anxiety. Change is inherently stressful, and children normally crave routine at certain stages of development, presumably to minimize the resultant anxiety. In keeping with the previously noted pattern, children with Fragile X can be exquisitely sensitive to changes in routine, or new situations. Reaction to these stresses can range from simple shyness, to panic, to full-blown tantrums. Parents (and certainly onlookers) might think the child simply does not want to do something, but the extent and the irrationality of the reaction argues for a different interpretation: this primal fear has once again been triggered, and the rest of the brain is unable to suppress it.

The cortical inhibition we refer to comes in many forms (chemically speaking), but one of the most important forms comes via the "serotonin system", the brain's primary regulator of moods and affect. This network of cells acts like the brain's automatic transmission, shifting gears without thinking to meet the demands of the environment, automatically setting our mood to fit the current situation. High levels of the neurotransmitter serotonin powerfully inhibit the *locus ceruleus* (the alarm system) and result in a sense of calm and contentment. Low serotonin sets a very different tone for the brain, leaving one feeling irritable, unhappy, anxious, or even aggressive. In other words, serotonin sends the signal that everything is OK and we can all relax; no serotonin means something is not right, and we'd better do something about it.

It is thought that derangements of this serotonin system underly most anxiety disorders and depression, and the ability to manipulate brain serotonin has been one of the great accomplishments of modern psychiatry. The medications which make this possible are called Selective Serotonin Re-uptake Inhibitors, or SSRIs; they are marketed under the trade names including Prozac, Zoloft, Celexa, Lexapro, and Luvox. They all work by blocking the inactivation (re-uptake) of serotonin at the synapse (neuronal junctions), thereby increasing the effect of the naturally occurring neurotransmitter. Other types of "antidepressant" medications do this also; the revolutionary thing about SSRIs is that this is all they do: they are pharmacologically pure and have no true side effects. What side effects they have in practice are simply the result of doing this one thing everywhere in the body.

Antidepressants in general, and the SSRIs in particular, can be quite helpful in the management of anxiety in Fragile X individuals of all ages. They offer the possibility of treating these various forms of anxiety cleanly, without the cognitive impairment usually associated with tranquilizer-type anti-anxiety medications (Valium, Xanax, et al.); indeed, they can enhance attention and concentration. Older antidepressants such as imipramine and nortriptyline must be used with caution, however, since they can cause many serious side effects, including changes in cardiac conduction. They also affect other neurotransmitter systems which we are not targeting, causing so-called anti-cholinergic effects like blurry vision and dry mouth; in especially vulnerable individuals (like children with Fragile X) they can even cause confusion, memory impairment, or delirium. This safety advantage alone probably explains why most child psychiatrists favor the SSRIs over the older drugs. But these newer medications will likely prove more effective as well, though large-scale comparison studies in children are lacking.

Clonidine and other centrally-acting alpha2 agonists, effective as they are in reducing CNS hyperarousal, can have some weak anxiolytic (anti-anxiety) effects. They can be combined safely with antidepressants to yield a greater effect, if needed.

Beta-blockers such as Inderal (propranolol) have been used by some child psychiatrists to treat anxiety disorders, but there is little research to support this; it has been conclusively shown that these medications are largely ineffective in serious anxiety disorders in adults, and these are not entirely benign medications.

Buspirone (BuSpar) is a novel anxiolytic with weak antidepressant and antiobsessional properties. While it can help with some forms of anxiety, especially social anxiety, it is not effective against panic anxiety. It is also short-acting, requiring multiple daily doses.

Again, at least as important as the medications to consider for the treatment of anxiety are the ones to avoid. Stimulants will invariably exacerbate anxiety in a dose-dependent fashion; they can often be used at lower doses to enhance attention, but children should be monitored carefully for a possible increase in anxiety. Minor tranquilizers (benzodiazepines like Valium and Xanax), which are commonly used to treat anxiety in the general population, are generally counterproductive in Fragile X individuals. All of them impair concentration, attention, memory, and motor coordination; they can lead to behavioral disinhibition — inappropriate behavior secondary to intoxication — or to *paradoxical excitement*, a state which is anything but tranquil.

The important point to remember is that Fragile X individuals as a group do not respond to these medications in the usual way. Major tranquilizers (anti-psychotics like Thorazine or Haldol) are fortunately and deservedly out of favor as treatments for any kind of anxiety, and should be avoided at all costs, since they can cause severe side effects and do very little to relieve anxiety. Nevertheless, some backward clinicians still believe that developmentally disabled individuals require the strongest possible "tranquilization" to keep their behavior in check, and thus these drugs are still prescribed to non-psychotic individuals, despite a lack of any evidence of efficacy.

Attention Deficit and Hyperactivity

Many parents are familiar with the term ADHD — Attention Deficit Hyperactivity Disorder — and it is often said that upwards of 75% of Fragile X boys have this disorder. This is not true. It is technically impossible for anyone with Fragile X syndrome to have ADHD, simply because anyone with known Pervasive Developmental Disorder is excluded from the diagnosis, and virtually all Fragile X boys have PDD. Hyperactivity and attentional problems are simply a basic part of Fragile X and many other developmental disorders.

Since ADHD is a diagnosis, not a disease, it is not surprising that it is seen in many forms and thought to have many causes. In Fragile X individuals this same heterogeneity holds true: many are quite hyperactive but seem able to concentrate when especially interested; others are rarely hyperactive (or "hyperkinetic") but still have difficulty attending. Attention deficit and hyperactivity can properly be considered two distinct symptoms which interact significantly and are often, but not always, seen together. Indeed, these two symptoms can be treated separately, pharmacologically dissected; therefore, they will each be discussed separately.

This is an appropriate time to discuss the differences between boys and girls with Fragile X, since these differences are most apparent with regards to the treatment of ADHD-like symptoms. It is well known that the average boy with Fragile X is more severely affected, especially cognitively, than the average girl with Fragile X (full-mutation female). However, given the variability of expression of Fragile X, it is possible that some girls will be more severely affected than some boys. In other words, some girls can present with classic, full-blown Fragile X syndrome; the approach to the treatment of this subset of girls is essentially the same as that for typically-affected boys. Typically-affected girls are mildly affected, most likely showing learning disabilities, ADHD-like symptoms, and possibly anxiety or mood disorders, all of which are quite treatable. Conversely, some Fragile X boys (usually mosaics) have surprisingly little impairment, and for psychopharmacologic purposes can be considered equivalent to Fragile X females. Typically-affected girls will usually be quite a bit less sensitive to the adverse psychiatric effects noted below and can ordinarily be considered similar in treatment responsiveness to the general population. So, if parents of a Fragile X girl or an unusually mildly-affected boy see side effects listed for stimulants, such as anxiety or aggression, they should keep in mind that their children are likely far less sensitive to these effects than the typical Fragile X male.

Attention Deficit

Males with Fragile X typically have difficulty paying attention, although this does not mean they cannot find some activities quite engrossing (i.e. watching a favorite TV show, playing with a certain toy). Some full-mutation females also have problems in this regard, usually showing up as difficulty in school. The problem is not that they cannot ever pay attention; the problem is not that they do not want to pay attention; the problem is that they have trouble on a basic level shifting and sustaining attention the way most other people do.

Attention is a very important and complex neural function that we are only beginning to understand. A large part of the brain, especially in the frontal lobes, is devoted to attentional mechanisms: it is easy to see why if one considers the importance of this basic function to the survival of the individual. Our brains are capable of performing some sophisticated tasks, but only if we can focus on the task at hand and ignore distractions. However, if we focus too much we are not alert to our surroundings and are vulnerable to many dangers in the environment. Evolution has developed for us a rather elaborated mechanism which enables us to focus when we need to, yet still maintain a watch, just in case. This represents a rather tricky balancing act: focus too much and you could literally be eaten alive, focus too little and you'll never get anything done. A delicate balance like this is easily disrupted, so it makes sense that a global neurodevelopmental disorder like Fragile X would cause some problems here. In this section we consider the effect of too little focus: attention deficit. Later we discuss the effect of too much focus: obsessive-compulsive behavior.

These attentional mechanisms in the frontal areas of the brain are thought to utilize dopamine as a primary neurotransmitter. It is thought that subtle deficiencies in this "dopaminergic" system can impair the ability to attend or to shift attention appropriately. Naturally, if a person is unable to pay attention appropriately in a given situation, he may become bored, restless, fidgety, or even disruptive. In this manner, it is theorized that some individuals with attention deficit become secondarily hyperactive, while others might just daydream and become somewhat socially isolated. Other theories of ADHD at large dispute this point, and at the very least it is a gross oversimplification. Nonetheless, individuals with Fragile X do show this type of attentional problem and enhancement of this dopamine transmission does seem to help.

The mainstay of treatment for attention deficit is the use of psychostimulant medication. These are medications virtually every parent has heard of, like Ritalin and Adderall (along with generic and newer time-release equivalents). Their use is widespread in the general population and in the treatment of Fragile X syndrome as well; millions of children and adults worldwide are prescribed stimulant medication safely and effectively. However, there are some particular precautions to be observed in treating Fragile X individuals with stimulants. These will be discussed later.

Psychostimulants will increase virtually anyone's attention and focus in a direct, dose-dependent fashion. Response to stimulants is neither specific to, nor diagnostic of, ADHD. You could even say that these medications are the ultimate in "cosmetic psychopharmacology", since most people can derive some enhancement of cognitive function from them. This is evident in the current fad in diagnosing adults with ADHD, including many with no history of childhood academic difficulty. This also explains why psychostimulants are highly controlled substances with significant abuse potential. While medically supervised use in treating attentional problems in school-age children rarely results in any form of dependence (because doses are too low), the illicit use of amphetamines can result in powerful addiction and numerous psychiatric side effects. Therefore, the use of stimulant medication should neither be taken lightly nor feared unnecessarily.

Although the abuse potential of psychostimulants is generally not a problem for Fragile X children, the attendant regulation of their prescription can be a bit of a hassle. Ritalin and

Adderall, the most commonly used drugs in this class, are both schedule II controlled substances — just like morphine or Dilaudid. In most states one can only receive a 30-day supply of medication, with no refills; identification is necessary to pick up a prescription, so only the parent can do this; usually, the written prescription (no phone-in's allowed) must be filled within 3 to 7 days, expiring thereafter. This is only an inconvenience, but a potentially major one, and it does often result in interruption in therapy.

Since all these medications increase the ability to "focus" on a cognitive task in a dose-dependent fashion, it is possible to become "over-focused", i.e. to get too much of this effect. Sometimes this results in problems with reciprocal social interaction, or just with the normal spontaneity we all associate with childhood. In practice, these are rarely problems for Fragile X children; instead, this may manifest itself as perseverative or "obsessive-compulsive" behavior in the Fragile X population. The anxiogenic (anxiety-inducing) side effects of these medications may also cause an increase in panic anxiety, social anxiety, difficulty with transitions, and other types of anxiety frequently seen in Fragile X. This effect usually limits the use of these medications to relatively low doses.

Another significant psychiatric side-effect of stimulants is aggression. Here again, the effect is neither specific to nor limited to ADHD or Fragile X. Anyone will get more aggressive if given a large enough dose of a psychostimulant (methamphetamine addicts are the stereotype here.) Fortunately, in most cases the dose required to produce aggression is much higher than usual therapeutic doses. Unfortunately, Fragile X individuals are usually much more sensitive to this effect than the average person, often limiting the usefulness of stimulants. Typically, Fragile X individuals will experience an increase in aggressive behavior at or near the therapeutic dose range; this can be an especially severe problem if the individual already displays a significant amount of aggression and should be considered a "relative contraindication".

As a result of these limitations, many clinicians have recognized an acute need for other methods to enhance attention in individuals with developmental disorders, especially Fragile X. In the first part of this section, we noted the alternative strategy of treating hyperactivity and hyperarousal selectively. This is often the most effective approach and is discussed at length in the next section.

However, psychopharmacologists have more recently become aware of other medications besides stimulants which enhance attentional mechanisms. In particular, the antidepressant class of drugs appears especially promising. While older antidepressants such as desipramine, imipramine, and nortriptyline have been used for many years to treat ADHD, recent concerns about their safety have led to a shift toward newer agents. Bupropion (Wellbutrin), venlafaxine (Effexor), and now atomoxetine (Strattera) all appear to selectively enhance attentional mechanisms in children with ADHD or Fragile X, with relatively little effect on hyperactivity or level of arousal. Other medications sometimes used (though with less certain results) include amantadine (Symmetrel), which increases frontal dopamine activity; folic acid, once thought to be a specific treatment for Fragile X, but now thought to work (at very high doses) for some individuals as a weak psychostimulant; or even caffeine, the most widely used psychostimulant of all, which may be useful as test medication to gauge the potential effects of more potent stimulants like Ritalin.

Drugs to be avoided when attentional difficulties are prominent include all tranquilizers, both major (the antipsychotics) and minor (the benzodiazepine anti-anxiety drugs), as well as some of the anticonvulsants (especially phenobarbital). All of these can significantly impair attention, concentration, and memory. Fragile X individuals appear even more sensitive to these effects than most people.

Hyperactivity/Hyperkinesis

The near universal presence of hyperactivity in Fragile X boys is thought to result from central nervous system hyperarousal; in other words, Fragile X children may not be able to properly integrate sensory stimuli, resulting in frequent "overstimulation" and behavioral dyscontrol. Once again, there are specific mechanisms in the brain for regulating the overall level of arousal or alertness. This is obviously another important function from an evolutionary standpoint, and one which is clearly linked to attention: too much or too little arousal can easily disrupt attention and make it impossible to focus on the task at hand. These mechanisms for regulating arousal are thought to reside in the so-called activating formations of the brain located in the brainstem and midbrain, the evolutionarily "primitive" areas that we share with all other vertebrate animals. This includes the "fight-or-flight" center and other areas which regulate heart rate, breathing, blood pressure, and other autonomic functions of the body.

Recent research has noted a particular connection between eye contact and hyperarousal in Fragile X boys, who may become physiologically hyperaroused simply by rather benign eye contact from adults. This report is quite consistent with previous observation by animal behaviorists that eye contact with predators causes powerful hyperarousal, and that even dominant members of the same species can "stare down" younger, submissive animals. This response appears quite basic and primitive, as well as universal, and is inhibited by the "higher areas" of the cortex. It is possible that Fragile X boys simply do not have enough of this calming inhibition as a result of impaired development, but that we can enhance this function pharmacologically.

One of the primary neurotransmitters in this system is norepinephrine (also called noradrenaline); in fact, more than half of all the neurons using norepinephrine in the brain are contained in one small formation, the *locus ceruleus*. It turns out that this anatomical formation of relatively few cells is the "fight-or-flight" center, the brain's own alarm system. If the locus ceruleus is electrically stimulated it will produce an immediate panic attack. This alarm system has connections to most other parts of the brain, and its output controls much of the sympathetic nervous system in the rest of the body. Not surprisingly, most of the strategies used to modify the hyperarousal and hyperactivity so often seen in Fragile X target this system.

As previously mentioned, "antidepressant" medications have been used extensively in the treatment of ADHD, so it is not surprising to learn that all antidepressant medications have one thing in common: they cause a "downregulation" (decreased density) of one important class of norepinephrine receptors (beta receptors) in the brain. This may explain why they can help with hyperactivity as well, although this is not fully established yet. In any event, the effect in Fragile

X is rather subtle, and often not adequate by itself to control severe hyperactivity, especially when less sedating medications are used.

A more powerful and selective way to decrease this hyperarousal is to directly inhibit the activity of the locus ceruleus and its "noradrenergic" transmission. This is actually a popular way to control high blood pressure, too, and a whole class of medications has been developed for this purpose and so are widely available for our use. This class is generally referred to as alpha-2 agonists, since they activate the alpha-2 subclass of norepinephrine receptors which inhibits the firing of norepinephrine-containing neurons. Clonidine (Catapres) is the prototype of the class and has been extensively used in psychiatry. Newer drugs such as guanfacine (Tenex) and guanabenz (Wytensin) may work as well or better, but psychopharmacologists have generally not had as much experience with them. These medications are extraordinarily potent in decreasing this "sympathetic outflow", as well as many cognitive aspects of hyperarousal. (They are also used to decrease the nightmares and flashbacks seen in Post-Traumatic Stress Disorder). Despite their potency, they are proven quite safe for very long-term administration, and are generally well tolerated, although children with Fragile X typically experience much sedation when starting these medications, or when increasing the dose. A long-lasting skin patch form of clonidine (Catapres Transdermal Therapeutic System-TTS) can decrease side effects and aid in compliance, since it lasts for 3-7 days and releases the drug constantly and gradually.

As mentioned in the previous section, stimulants can help secondarily with hyperactivity by enhancing concentration and attention, and they can be combined with clonidine or antidepressants if necessary for greatest effect. However, they are anxiogenic (anxiety-producing) and can worsen or cause aggression, effectively limiting their use to much lower doses than those prescribed for run-of-the-mill ADHD. Since there is no evidence that Fragile X children are more sensitive than other children to the therapeutic effects of psychostimulants, as they are to the side effects, it stands to reason that parents cannot expect dramatic beneficial effects from these medications; rather, mild improvement is most typical.

Irritability

Irritability can be thought of as the flip side of depression. When most people think of depression, they think of feeling down or blue; just as often, however, people who are depressed are irritable or grouchy. Extreme irritability is often a problem in Fragile X syndrome, and we can best conceptualize this as a disorder of mood. People with Fragile X do seem to have a problem with the serotonin system, the brain's mood-regulating mechanism, and this often results in unstable (labile) moods, with rather sudden shifts from one extreme to another. This, too, can be viewed as a failure of development. Children in early stages of development normally have relatively unstable moods (at least by adult standards); as they develop, this mood-regulating system gradually smoothes things out to such an extent that we take stable moods for granted. However, for Fragile X children this aspect of development, like many others, does not seem to proceed according to plan, leaving them especially susceptible to wild fluctuations in mood. Often, this "switch" appears to be spontaneous, or brought on by only the slightest provocation. Once again, parents and family need to remember that this is not voluntary or intentional, that the

child is not "pitching a fit" to get his way. This is simply a manifestation of the affective (mood) instability which is an intrinsic part of Fragile X syndrome, and it can be treated.

Since we conceptualize this irritability and affective instability as related to depression, and presumably involving dysfunction of the serotonin system, we might anticipate that antidepressant medications could improve this particular situation. In fact, this turns out to be quite helpful, and once again the SSRIs seem to be the best-tolerated alternative. Normal adults who take these medications for a variety of reasons most often describe the effect of SSRIs in exactly these words: "Things just don't seem to bother me as much anymore." This is precisely the effect we are hoping for when prescribing SSRIs to people with Fragile X syndrome, and this does seem to be the effect in most cases.

Other medications can help with irritability as well. Clonidine (and similar medications) can decrease irritability by limiting hyperarousal and overstimulation, but many parents find that higher doses or peak levels right after an oral dose can cause increased irritability, probably by causing excessive sedation and confusion. This is one reason why the clonidine patch is often a superior method for administering this medication. There are never any peaks or troughs; just constant, gradual absorption of the drug through the skin.

BuSpar (buspirone) is marketed for treatment of anxiety, but also has some antidepressant effects, and can help with irritability, too. Since it is less convenient and probably less effective than the SSRIs in this situation, it should be considered a second-line treatment option.

Individuals with significant irritability should avoid higher doses of psychostimulants, which may make matters worse. Even caffeine can exacerbate irritability, so monitor dietary intake. Here again, tranquilizers (both minor and major) are not especially effective and may be counterproductive; they should not be considered a routine treatment for this target symptom.

Mania

At the opposite end of the mood disorder spectrum from irritability and depression is mania. We often think of mania occurring primarily in adults with manic-depressive illness (bipolar disorder), but a surprising number of children with developmental disorders present with a bipolar type of mood disorder, experiencing highs and lows as well as mixed states in between. Mania is usually not hard to recognize, although in Fragile X it can be difficult to distinguish from the commonplace severe hyperactivity. Mania is a persistent elevation of mood, accompanied by increased motor activity, increased impulsivity, decreased need for sleep, and (in extreme cases) psychotic thought processes. It is sometime described as "losing touch with reality".

The neurobiology of mania is not well understood, even though this phenomenon has been observed for thousands of years; but it is thought to arise from dysfunction of the "limbic system", a large, interconnected group of formations in the brain apparently responsible for controlling the full range of emotions. This is not a single-neurotransmitter system, but rather an

anatomical array of cell clusters which seem to function together electrically to register and express emotion. This is also an evolutionarily primitive part of the brain, one which we share with many other animals, but which is far more complex in humans.

Since this system does not rely on any one primary neurotransmitter, the approach to pharmacotherapy of mania is somewhat different. The mainstay of treatment is the use of so-called mood stabilizers, drugs which have the net effect of electrically stabilizing the limbic system. This class of drugs includes lithium, carbamazepine, valproic acid, and clonazepam. Lithium is actually not a drug, but a simple salt which was serendipitously discovered to have mood stabilizing effects. The others all started out as anticonvulsants (anti-seizure medicines) and were subsequently found to have beneficial psychotropic effects probably directly related to their ability to stabilize the electrical activity of the limbic system. Not all anticonvulsants have this effect; phenytoin (Dilantin) and phenobarbital act primarily on the cortex and do very little in the limbic areas of the brain. Consequently, they are not effective as mood stabilizers. Since 10-20% of Fragile X boys have seizure disorders and many are treated with anticonvulsants, it makes sense to use one of the anticonvulsants with beneficial psychotropic effects where appropriate. Killing two birds with one stone is good psychopharmacology.

Mania is one of the few symptoms which justifies the use of major tranquilizers (antipsychotics) in Fragile X syndrome. A short course of an antipsychotic (also called neuroleptic) can help to control mania, although a mood stabilizer alone will often do the trick and is a better long-term solution.

One important consideration in the evaluation of mania is the possibility that the condition could be drug-induced (iatrogenic). The major drawback of the use of antidepressants in Fragile X syndrome is the possibility of manic activation. In studies of antidepressants among the general population, the occurrence of mania during treatment with antidepressants is only about 1-2% — not much of a risk. However, children in general — and Fragile X children in particular — seem to be much more susceptible to this adverse effect; in this population manic activation may occur as much as 10-15% of the time when antidepressants are used. In most cases discontinuation of the offending agent will resolve the mania, but in some cases use of a mood stabilizer is necessary to restore normal mood (euthymia).

Children who have shown this "bipolar" course of illness, or who have had manic episodes when given antidepressants should probably be considered for a trial of buspirone (BuSpar) if the need arises for treatment of irritability, anxiety, or aggression. This medication can be effective for these target symptoms and seems to entail much less risk of manic activation than SSRIs or conventional antidepressants. Many physicians, including psychiatrists, consider buspirone to be generally ineffective; however, numerous studies support its use in the developmentally disabled population and demonstrate consistent efficacy without significant adverse effects.

Medications to be strictly avoided in Fragile X children with a known susceptibility to mania include all psychostimulants. Ritalin, Dexedrine, Adderall, and even caffeine have all been reported to cause agitation, hypomania, mania, or even frank psychosis in this subgroup. This is generally true throughout the population, but children seem more sensitive, and Fragile X children appear to be especially sensitive. Remember that stimulants can be quite helpful for

some children with Fragile X; this is simply one criterion used to decide which children might be most likely to benefit, and which are most at-risk for adverse effects. Keep in mind also that FMR1 is only one of thousands of human genes; the rest of an individual's genome determines much of his or her susceptibility to disease, or response to pharmacotherapy. So, family history of other psychiatric disorders is still an important factor in determining treatment for a Fragile X individual, and your doctor needs to know this information, too.

Obsessive-Compulsive Behavior

Perseverative speech, ritualistic behavior, constant chewing of clothing or other objects, and a general love of routine and repetition are frequently noted traits of people with Fragile X syndrome. These traits have been noted in all age groups, far more often in fully-affected males. While the specific behaviors vary greatly from one person to another, these are all often categorized as obsessive-compulsive behaviors, because of their similarities to aspects of *obsessive-compulsive disorder* (OCD), one of the major anxiety disorders in the general population. Here again, we draw an analogy between specific symptoms of Fragile X and a discrete disorder seen in developmentally normal people as a way of understanding some of the basic pathophysiology of Fragile X. Unlike Fragile X, OCD has been the subject of enormous amounts of medical research; therefore, even though our knowledge of OCD is far from perfect, we know much more about the basic mechanisms underlying OCD, and many useful inferences can be derived from the comparison of the two disorders.

In fact, many other disorders are thought to share features of OCD, including eating disorders, kleptomania, compulsive gambling, and trichotillomania (compulsive hair-pulling). Many people with Tourette's syndrome, a major neuropsychiatric disorder characterized by motor and vocal tics, also display severe OCD. Frequent comparisons are made between autism and OCD, and many of the OCD-like symptoms seen in Fragile X are also common in autistic children. Since few Fragile X individuals would qualify for the formal diagnosis of OCD, we will simply refer to "O-C behavior" or "O-C symptoms".

A true obsession is technically required to be *ego dystonic*, or upsetting and unpleasant to the individual. In this sense, much of the perseveration experienced by FXS children does not qualify because they often derive hours of enjoyment from their "obsessions". However, a common etiology may well underly both phenomena. It is theorized that both arise from an inability to inhibit certain types of thoughts originating in the "planning centers" of the brain, particularly in the frontal lobes. The idea is that thoughts in the brain buzz around through circuits of neurons, which often feed back on themselves, forming a continuous loop. Psychosurgery has even been used to treat particularly intractable cases of OCD, with surprising success (though definitely not appropriate for anyone with Fragile X). Normally, a great deal of inhibition is provided to keep these feedback loops from getting out of control. Much of this inhibition comes via the serotonin system, but in a different part of the brain from the areas which regulate moods and anxiety. Thus, it is thought that hypofunction of this branch of the serotonin system results in OCD, and this has been confirmed in numerous research paradigms: enhancing serotonin improves OCD, decreasing serotonin worsens it consistently.

As one might expect, then, the SSRIs are particularly effective for treating this class of target symptom, just as they are the treatment of choice for bulimia, OCD, trichotillomania, and a variety of other conditions in the general public. The non-selective serotonin re-uptake inhibitors, clomipramine (Anafranil) and venlafaxine (Effexor), are also quite effective in this regard, however with somewhat more side effects and less convenient dosing. Clomipramine, in particular, has been used extensively in the developmentally disabled population with well-documented efficacy.

A good response to these medications can include a dramatic decrease in perseverative behavior, less chewing or mouthing, more fluent and relevant speech, elimination of ritualistic behaviors, and generally greater flexibility with fewer catastrophic reactions to changes in routine. As mentioned in the section on mania, however, some Fragile X children cannot tolerate the activating effects of antidepressants, and for this subgroup the novel anxiolytic buspirone (BuSpar) can be effective for O-C symptoms, though usually only at high doses, without any apparent risk of activating mania. Another unique medication, fenfluramine (Pondimin), which acts as a serotonin agonist, has been investigated in treating autistic individuals, for the same reasons SSRIs are recommended for so many of the symptoms discussed previously. However, results have been equivocal — perhaps because of the heterogeneity of autism — and this medication seems to have far more side effects than SSRIs. It is a controlled substance with some potential for causing dependence, and there have been reports of tolerance developing to the therapeutic effects in some individuals who experience a good initial effect. There have also been no specific reports of its use in Fragile X syndrome, so it cannot be recommended, especially with a safe and effective alternative like an SSRI available.

Individuals with Obsessive-Compulsive type symptoms should avoid stimulant drugs, especially at high doses, as well as caffeine; their anxiogenic effects can be expected to consistently worsen this type of target symptom. Hyperkinetic children with Fragile X can be treated with one of the centrally acting alpha-2 agonists (clonidine, Tenex, etc.) if concomitant O-C symptoms preclude the use of stimulants; these agents appear to augment the effects of anti-obsessional medications in addition to decreasing hyperarousal. Antipsychotic medication was often prescribed inappropriately in the past for all types of people with OCD or O-C symptoms, usually with little effect; this often meant that doses would be increased to dangerously high levels before considering the trial a failure. Fortunately, the increasing awareness of OCD today makes this less likely; however, the developmentally disabled have always been at greatest risk for this kind of mistreatment, and presumably this will not change overnight. Beware of any physician recommending antipsychotic drugs as first-line treatment for these symptoms.

Aggression and Self-Injurious Behavior (SIB)

One of the more frequent reasons for Fragile X males to be hospitalized or even institutionalized is the common occurrence of aggressive or violent behavior. This seems to be confined to males and more severely affected females. It should be emphasized that not every Fragile X male has the potential for aggressive behavior, but when it occurs, it can and should be treated. Improvements in the treatment of aggression over the last 10-15 years have been especially

dramatic; whereas few effective drugs existed then, this target symptom can be considered readily treatable nowadays.

Aggression in Fragile X males is sometimes seen at an early age, often closely associated with intense anxiety. Some parents note this behavior as early as 2-3 years of age, when the greatest concern is often for the safety of siblings. However, adolescence is strongly associated with an increase in aggressive behavior, which is even more alarming when these boys rapidly gain size and strength. It is generally assumed that increasing testosterone levels during puberty underlie the timing of this effect. Testosterone increases aggressive behavior in experimental animals, as well as in athletes abusing anabolic steroids for muscle-building. It is likely that most Fragile X individuals are more vulnerable to inappropriate aggression by virtue of the aforementioned serotonergic dysfunction, but that pubescent fluctuations in androgens (male hormones) are most likely to precipitate problems.

Much recent research has shown that certain types of violent behavior, especially involving episodic dyscontrol rather than calculated or sociopathic violence, are strongly correlated with low levels of serotonin metabolites in cerebrospinal fluid (CSF), suggesting a decrease in brain serotonin levels. Curiously enough, a similar finding suggests that low levels of brain serotonin — serotonergic dysfunction — is quite common among people who commit suicide. Studies in the developmentally disabled population of mixed samples of different ages and diagnoses show that self-injurious behavior is likewise strongly associated with low levels of brain serotonin. It looks likely that violent behavior is biologically similar, whether directed at self or others. This is a surprising finding which contradicts many earlier hypotheses. Studies of CSF levels of serotonin metabolites (like 5-HIAA) have not yet been done in Fragile X, but they should be and hopefully will be.

By now, just about everyone has heard the "Dogs on Prozac" story: self-injurious behavior is remarkably common among dogs and other animals kept penned up for too long. Dogs will often bite themselves incessantly, inflicting great harm and causing a major problem for veterinarians. Some ingenious veterinarians have been using SSRI antidepressants with great success to stop this behavior. Interestingly, the predisposition to this type of SIB is reported to vary widely among different breeds of dogs, illustrating the strongly genetic basis for this trait.

If this text is starting to read like "The Serotonin Story", rest assured: there are certainly many other neurotransmitter systems involved in Fragile X symptoms. Psychiatry has simply begun to understand the important role this one neurotransmitter plays in all these symptoms because we can manipulate this system so well. The serotonin system also seems especially vulnerable to disruption by a variety of factors, not only stress in the environment (leading to depression or an anxiety disorder), but also (most likely) Fragile X. It also appears to be intimately involved in so many of the things we consider "personality traits" that we are probably especially sensitive to serotonergic dysfunction in another person. Most importantly, we can use this hypothesis to further treatment.

Earlier theories of SIB may still have some utility. One notion conceptualized SIB as an attempt to self-soothe and speculated that the (usually minor) physical injury provoked a release of endogenous opioid compounds, i.e. endorphins and enkephalins. Thus, autistic or Fragile X

children who engage in persistent headbanging might actually be getting a euphoric "rush" from their own natural painkillers, reinforcing the behavior and perhaps even leading to some "addiction". This is the rationale for the use of naltrexone (Trexan, ReVia), an opioid antagonist (blocker) which has shown some success in open trials for treatment of SIB; it simply keeps the endorphins and enkephalins away from their natural receptor sites, where they would otherwise exert their effect. If the effect of the opium-like neurotransmitters can be blocked, then the behavioral cycle reinforcing the SIB can be interrupted. If this treatment is going to work, the individual will most likely (if able to talk) describe in advance that his episodes of SIB are analgesic (painless) and/or euphoric. Asking about this in advance can save a long and pointless trial for an individual who hits himself out of frustration but finds the experience painful and otherwise unpleasant; he will likely not benefit from a trial of naltrexone. (Naltrexone has proven to be remarkably effective as a treatment for individuals in the general population with severe personality disorders who engage in ritualistic “cutting” behaviors — a surprisingly common problem.)

It also helps to define the nature of aggressive behavior. Some younger children with Fragile X will hit playmates and siblings when highly aroused without intending any harm; this is not usually considered true aggression, but simply a reflection of impulsivity and lack of judgment in a hyperaroused state. Behavioral measures to limit the level of arousal or to help the child understand that hitting hurts can be effective in this example. Teaching siblings or playmates not to get the child "riled up" can be even more effective, since they can probably learn more quickly (and have plenty of incentive!). Should these methods fail, treatments of hyperactivity and hyperarousal (such as clonidine) can help with this "pseudo-aggression".

Many episodes of aggressive behavior are preceded by a long period of mounting tension. In this sense, we often think of aggression as related to anxiety, and strategies for decreasing anxiety have also proven effective in reducing aggressive outbursts, presumably by eliminating this long build-up of tension. The analogy has often been made to a spring being wound up tight, until it finally snaps; this also seems to occur in a family of disorders diagnosed in the general population, called Disorders of Impulse Control. This family includes kleptomania, paraphilias, pyromania, pathological gambling, and other, even stranger compulsive behaviors. Most of the individuals suffering from these conditions describe a similar sense of mounting tension with eventual discharge only through the abnormal behavior. Not coincidently, most of these disorders respond quite well to medications with significant anti-obsessional and anti-anxiety effects, such as buspirone, clomipramine, or SSRIs. Thus, the original rationale for utilizing these medications for the treatment of aggression; drugs of this class were noted to be effective in the developmentally disabled patient with aggressive behavior long before studies demonstrated any link to serotonergic dysfunction.

In both examples above, the obvious links are physical tension, arousal, and adrenaline. Earlier treatments of aggression tended to focus on this aspect of aggression, and for many years beta blockers, drugs that block some of the effects of adrenaline, were the mainstay of specific treatment. While some aggressive individuals do benefit from beta blocker treatment, the effect is rather weak; high doses are often required, and other medications are often required to be used additionally. They are still widely prescribed for this purpose and are generally considered fairly

benign medications whose use entails relatively little risk, though they are gradually being supplanted by newer and more selective agents.

Some Fragile X individuals, as previously noted, may suffer especially unstable moods. This mood lability may well predispose these individuals to violent or aggressive behaviors under certain circumstances and stabilizing their mood pharmacologically can be a particularly effective way to prevent aggressive outbursts. Resorting again to the evolutionary perspective, we can think of aggression as a natural mood state under certain circumstances. We are all (especially men) designed to be capable of aggression if we feel threatened or our social status in at stake. So, aggression may just be one end of the normal mood spectrum, albeit an extreme that we should not experience too often. People with especially unstable moods may reach this extreme more easily and more often.

It has been known for some time that lithium, the first treatment for manic-depressive illness (bipolar disorder), is quite effective for treatment of aggressive outbursts in some people, even if they clearly do not have bipolar disorder. Newer mood-stabilizers like carbamazepine and valproic acid seem to be even more effective and have been used extensively to treat aggression. These are anticonvulsant medications first and foremost, leading some to speculate that since they are effective for some types of aggression, these forms of "episodic dyscontrol" might be a variant of seizure disorder. However, several studies have indicated they are just as effective for people with entirely normal electroencephalograms as for those with known abnormalities. The leading theory is that these mood-stabilizing drugs exert their effects by decreasing the excitability of the limbic system, the hypothesized seat of emotion. In either case, since many Fragile X boys will require treatment for a seizure disorder, it makes sense to consider use of one of these "psychoactive anticonvulsants" if aggressive behavior is also a problem.

Other medications used to treat aggression include trazodone, a novel antidepressant which is non-toxic but quite sedating. The major tranquilizers (antipsychotics like Mellaril, Haldol, and Thorazine) can sometimes work, but with all the aforementioned risks; they are definitely not as effective for aggression in Fragile X children (or adults) as some other, safer treatments. Minor tranquilizers (sedative/anxiolytics like Valium, Ativan, or Xanax) are usually of no benefit and often make matters worse by causing intoxication, confusion, and disinhibition — just as some people we know are more likely to get in a fight when drunk.

Psychostimulants increase aggressiveness in a dose-dependent fashion; while low doses are unlikely to cause aggression *de novo*, it would be tempting fate to prescribe a stimulant to a Fragile X child who is already having problems with aggressive behavior. Likewise, if a child already on stimulant medication begins to show increasingly aggressive behavior after a dosage increase, the medication is probably to blame. One of the nicest things about this class of medications is that any adverse effects usually subside rapidly once the medication is discontinued, so a careful trial is often worthwhile — as long as everyone knows what to look out for.

Severe aggression is being treated more often with atypical antipsychotics (Risperdal, Zyprexa, Seroquel, Abilify, et al.) when it arises in the context of a developmental disorder. Since Risperdal has been around longest, it has been studied most, with generally good results. Clearly,

it can treat aggression relatively rapidly and potently; however, even these "new and improved" antipsychotics can impair attention and cause movement disorders. This is one reason that the introduction of Abilify (aripiprazole) represents a major advance in treatment of developmental disorders. This drug does not simply block dopamine receptors (like conventional antipsychotics) but actually modulates dopamine activity. So, in areas of the brain where dopamine may be excessive, it will decrease dopamine function; at the same time, it can increase dopamine function in other areas if it is low or have little effect if it is normal. This is an ideal pharmacologic profile for treatment of the psychiatric problems that accompany developmental disorders, since agitation and aggression often go hand in hand with attention deficit and hyperactivity. Clinical experience with Abilify (aripiprazole) in Fragile X has been very good, and this agent is emerging as the treatment of choice for severe behavioral problems in Fragile X, autism, and general developmental disorders.

Insomnia

Insomnia is a frequent complication of Fragile X syndrome, but psychiatrists usually prefer to treat all cases of sleep disturbance according to the presumed cause of the problem, because this usually yields much better results. Treating insomnia symptomatically, without regard to the underlying cause of the symptom, is sometimes successful in the short term; more often, though, the result is a chronic and seemingly intractable struggle.

The most common cause of insomnia in children with Fragile X appears to be hyperarousal, so reference can be made to those sections dealing with this target symptom for more specific comments. Clonidine is frequently prescribed for hyperactive children with sleep disturbance and can work very well. It is highly sedating and greatly decreases central nervous system hyperarousal; its half-life is long enough to ensure a good night's sleep without undue sedation the next day. However, one must be aware of the possibility of behavioral rebound — increased hyperactivity the next day — if clonidine is given only once a day at bedtime. The use of a small daytime dose, or the use of the transdermal clonidine patch with a supplemental oral dose at night will minimize the risk of rebound.

Another significant cause of sleep disturbance in individuals with Fragile X is mania; this can often be difficult to distinguish from hyperarousal (as previously discussed). Nevertheless, this is an important distinction, since the use of a mood-stabilizing agent is critical to the management of mania and will be the most effective way to restore regular sleep in a manic individual. Evaluation by an experienced clinician is the best way to make this distinction.

Finally, one factor which must be kept in mind when dealing with a sleep disturbance is seasonal change in sleep patterns. Many people show great sensitivity to seasonal changes and find that their sleep patterns fluctuate tremendously as the length of the day changes. Typically, people in northern latitudes sleep more as the days get shorter in the fall; they often have much less energy during the day, and they may eat more and gain weight. In short, they hibernate. This effect is much less pronounced in the Southern U.S. (Florida, for example) than it would be in New

England or Canada, because there is significantly less variation in the length of days as one approaches the equator.

In extreme cases, we refer to this as Seasonal Affective Disorder; however, almost everyone experiences a little of this effect, and individuals with Fragile X are no exception. Some individuals actually have "reverse seasonal" effects and sleep less in the winter. They may respond well to light therapy; this kind of insomnia is often accompanied by irritability and dysphoria, which also improve with light treatment. The key to successful light treatment is to use a lot of light (1000 watts or more of incandescent light, 250 watts of fluorescent), close to the eyes (within 2-3 feet), for 30-60 minutes every day during the dark season. Precise timing is still a bit controversial, but early evening just after sunset seems to be the best time to use the bright lights to trick the body into thinking the days are longer than they really are.

Many people have used melatonin, the hormone which the body uses to regulate the sleep/wake cycle, as a sleep aid. This is promoted as universally effective and completely safe, but in fact it is neither. Little research has been done on the effects of administering huge excesses of this hormone over extended periods of time, and the usual 3 mg dose obtained over the counter is indeed much more than is normally present in the body. It is known that this is not acutely toxic, so it is probably safe for occasional use. Clinical experience suggests that this "nutritional supplement" is not especially effective for treating severe sleep disturbances, and it definitely can cause transient dysphoria and even brief depressive episodes in individuals with bipolar mood disorders. Since many individuals with Fragile X have a bipolar pattern of mood disorder, this should be considered a potential risk.

Basic research in animal models of Fragile X has shown that signaling pathways in multiple neurotransmitter systems are probably affected in a similar way. The common denominator is a signaling mechanism in cells known as "Gq". The best known Gq pathway involved in Fragile X is the one linked to mGluR5, and this is probably the most important one, but there are several others which may be responsible for specific symptoms of Fragile X. One of the other neurotransmitter receptors linked to Gq is the alpha 1 receptor for norepinephrine, so it appears that there is excessive activity linked to alpha 1. This would be expected to cause autonomic nervous system dysfunction, including autonomic hyperarousal and insomia, which is consistent with the clinical presentation of Fragile X. A similar clinical presentation is seen in Post-Traumatic Stress Disorder, and drugs which block alpha 1 have been used successfully to treat insomnia in PTSD. The prototype of the class is an antihypertensive agent, prazosin, which has demonstrated efficacy in treating the insomnia frequently seen in association with PTSD. This strategy awaits clinical trials.

Planning A Pharmacologic Strategy

When treating a complex neuropsychiatric illness like Fragile X syndrome, it is essential that an overall strategy be employed which addresses all the target symptoms, as well as incorporating pertinent negatives. No one should infer from our previous discussion of individual target symptoms that these features of an individual's disorder can be effectively treated in isolation. The most important task of the treating physician is to thoughtfully construct a profile of each patient's symptoms, then carefully match it to the pharmacologic profile of available treatments. A good physician will also plan ahead, attempting to anticipate future problems such as non-response, partial response, or inability to tolerate the initial treatment; as in a chess game, the strategy for the next move in treatment needs to be considered well in advance, so that treatment does not simply consist of reacting to the latest changes in the patient's mental status. Unfortunately, caught up in the everyday pressures of a busy practice, many physicians of all specialties fail at precisely this task. This is where parents and well-informed caregivers can assist greatly, by taking the time to think about overall treatment strategy, so that their Fragile X children do not fall victim to shortsighted attempts to control the most recent, most obvious, or most embarrassing symptoms without adequately considering their overall, long-term well-being.

There can be many different, but equally successful ways to approach the Fragile X patient. The simplest, conceptually, is to plan treatment based on a hierarchy of target symptoms. Thus, we would focus our treatment efforts on the most important symptoms first, hoping to encompass as many of the subsidiary symptoms along the way as possible. This approach assures us that we will not exacerbate a more significant problem in an attempt to treat a relatively minor one. Let us consider the following fairly common example:

An 8-year-old boy with Fragile X syndrome shows significant hyperactivity at school and at home, causing significant disruption of his education and family life. He appears to be easily "overstimulated", and his behavior can rapidly escalate out of control under certain circumstances. He is also quite prone to aggressive outbursts, most often in situations where he is obviously anxious around transitions, or with strangers in the house, or novel situations. His mother and younger siblings are frequent targets of the aggression, subject to hitting, biting, or scratching. This is also causing problems in the family, leading to fear and aversion among others in the household; this aggressive behavior has been refractory to numerous behavioral interventions; curiously, it is not observed in the structured environment at school. Teachers have recommended an "evaluation for ADHD" and suggested that this may also help with problems at home.

This child is typical of many children with Fragile X in two important ways: he has significant problems with hyperactivity, and there is much more to the story than simple, uncomplicated ADHD. If the treating physician focuses too narrowly on the chief complaint of "ADHD" and ignores the other, significant problems with anxiety and aggression, he may choose a treatment (like a stimulant) which will improve the hyperactivity while simultaneously worsening the other symptoms. In a sense, he has unwittingly prioritized this child's symptoms, attaching primacy to the ADHD-like symptoms, and considering all others subordinate. If he were to consider

aggression the primary problem, since it has the greatest potential to cause immediate harm, he would be unlikely to choose a stimulant; rather, he might reason that clonidine would have a favorable effect on the outbursts as well as the anxiety, and that it could decrease the amount of autonomic hyperarousal and control hyperactivity. Thinking ahead, he might also consider that oral clonidine could cause excessive sedation during school, so he might need to switch to the transdermal patch to optimize this treatment.

Here we see that the physician has tailored the treatment to fit the patient's profile best. All the symptoms can be expected to improve, rather than having to trade improvement in one area for exacerbation in another. This is the simplest and most elegant fundamental aspect of psychopharmacology. Thus, even though clonidine might be considered a second-line treatment for ADHD, and only an adjunctive treatment of aggressive behavior in the general population, for this patient it represents a rational first treatment.

Experts could reasonably debate the proper hierarchy of target symptoms, but this author would suggest the following ranking for Fragile X treatment, with the corresponding rationale:

1. **Self-Injurious Behavior —** This is the symptom most likely to cause immediate harm to the child, and also likely to become behaviorally entrenched, making later treatment more difficult.
2. **Aggression —** Most likely to cause immediate harm to others, especially in older children, it can also become an entrenched behavior over time, as well as causing irreparable damage to relationships within the family.
3. **Mania —** This is a serious psychiatric condition, requiring prompt attention; it is usually manageable in younger children, where it is often mistaken for ADHD; children with a history of mania need to be treated differently for a great many psychiatric conditions, so this target symptom requires due consideration before commencing treatment for less severe symptoms such as anxiety or attention deficit.
4. **Irritability —** Severe disturbances of mood can make many aspects of everyday life extraordinarily difficult, and (most importantly) impair the individual's quality of life; just as depression in the general population (and Fragile X girls) is a serious disorder not to be taken lightly, irritability and mood lability in Fragile X boys is serious business and should not be neglected.
5. **Anxiety —** Just as developmentally normal people with panic attacks and agoraphobia can be totally disabled by anxiety, Fragile X individuals (male and female) often suffer needlessly and fail to achieve their full potential because of disabling anxiety; this anxiety can be exacerbated by some treatments for the nearly-universal hyperactivity of Fragile X syndrome, so children should always be evaluated for the presence of this target symptom before beginning treatment for ADHD-like symptoms.
6. **Hyperactivity —** Hyperarousal and hyperkinesis cause a large amount of functional impairment in Fragile X children by interfering with education and family life; this symptom rarely exists alone, however, and since some of the primary pharmacologic agents used to treat hyperactivity can worsen other core symptoms of Fragile X, it should

be considered the primary target symptom only when other symptoms such as anxiety and aggression have been ruled out.

7. **Attention Deficit —** Since Fragile X causes attentional problems in most affected children, this is a common chief complaint, even in children without hyperactivity; however, attentional problems in Fragile X children are usually multifactorial, and no single treatment can be expected to restore "normal" attentional function; as noted for hyperactivity, some medications used to enhance attention (psychostimulants) can adversely affect other symptoms common to Fragile X syndrome, and must be used with caution.
8. **Obsessive-Compulsive Behavior —** This target symptom is usually least harmful in the immediate sense, but can still cause great disruption and frustration. Obsessive-compulsive behavior (OCD) is certainly important, just not the first priority.

As a simple way of outlining a treatment strategy based on this hierarchic method, one could move down the list through the 8 target symptom categories, rating each symptom as absent, mild, moderate, or severe for a particular child. Hopefully, only a few will be present to a moderate or marked degree, and these can be addressed in rank order. For example, let us use for an example a 6-year-old boy who presents with the following profile:

1. self-injurious behavior	absent
2. aggression	mild
3. mania	absent
4. irritability	moderate
5. anxiety	severe
6. hyperactivity	severe
7. attention deficit	moderate
8. obsessive-compulsive behavior	mild

This child fortunately has little trouble with SIB or aggression and has not shown any evidence of mania. However, he does have significant problems with irritability, anxiety, and ADHD-like symptoms. If one considers mood and anxiety disorders to be more "important" than hyperactivity, then the obvious choice is an antidepressant; indeed, attention may well improve significantly on an antidepressant. However, knowing that hyperactivity and attention deficit are also problems should influence the choice of the specific agent, perhaps arguing in favor of a less-activating medication.

Another child, perhaps a more severely affected 10-year-old, might present with the following profile:

1. self-injurious behavior	severe
2. aggression	moderate
3. mania	moderate
4. irritability	moderate
5. anxiety	mild
6. hyperactivity	mild
7. attention deficit	moderate
8. obsessive-compulsive behavior	moderate

This child has serious problems with behavioral dyscontrol, resulting in violent behavior directed toward self and others, as well as significant mood lability. An anticonvulsant mood stabilizer such as carbamazepine or valproic acid might be effective in controlling this constellation of symptoms. Most importantly, this type of treatment would not exacerbate any of these target symptoms. The mood stabilizing effect would also lay a solid foundation upon which an effective combination regimen could be built; for example, the addition of an antidepressant/antiobsessional medication such as sertraline would carry much less risk of manic activation if this child were already on carbamazepine, because its mood stabilizing properties could be expected to provide some degree of prophyllaxis against mania.

Augmentation

While we do not usually start out with the intention of using multiple medications, it often happens that a single drug is only partially effective. This leaves us with a dilemma: do we discontinue this partially effective treatment in the hope of finding another which will be more effective (but which might be totally ineffective)? Psychiatrists are confronted with this question every day, even in the treatment of relatively simple disorders like depression. In the treatment of Fragile X syndrome, partial responses are probably much more common, making it even more difficult to tell how well a particular treatment is working. However, there is an alternative to switching medications, a technique psychopharmacologists refer to as *augmentation*.

Augmentation is the addition to a drug regimen of a second agent which can be expected to enhance the overall effect of treatment. While the very idea of combining medications may strike some parents as risky, this technique is quite commonly used and is usually very safe. In treating a Fragile X individual, combinations of medications may be used simultaneously to treat different symptoms. Strictly speaking, this is not always true augmentation, but rather symptomatic treatment of a multi-faceted illness. Many different medications are used in a variety of augmentation strategies, and a detailed discussion of these is well beyond the scope of this manual. However, some familiarity with basic techniques can be helpful.

As mentioned earlier, stimulants are commonly used in Fragile X children, but their use is often limited by side effects to lower doses. Doses in the lower end of the therapeutic range may help somewhat with attention but are often less helpful in controlling hyperactivity and/or impulsivity. The addition of clonidine or a related medication can often greatly enhance the effectiveness of treatment and also can counteract some of the adverse effects of stimulants. If a particular individual has little trouble with hyperactivity, but simply obtains inadequate enhancement of attention, the addition of an antidepressant medication to a stimulant regimen can be effective.

Antidepressant effects are often partial, and there is a wealth of literature concerning the augmentation of antidepressants. Lithium can greatly enhance the effectiveness of antidepressants in a wide range of conditions, though this is rather involved, requiring frequent blood tests. Buspirone can augment the effect of many antidepressants, and is frequently combined with SSRIs, usually with little or no increase in side effects; this is particularly useful in the treatment of anxiety disorders and aggression. The addition of a second antidepressant (such as trazodone or a tricyclic) to an SSRI can be a potent treatment, though usually resulting in more side effects. Other strategies employed involve addition of thyroid hormone, the beta blocker pindolol, stimulants, amantadine, antipsychotics, benzodiazepines, and even more esoteric compounds, though most of these are best left to a specialist.

Mood stabilizers often work best in combination, a fact well known to those involved in treating bipolar disorder. Typically, lithium is supplemented with an anticonvulsant or an antipsychotic, though the latter is not recommended for routine use in Fragile X syndrome. A completely different class of medications, the calcium channel blockers such as verapamil, otherwise marketed for hypertension, show some promise for use as mood stabilizers, although there is no experience reported thus far with calcium channel blockers in Fragile X.

In any application, augmentation treatment and combination therapies are always more difficult to study rigorously. Not surprisingly, there has been no systematic study of any augmentation strategies in Fragile X, so one must rely entirely on the experience of the physician. Nevertheless, augmentation of existing medications can be quite effective and appropriate, as well as safe and easily tolerated.

Medication Reference Section

The following section of this manual provides a detailed evaluation of each medication commonly used in individuals with Fragile X syndrome.

About the Ratings for Medications

To simplify rapid comparison of a wide array of medications, a basic rating mechanism is employed in the following pages. Roughly, these should be interpreted as follows:

Effectiveness:

😊😊😊😊 an exceptionally effective treatment for the indications noted

😊😊😊 a very effective treatment for the indications noted

😊😊 a partially effective treatment, full resolution of target symptoms unlikely

😊 unlikely to be effective; may have partial effect in some cases

Safety:

✅✅✅✅ non-toxic at any dose; no major medical or psychiatric side effects

✅✅✅ non-toxic, but may have significant side effects in some cases

✅✅ potentially toxic and/or high incidence of significant side effects

✅ very high incidence of serious adverse effects; not recommended

Cost:

$$$$ very expensive

$$$ expensive

$$ moderately priced and easily affordable

$ practically free (in generic form only; brand name versions may cost much more)

Convenience:

👌👌👌👌 medication taken once a day or less, convenient form of drug

👌👌👌 needs to be taken more than once a day or requires monitoring

👌👌 multiple daily doses required

👌 multiple daily dosing plus monitoring and/or highly controlled substance

Medications by Generic Name (Grouped by Class)

Stimulants

Generic Name	Brand Name	Brief Description
dextroamphetamine	Dexedrine, Dextrostat	Stimulant for ADHD; improves attention and impulse control
methylphenidate	Ritalin, Concerta, Metadate	Stimulant commonly used in ADHD; available in many formulations
amphetamine/ dextro-amphetamine	Adderall	Combined stimulant for ADHD; similar to dextroamphetamine
Atomoxetine	Strattera	Selective norepinephrine reuptake inhibitor; an alternative to stimulants
lisdexamfetamine	Vyvanse	long-acting stimulant; not a first-line treatment for Fragile X
methylphenidate ER	Jornay PM	Extended-release formulation of methylphenidate

SSRIs

Generic Name	Brand Name	Brief Description
fluoxetine	Prozac	Common SSRI for mood, anxiety, and behavior

		regulation
citalopram	Celexa, Lexapro	SSRI used for anxiety, depression, and emotional regulation
sertraline	Zoloft	SSRI often used in Fragile X; good tolerability
fluvoxamine	Luvox	SSRI often used in OCD and anxiety disorders
vortioxetine	Trintellix	SSRI; thought to enhance aspects of cognition
venlafaxine	Effexor	SSRI with dual-action mechanism

Atypical Antipsychotics

Generic Name	Brand Name	Brief Description
aripiprazole	Abilify	Atypical antipsychotic with mood-stabilizing properties
quetiapine	Seroquel	Atypical antipsychotic; sedating, used off-label for mood and behavior
risperidone	Risperdal	FDA-approved for irritability in autism; effective for aggression
brexpiprazole	Rexulti	Newer antipsychotic closely related to aripiprazole (Abilify)
cariprazine	Vraylar	Atypical antipsychotic;

		may enhance cognition and motivation

Mood Stabilizers & Anticonvulsants

Generic Name	Brand Name	Brief Description
carbamazepine	Tegretol	Anticonvulsant and mood stabilizer; used for behavioral issues
valproic acid	Depakote	Anticonvulsant and mood stabilizer; used for aggression and bipolar
lithium	Eskalith, Lithobid, Lithonate	Mood stabilizer; used in bipolar disorder and aggression
topiramate	Topamax	anticonvulsant with multiple mechanisms; can dull cognition

Alpha Agonists

Generic Name	Brand Name	Brief Description
clonidine	Catapres	Alpha-2 agonist; used for hyperactivity, arousal, and sleep issues
guanfacine	Tenex	Alpha-2 agonist for hyperactivity and sleep; fewer side effects than clonidine

guanfacine extended-release	Intuniv	Alpha-2 agonist which has been approved for ADHD
clonidine extended-release	Kapvay	extended-release clonidine; another blood pressure medication repurposed for ADHD

Tricyclics & Other Antidepressants

Generic Name	Brand Name	Brief Description
clomipramine	Anafranil	Tricyclic antidepressant with strong serotonin reuptake inhibition
desipramine	Norpramin	Tricyclic antidepressant; sometimes used for ADHD
imipramine	Tofranil	Tricyclic antidepressant; sometimes used for enuresis and anxiety
nortriptyline	Pamelor	Tricyclic; used in ADHD and anxiety disorders
trazodone	Desyrel	Sedating antidepressant; used primarily for sleep
venlafaxine	Effexor	SNRI; used when SSRIs are ineffective
bupropion	Wellbutrin	Norepinephrine-dopamine reuptake inhibitor; also used in ADHD

Others

Generic Name	Brand Name	Brief Description
atomoxetine	Strattera	Non-stimulant ADHD treatment; norepinephrine reuptake inhibitor
buspirone	BuSpar	Non-benzodiazepine anxiolytic; mild antidepressant effect
baclofen	none	Centrally acting muscle relaxant; GABA-B agonist
folic acid	none	Vitamin supplement; studied for potential cognitive benefit
naltrexone	ReVia	Opioid blocker; used off-label for self-injury
propranolol	Inderal	Beta-blocker sometimes used in performance or social anxiety

Medications by Brand Name (Index)

Brand Name	Generic Name
Abilify	aripiprazole
Adderall	amphetamine/dextro-amphetamine
Anafranil	clomipramine
Baclofen	baclofen
BuSpar	buspirone
Catapres	clonidine
Celexa	citalopram
Cylert	pemoline
Depakote	valproic acid
Desyrel	trazodone
Dexedrine	dextroamphetamine
Effexor	venlafaxine
Eskalith, Lithobid, Lithonate	lithium
Inderal	propranolol
Intuniv	guanfacine ER
Jornay PM	Methylphenidate ER
Kapvay	Clonidine ER

Klonopin	clonazepam
Lexapro	s-citalopram
Lithonate, Lithobid	lithium
Luvox	fluvoxamine
Mellaril	thioridazine
Norpramin	desipramine
Pamelor	nortriptyline
Paxil	paroxetine
Prozac	fluoxetine
ReVia	naltrexone
Rexulti	brexpiprazole
Risperdal	risperidone
Ritalin	methylphenidate
Seroquel	quetiapine
Serzone	nefazodone
Strattera	atomoxetine
Tegretol	carbamazepine
Tenex	guanfacine
Tofranil	imipramine

Topamax	topiramate
Trintellix	vortioxetine
Wellbutrin	bupropion
Vraylar	cariprazine
Vyanse	lisdexamfetamine
Zoloft	sertraline
Zyprexa	olanzapine

Stimulants

Stimulants remain the most prescribed class of psychoactive medications in children, particularly for the treatment of attention-deficit/hyperactivity disorder (ADHD). These medications — primarily methylphenidate and amphetamine-based compounds — enhance dopaminergic and noradrenergic transmission, particularly in frontal brain regions, which improves attention and executive function. While their use is well established in general ADHD populations, their application in Fragile X syndrome (FXS) requires careful consideration.

Clinical Use and Overdiagnosis

The ADHD diagnosis has broadened in recent years, contributing to growing concerns about overprescription of stimulants in the general population. Many children diagnosed with ADHD may simply lie at the low end of the attentional variability spectrum. In those cases, prescribing stimulants can amount to "cosmetic psychopharmacology."

However, this argument does not apply to Fragile X. FXS is a well-characterized neurodevelopmental disorder with frequent attentional deficits rooted in underlying neurobiology. Stimulants can be helpful in select Fragile X individuals, especially those with attentional impairment, but carry significant risks not typically seen in idiopathic ADHD.

Fragile X-Specific Considerations

Children with Fragile X are uniquely vulnerable to the overstimulating and anxiety-provoking properties of stimulants. Many individuals exhibit baseline hyperarousal, anxiety, and sensory sensitivity. Because stimulants mimic sympathetic nervous system activation, they can worsen these symptoms, sometimes abruptly.

That said, some Fragile X individuals respond well to low doses of stimulants, showing improved focus and cognitive engagement. However, treatment rarely leads to the dramatic reductions in hyperactivity seen in typical ADHD. In many cases, side effects such as irritability, aggression, anxiety, or even psychosis lead to early discontinuation. These side effects are often dose-dependent and reversible with prompt cessation.

Long-Term Concerns and Clinical Vigilance

Short-term side effects (mood changes, agitation) are often obvious and easily detected. More insidious problems, including worsening obsessive-compulsive behaviors, mood dysregulation, or increased tantrums, can emerge months later. Unfortunately, the stimulant's physiological dependence may obscure the link, as withdrawal worsens symptoms and is misinterpreted as relapse.

While stimulants may seem like a quick fix for inattention, the long-term risks in Fragile X often outweigh the short-term gains. Many cases reveal subtle psychiatric decompensation months or years after an initially positive response.

Other Side Effects

Stimulants can cause motor tics, especially if early signs are missed. Monitoring is key: persistent tics are more likely when subtle movements are overlooked. If tics develop, dosage reduction or use of clonidine may help. Growth suppression may also occur due to appetite suppression, although catch-up growth is typical with drug holidays. Regular tracking of height and weight is advised.

New Developments

New formulations like Azstarys (serdexmethylphenidate) and Jornay PM offer extended-release profiles that may reduce peak-related side effects. The non-stimulant viloxazine (Qelbree) is now FDA-approved for pediatric ADHD and may be safer in Fragile X, though not yet well studied in this population.

Emerging research in pharmacogenomics may soon guide individualized dosing, especially in patients with CYP2D6 variants affecting stimulant metabolism.

Summary

In Fragile X, stimulants should be used cautiously, starting at low doses and with clear attentional goals, and not as a default response to hyperactivity. Monitoring for behavioral changes is critical throughout treatment. When adverse effects occur, slow tapering is strongly preferred to abrupt cessation.

Stimulants may still benefit select Fragile X individuals but must be approached with a long-term view and close follow-up.

Methylphenidate (Ritalin, Concerta, Daytrana, Jornay PM, Azstarys, etc.)

Effectiveness	Safety	Cost	Convenience
😊 😊	✅ ✅	$$	👌 👌

Drug Class

Stimulant – dopamine and norepinephrine reuptake inhibitor.

Indications

Primarily indicated for ADHD. Often trialed in Fragile X syndrome to improve attention, reduce impulsivity, and support cognitive engagement. Effects on hyperactivity are more modest in this population.

Pros

Works almost immediately, usually well tolerated.
Highly effective for attention, focus, and impulse control.

Cons

Tolerance (dependence) develops quickly (which is why these are controlled substances).
High incidence of psychiatric side effects.
Controlled substance; subject to abuse and diversion.

Overview

Methylphenidate is among the most widely used stimulant medications in pediatric psychiatry. It has a long history of use, a well-established pharmacological profile, and multiple available delivery systems. It works by increasing dopamine and norepinephrine in frontal brain circuits, enhancing focus and executive function.

In Fragile X syndrome, methylphenidate can be helpful in improving attention and reducing distractibility, but often triggers side effects such as irritability, anxiety, or emotional dysregulation. Children with Fragile X frequently respond best to lower doses than those used in typical ADHD.

Use in Fragile X Syndrome

Highly variable response; many children do not tolerate methylphenidate long-term. Best results seen in children with moderate hyperactivity and minimal baseline anxiety. Frequent trial-and-error is required to find the optimal formulation and dose.

Formulations (2025)

Immediate release (IR): Ritalin (2–4 hr duration)
Extended release (ER): Ritalin LA, Concerta (up to 12 hr), Metadate CD, Aptensio XR
Transdermal patch: Daytrana (applied daily, flexible duration)
Evening-dose ER: Jornay PM (taken at night, effect begins in morning)
Liquid/chewable: Quillivant XR (liquid), Quillichew ER (chewable)
Prodrug combo: Azstarys (contains serdexmethylphenidate for smoother onset/offset)

> These newer forms may offer better tolerability in sensitive children.

Dosing Guidance

Start low: often 2.5–5 mg/day (or patch for 4–6 hrs) in Fragile X.
Increase slowly while monitoring for side effects.
Avoid assumptions based on age or weight; instead base dosing on observed sensitivity and function.
Consider “drug holidays” during summer or weekends to reduce long-term appetite or growth impacts.

Common Side Effects

Irritability, agitation, tearfulness.
Worsened anxiety.
Reduced appetite and weight loss.
Sleep disruption.
Tics (motor or vocal).
Emotional "rebound" in late afternoon.

> Many of these side effects are dose-related and reversible upon discontinuation.

Rare but Serious Risks

Persistent tics if not recognized early.
Increased aggression or tantrums over time.
Obsessive-compulsive behaviors (delayed onset).
Growth delay (usually reversible).
Physiological dependence with prolonged use → tapering is strongly recommended.

Alternatives

Non-stimulants: Atomoxetine (Strattera), Guanfacine (Intuniv), Clonidine (Kapvay), Viloxazine (Qelbree).
Off-label alternatives: Modafinil, Armodafinil (less emotional reactivity; more cognitive benefits).

Cautions and Clinical Tips

Monitor closely for irritability, aggression, or withdrawal symptoms.
Growth charts should be reviewed at least twice yearly.
Taper off gradually if discontinuing.

Dr. Mike's Unvarnished Opinion

🚨 Effective in a lucky few, but watch out! Methylphenidate tends to provoke extreme side effects in Fragile X kids. Start low, go slow, and if you see even mild irritability, stop and reassess. Overrated and overused but still has a place.

Dextroamphetamine (Dexedrine, Zenzedi, ProCentra, etc.)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅	$$	👌

Drug Class

Stimulant – dopamine and norepinephrine reuptake inhibitor.

Indications

ADHD, often trialed in Fragile X to support attention, though psychiatric side effects are more common.

Pros

Works almost immediately, usually well tolerated.
Enhances attention and concentration.

Cons

Tolerance (dependence) develops quickly (which is why these are controlled substances).
High incidence of psychiatric side effects.
Short acting; requires frequent dosing.
Controlled substance; subject to abuse and diversion.

Overview

Dextroamphetamine is the active isomer of amphetamine and a prototype stimulant. It typically lasts longer than methylphenidate, though still requires dosing 2–3 times daily

unless an extended-release version is used. Compared to methylphenidate, it often causes more euphoria, greater cardiovascular stimulation, and stronger appetite suppression.

Differential response is highly individualized; some who fail methylphenidate respond well to dextroamphetamine, and vice versa.

Several newer amphetamine options are now widely used, including **Vyvanse**, **Adderall XR**, and **Adzenys XR-ODT**. These may be better tolerated due to smoother absorption or novel delivery forms.

Use in Fragile X

While some individuals with Fragile X tolerate low-dose amphetamines well, many experience increased anxiety, irritability, or aggression. Trialing with careful monitoring is appropriate, especially when methylphenidate is ineffective or poorly tolerated.

Formulations (2025)

Immediate-release (IR): Dexedrine tablets, Zenzedi
Extended-release (ER): Generic dextroamphetamine ER capsules
Liquid: ProCentra
Prodrug formulations (related): Vyvanse (lisdexamfetamine) – smoother delivery

Dosing Guidance

Children: Start at 2.5 mg/day, increase in 2.5 mg steps as tolerated. Max: ~20–25 mg/day for Fragile X.

Teens/Adults: Start at 5 mg twice daily, titrate upward to 30–40 mg/day as needed. ER may provide smoother, less potent effects.

Common Side Effects

Appetite suppression → dose after meals.
Rebound hyperactivity → use ER formulation or increase frequency.
Insomnia → move last dose earlier.
Anxiety → reduce dosage.

Nausea → administer with food.
Headache → consider temporary dose reduction

Uncommon Side Effects

Motor tics → reduce dose or discontinue; clonidine may help.
Palpitations → dosage reduction.
Rash → discontinue immediately.
Hallucinations or severe psychiatric symptoms → stop medication.

Alternatives

Non-stimulants: Atomoxetine, Guanfacine XR, Clonidine XR, Viloxazine (Qelbree).
Non-schedule: Modafinil (Provigil) – fewer emotional side effects.

Dr. Mike's Unvarnished Opinion

🚨 Less popular than methylphenidate, but still valuable in the right cases. Edgier. Can make kids sharp or can make them angry. Proceed with caution. If it works, great. If not, back off fast.

Amphetamine/Dextroamphetamine (Adderall)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊 😊	✅ ✅	$$$	👌 👌

Drug Class

Stimulant (Mixed Amphetamine Salts).

Indications

Attention-deficit/hyperactivity disorder (ADHD).
Narcolepsy (FDA-approved).
Off-label: executive dysfunction, daytime sleepiness, some mood disorders.

Pros

Highly effective for attention, focus, and impulse control.
Multiple formulations (short and long-acting) available.
Well-studied in pediatric and adolescent populations.

Cons

Can worsen anxiety, irritability, or aggression in some individuals.
Risk of appetite suppression, sleep disturbance, and dependency.
Controlled substance; subject to abuse and diversion.

Overview / Pharmacology

Adderall is a mixed-salt stimulant composed of equal parts dextroamphetamine and levoamphetamine. These act by increasing dopamine and norepinephrine levels in the brain, enhancing alertness, focus, and behavioral regulation. Amphetamine-based

stimulants tend to have longer duration and slightly stronger effect than methylphenidate-based medications. Immediate-release forms last about 4–6 hours; extended-release versions such as Adderall XR and Mydayis can last up to 12–16 hours depending on the formulation and individual metabolism.

Use in Fragile X

Adderall may be considered for Fragile X individuals with clear symptoms of ADHD or executive functioning deficits. However, amphetamines can increase anxiety and irritability, both of which are already common in Fragile X. For this reason, careful selection and slow titration are key.

Amphetamines are generally less well tolerated than methylphenidate in Fragile X, particularly in those with heightened emotional sensitivity. Low starting doses, and possibly limiting use to specific times (e.g., school hours), may help mitigate side effects.

Common Side Effects

Appetite suppression.
Insomnia.
Irritability.
Headache or stomach upset (usually transient).

Uncommon Side Effects

Tics or exacerbation of pre-existing tics.
Mood swings or emotional flatness.
Elevated heart rate/blood pressure.
Anxiety or social withdrawal.

Dosage

Children: Start with 2.5–5 mg in the morning (immediate-release); titrate weekly

Adolescents/Adults: Start with 5–10 mg; increase gradually every 5–7 days
Extended-release: Typically taken once daily in the morning
Maximum doses vary; most individuals respond within 10–30 mg/day

Dr. Mike's Unvarnished Opinion

Adderall is the sales champ of the stimulant class, though not especially distinct from d-amphetamine. As with other forms of amphetamine, can make kids sharp or can make them angry. Proceed with caution. If it works, great. If not, back off fast.

Atomoxetine (Strattera)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅	$$$	👌👌👌

Drug Class

Selective norepinephrine reuptake inhibitors (SNRIs).

Indications

Attention deficit, hyperactivity.

Pros

Long-acting; flexible dosages; less rebound than stimulants; not a controlled substance (refills allowed); may have antidepressant effects.

Cons

Delayed onset; longer titration period; relatively high rate of psychiatric side effects.

Overview

Strattera is a selective norepinephrine reuptake inhibitor originally developed as an antidepressant. It is not a stimulant and not a controlled substance. Its use in Fragile X has produced mixed results. While some benefit from its non-stimulant profile and mild antidepressant action, others experience agitation or activation early in treatment.

Atomoxetine typically takes 2–4 weeks to become effective, with side effects emerging in the first few days to weeks. This timeline is the reverse of stimulant medications,

which act quickly but show side effects and tolerance over time. Careful counseling of families can prevent premature discontinuation.

Use in Fragile X

Children with Fragile X often show increased sensitivity to side effects, such as irritability and emotional dysregulation.

Strattera remains a valuable non-stimulant alternative, though success in Fragile X continues to be limited. High sensitivity to side effects often precludes optimal dosing. Fewer than one third of Fragile X patients complete a successful trial.

Common Side Effects

Upset stomach, decreased appetite, nausea or vomiting, dizziness, tiredness, and mood swings.

Uncommon Side Effects

Weight loss, allergic reactions, agitation, aggression.

Dosing Guidance

Children: Start with 10 mg twice daily for 1–2 weeks, then increase to 20–25 mg twice daily as tolerated. Full effect may take 2–4 weeks. Larger or older children can go up to 80 mg/day.

Adults: Start with 25 mg twice daily and titrate to 40 mg twice daily if needed. Allow 2–4 weeks before further increases. Max dose is 150 mg/day, though doses above 120 mg/day should be used cautiously in Fragile X.

If combined with SSRIs (e.g., Prozac, Zoloft), dosage should be reduced due to CYP2D6 inhibition.

Dr. Mike's Unvarnished Opinion

⚖️ A thoughtful option when stimulants fail or aren't tolerated, but a gamble. Works beautifully for a few but often backfires in Fragile X. Try low and slow, and don't push past side effects.

Vyvanse (Lisdexamfetamine)

Effectiveness	Safety	Cost	Convenience
😊😊😊😊	✅✅	💲💲💲💲	👌👌

Drug Class

Prodrug Stimulant (Amphetamine-based).

Indications

ADHD, hyperactivity, impulsivity, inattention.

Pros

Smooth onset and offset, long-acting, reduced abuse potential, less rebound than other stimulants.

Cons

Expensive; potential for appetite suppression, insomnia, and irritability; not ideal for individuals with anxiety or tics.

Overview

Vyvanse (lisdexamfetamine dimesylate) is a long-acting stimulant used primarily in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). It belongs to the amphetamine class but is unique among stimulants as a prodrug—meaning it is inactive until metabolized in the body. This design results in a smoother onset and offset of action, reducing the 'crash' or rebound symptoms often seen with other stimulants like Adderall or Ritalin.

Originally developed to minimize abuse risk, Vyvanse cannot be easily misused via intranasal or intravenous routes. Its consistent absorption and gradual activation make it one of the more tolerable stimulant options for children and adults.

Use in Fragile X

Stimulants are often considered for Fragile X individuals who display prominent hyperactivity, impulsivity, or attentional problems. Vyvanse may be preferred over shorter-acting stimulants due to its once-daily dosing and reduced fluctuations in blood levels. However, Fragile X individuals are particularly vulnerable to stimulant side effects like irritability, emotional lability, or increased anxiety—especially when underlying sensory sensitivities are present.

For those who tolerate stimulants well, Vyvanse can offer substantial improvements in focus and activity regulation. However, it is not recommended as a first-line treatment for Fragile X unless ADHD-like symptoms are clearly dominant and other options (e.g., alpha-agonists or SSRIs) have been ineffective.

Common Side Effects

Appetite suppression: Most common; may lead to weight loss over time.
Insomnia: Especially if taken later in the day.
Irritability or emotional lability → May require dose adjustment or discontinuation.

Uncommon Side Effects

Tics or repetitive movements: Can emerge or worsen.
Increased heart rate or blood pressure → Monitor in those with cardiac history.
Anxiety: May increase in some individuals, especially those with Fragile X.

Dosage

Children (6+): Start at 20–30 mg once daily in the morning; titrate by 10–20 mg every 1–2 weeks as tolerated; maximum dose 70 mg/day

Teens and Adults: Start at 30 mg daily; titrate gradually to achieve optimal effect

Note: Capsules can be opened and mixed with yogurt or water for easier administration, but must be swallowed without chewing.

Jornay PM (Methylphenidate Extended Release)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $ $ $	👌👌👌

Drug Class

Stimulant – dopamine and norepinephrine reuptake inhibitor.

Indications

ADHD (Attention Deficit Hyperactivity Disorder).

Pros

Evening dosing; improves early-morning ADHD symptoms; once-daily administration.

Cons

Only approved for ADHD; expensive; stimulant-related side effects (insomnia, appetite suppression, irritability).

Overview / Pharmacology

Jornay PM is an extended-release formulation of methylphenidate designed to be taken at night. It uses delayed-release and extended-release technology so that blood levels begin rising in the early morning hours, offering symptom control shortly after waking. This solves a common problem for children with ADHD who struggle most in the early mornings before traditional stimulants take effect.

Use in Fragile X

Jornay has not been specifically studied in Fragile X syndrome but may be useful for individuals with FXS who meet criteria for ADHD and have significant early-day difficulties. Its stimulant properties require caution in patients with anxiety or tics.

Common Side Effects

Decreased appetite, insomnia, irritability, headache.

Uncommon Side Effects

Tics, emotional lability, stomach upset, increased blood pressure or heart rate.

Dosage

Start at 20 mg at night; adjust weekly in 20 mg increments to a maximum of 60 mg/day.

Antidepressants

What Are Antidepressants?

Despite the name, antidepressants are effective for far more than just depression. SSRIs have demonstrated effectiveness across a surprisingly wide range of psychiatric and behavioral conditions. Originally developed for depression, they are now considered first-line treatments for numerous disorders, including Major Depressive Disorder, Dysthymia, Panic Disorder, Social Anxiety, Post-Traumatic Stress Disorder (PTSD), Obsessive-Compulsive Disorder (OCD), Bulimia Nervosa, Binge Eating Disorder, and Premenstrual Dysphoric Disorder. They have also shown benefit in certain impulse control disorders, such as Trichotillomania (compulsive hair-pulling), Onychophagia (nail-biting), Kleptomania, and Pathological Gambling, as well as some paraphilic disorders.

While not universally effective, and often producing only partial response, SSRIs have nonetheless changed our whole view of what is treatable and what is not.

The Rise of SSRIs

Selective Serotonin Reuptake Inhibitors (SSRIs) like fluoxetine (Prozac), sertraline (Zoloft), and escitalopram (Lexapro) revolutionized psychiatric treatment by offering high efficacy with relatively low risk of serious side effects. These medications enhance serotonin signaling in the brain and are now considered first-line treatment for a wide range of psychiatric conditions.

SSRIs for Fragile X

One condition which we now see as treatable is the repetitive/stereotypic/perseverative behavior associated with developmental disorders; this problem is certainly seen in the majority of individuals with Fragile X syndrome. These behaviors are considered to be a variant of Obsessive-Compulsive Disorder, the primary distinction being that an obsession (strictly speaking) must be perceived as unpleasant or intrusive, whereas Fragile X individuals often derive much enjoyment from their "obsessions" and their “compulsive” behaviors. In either case the symptoms can be significantly alleviated by antidepressant medications with sufficient serotonergic activity.

As noted previously, aggressive behavior is another symptom of Fragile X which had always been thought of as relatively refractory to treatment, and this continues to be one of the main reasons for Fragile X men to be institutionalized. SSRIs can make a dramatic

difference in the quality of life of older Fragile X individuals by decreasing the frequency of episodic dyscontrol or "catastrophic reactions" (in many cases eliminating them altogether).

Target Symptoms

SSRIs are especially helpful in reducing:

Repetitive behaviors and obsessive thinking.
Irritability and aggression.
Anxiety, especially social anxiety and generalized worry.
Mood lability and emotional dysregulation.

Use in Children vs. Adults

Children with Fragile X often experience more pronounced side effects, especially emotional overstimulation or 'activation'. Starting with low doses and increasing gradually is essential. Adults typically tolerate higher doses better and may benefit from doses used in OCD treatment.

Non-SSRI Antidepressants

Other classes of antidepressants such as SNRIs (e.g., venlafaxine), tricyclics, and novel agents like vortioxetine (Trintellix) may offer benefits when SSRIs are ineffective or poorly tolerated. However, agents like nefazodone are no longer recommended due to safety concerns, including risk of liver damage.

Common Side Effects

Initial side effects may include gastrointestinal discomfort, increased anxiety, sleep disruption, or emotional sensitivity. These typically diminish over the first few weeks. Serious side effects are rare, but parents should watch for increased agitation or aggression.

Current Safety Overview (2025)

No significant adverse events (e.g., suicidality or seizures) have been linked to SSRIs in Fragile X syndrome. Nonetheless, regular follow-up and dose monitoring remain important, particularly in children. SSRIs are considered among the safest psychotropic options for Fragile X.

Emerging Antidepressants

Research continues into more selective antidepressants with fewer side effects. Newer agents like vortioxetine show promise, offering both serotonin modulation and pro-cognitive effects. Further studies in Fragile X populations are still needed.

Dr. Mike's Unvarnished Opinion

🧠 The most useful class of meds for Fragile X by far, but use caution in younger kids. Go low and slow. SSRIs won't fix everything, but they make life a whole lot easier for many families.

Fluoxetine (Prozac)

Effectiveness	Safety	Cost	Convenience
😊😊😊😊	✅✅✅	$	👌👌👌👌

Drug Class

Selective Serotonin Reuptake Inhibitor (SSRI).

Indications

Aggression, anxiety, irritability, self-injurious behavior, obsessive-compulsive symptoms.

Pros

Broad spectrum of action, treats numerous symptoms of Fragile X; not toxic, even in massive overdose; once-a-day dosing with prolonged duration of action; non-sedating; generic available.

Cons

Can cause excessive activation, even mania in extreme cases; frequent nausea and/or insomnia at initiation.

Overview

SSRIs are rapidly becoming the treatment of choice in a wide variety of neuropsychiatric disorders because of their broad spectrum of efficacy. They can improve disorders of mood, anxiety, and impulse control in a wide variety of patients with essentially no toxicity. Fluoxetine is the prototype of this class and is distinguished by its ultra-long half-life, allowing every-other-day dosing. Compared to other SSRIs, fluoxetine is often

more activating and has a higher incidence of insomnia and restlessness. Though most people find this either pleasant or at least tolerable (and usually transient), this can be a major complication in the treatment of children, who seem to be especially susceptible to this side effect.

The only significant medical concern when using fluoxetine is the potential for drug interactions. SSRIs tend to be potent inhibitors of liver enzymes that metabolize some prescription medications—most notably tricyclic antidepressants and some anticonvulsants. When these medications are administered along with an SSRI, they can reach much higher concentrations in the bloodstream.

Use in Fragile X

Fluoxetine has a strong track record of reducing core behavioral symptoms in Fragile X syndrome. Keep in mind that these medications work gradually over a long period of time. Most Fragile X families report noticeable effects from SSRIs only after 4–6 weeks of treatment, with the greatest effect usually occurring at 3–4 months. A significant decrease in irritability, social and panic anxiety, obsessive-compulsive symptoms, and temper tantrums can be expected. Aggression and self-injurious behavior (SIB) may be the first symptoms to improve, even before mood symptoms are noticeably better. Attention may also improve, although hyperactivity might not, especially if the medication is overly activating.

If no response is observed, a higher dose may be warranted; however, time is often more important than dosage and waiting may yield better results. If one SSRI is not well tolerated or fails to work, trying another is a sensible next step.

Common Side Effects

Nausea → take with food; divided doses may reduce stomach upset; usually transient.

Tremor → typically benign and improves in 1–2 weeks; beta blockers may help.

Activation/Restlessness/Insomnia → take early in the day; dosage reduction may help; clonidine may also help.

Uncommon Side Effects

Headache → can be managed with OTC pain relievers; often transient.

Flushing/Sweating → maintain hydration.

Mania → discontinue immediately if manic symptoms appear (e.g., elation, lack of sleep); symptoms usually resolve in a few days.

Dosage

Children: Start with 2–4 mg daily in the morning with food. Use liquid formulation or mix capsule contents in juice. Increase every 3–4 weeks to 5–20 mg/day as tolerated. Most young children require no more than 10 mg/day.

Adults: Start with 10 mg/day for 3–4 weeks, then increase to 20–40 mg/day if needed. Maximum benefits may take months.

Citalopram (Celexa) and Escitalopram (Lexapro)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊 😊	✅ ✅ ✅	$	👌 👌 👌 👌

Drug Class

Selective Serotonin Reuptake Inhibitor (SSRI).

Indications

Aggression, anxiety, irritability, self-injurious behavior, obsessive-compulsive symptoms.

Pros

Broad spectrum of action; treats numerous symptoms of Fragile X. Not toxic, even in massive overdose. Once-a-day dosing with prolonged duration of action. Non-sedating.

Cons

Moderately expensive. Can cause excessive activation, even mania in extreme cases. Frequent nausea and/or insomnia at initiation.

Overview

SSRIs are rapidly becoming the treatment of choice in a wide variety of neuropsychiatric disorders because of their broad spectrum of efficacy; they can improve disorders of mood, anxiety, and impulse control in a wide variety of patients with essentially no toxicity. Citalopram is one of the newer drugs in this class; Lexapro is an “improved” version of Celexa which contains only one stereo-isomer of the drug (the “left-handed”

molecule, which is more active). Since it is newer, there is somewhat less experience in treating children with citalopram than with other SSRIs, but this is likely to change, since this drug is widely prescribed in the general population. It appears to offer a benign side-effect profile, though excessive activation is still likely to be the main problem in the treatment of children.

The only significant medical concern when using citalopram is the potential for drug interactions. SSRIs tend to be potent inhibitors of liver enzymes which metabolize some prescription medications, most notably the tricyclic antidepressants and some anticonvulsants; when these other medications are administered along with an SSRI, they can reach far higher concentrations in the bloodstream.

Use in Fragile X

Keep in mind that these medications all work gradually over a long period of time: most Fragile X families report noticeable effects from SSRIs only after 4–6 weeks of treatment, and the greatest effect will usually occur in 3–4 months. Expect to see a significant decrease in irritability, social and panic anxiety, obsessive-compulsive symptoms, and temper tantrums. Aggression and self-injurious behavior (SIB) may be the first symptoms to respond, even before obvious effects on mood are observed. Attention should be enhanced, though hyperactivity does not always decrease and could even worsen if activation is excessive.

If one SSRI is not tolerated or effective, trying another is a reasonable strategy.

Common Side Effects

Nausea → Take with food; divided dosing can reduce stomach upset. Typically improves within 7–10 days.

Tremor: Usually transient → if persistent, beta blockers may help.

Activation/Restlessness/Insomnia → Try temporary dose reduction or shift to earlier dosing; clonidine may help.

Uncommon Side Effects

Headache: → Often improves with dose adjustment or splitting. OTC remedies may be used.

Flushing/Sweating: Usually transient → maintain hydration.

Mania → Discontinue immediately if child shows signs of mania (elation, hyperactivity, sleeplessness). Tapering is not necessary. Clonidine or mood stabilizers (e.g., valproate, carbamazepine) may be used if symptoms persist.

Dosage

(Numbers below refer to Celexa; Lexapro doses are typically half.)
Children: Start with 5 mg daily, increasing gradually to 5–20 mg/day as tolerated. Young children often do well at 10 mg/day. Some teens tolerate 40 mg/day.

Adults: Start at 10 mg/day. Increase after 3–4 weeks as needed to 20–40 mg/day. Most respond to 20 mg/day.

Note: The FDA advises caution with Celexa doses above 40 mg/day due to QT prolongation risk. This is especially important in older adults or those with cardiac concerns.

Sertraline (Zoloft)

Effectiveness	Safety	Cost	Convenience
😊😊😊😊	✅✅✅	$	👌👌👌👌

Drug Class

Selective Serotonin Reuptake Inhibitor (SSRI).

Indications

Aggression, anxiety, irritability, self-injurious behavior, obsessive-compulsive symptoms.

Pros

Broad spectrum of action, treats numerous symptoms of Fragile X; not toxic, even in massive overdose; once-a-day dosing with prolonged duration of action; non-sedating; generic available.

Cons

Can cause excessive activation, even mania in extreme cases; frequent nausea and/or insomnia at initiation.

Overview

Sertraline is a selective serotonin reuptake inhibitor (SSRI) widely used in the treatment of mood, anxiety, and impulse control disorders. Introduced shortly after fluoxetine, it quickly gained popularity due to a favorable side-effect profile and more consistent tolerability in some individuals. Compared to other SSRIs, sertraline is associated with a slightly higher rate of gastrointestinal side effects such as nausea and diarrhea but may

produce less activation and restlessness — potential advantages when treating children with Fragile X syndrome. Sexual side effects are common in adults, though typically not a factor in pediatric use.

As with other SSRIs, the main medical concern is the potential for drug interactions. Sertraline is a relatively mild inhibitor of cytochrome P450 enzymes, especially compared to fluoxetine or paroxetine, and is therefore less likely to interfere with the metabolism of other medications such as tricyclic antidepressants and anticonvulsants. Nonetheless, care should be taken in individuals on multiple medications.

Use in Fragile X

Sertraline has a strong track record of reducing core behavioral symptoms in Fragile X syndrome. Improvements are most notable in irritability, social and panic anxiety, obsessive-compulsive behaviors, and temper tantrums. Aggression and self-injurious behavior may be the first to respond. Attention may improve, though hyperactivity can worsen with activation. Sertraline delayed onset means time is more critical than dose: it can take several weeks to months for maximal benefit. If not tolerated or effective, switching to another SSRI is reasonable, as response varies individually.

Sertraline is often better tolerated in younger children with Fragile X. Compared to fluoxetine (which is often too activating), sertraline is frequently preferred for its **more moderate activation profile**, making it a better first SSRI for young Fragile X children, especially preschool and early school-age. It reduces anxiety, obsessive behaviors, and social withdrawal. Close titration and monitoring are needed due to variable tolerability.

Common Side Effects

Nausea → take with food; Pepto-Bismol may be used; divided doses may result in less initial stomach upset; always transient and will improve in 7-10 days.

Diarrhea: usually transient → may use any over the counter (OTC) remedy; be sure to take with food (this also boosts absorption of sertraline by about 30%).

Tremor: benign and transient; usually improves in 1-2 weeks → if not, can be treated with a beta blocker.

Activation/restlessness/insomnia → temporary dosage reduction helpful; take medication as early in the day as possible; usually transient. If not, can be treated with clonidine.

Uncommon Side Effects

Headache → temporary dosage reduction or divided dose often helpful; usually transient, but can be treated with any OTC headache remedy.

Flushing/sweating: benign and transient → maintain proper hydration.

Mania → if child becomes abnormally active, elated, and is not sleeping at all, the medication should be discontinued immediately. This can be done abruptly without any tapering; no significant withdrawal syndrome can occur. Symptoms of mania will usually subside quickly, over a few days; if symptoms persist, clonidine can help, but in rare cases a mood stabilizer such as carbamazepine or valproic acid may be necessary. Some experts in mood disorders believe that manic activation during antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

Usual Dosage

Children: Start with 12.5 mg (¼ of a 50 mg tablet) each morning with food. The tablet is bitter but can be hidden in a small amount of applesauce, peanut butter, or candy to improve palatability. Increase gradually every 3–4 weeks as tolerated to an effective dose, typically between 25–75 mg/day. Young children usually respond to 25–50 mg/day; some teens may tolerate up to 100–200 mg/day.

Adults: Start with 25 mg per day with food for the first 3–4 weeks. If needed, increase to 50–200 mg/day for optimal effect. Most adults respond well to 100 mg/day, given enough time.

Fluvoxamine (Luvox)

Effectiveness	Safety	Cost	Convenience
😊😊😊😊	✅✅✅	$	👌👌👌👌

Drug Class

SSRI (Selective Serotonin Reuptake Inhibitor).

Indications

Aggression, anxiety, irritability, self-injurious behavior, obsessive-compulsive symptoms.

Pros

Broad spectrum of action, treats numerous symptoms of Fragile X; not toxic even in massive overdose; once-a-day dosing with prolonged duration of action; non-sedating; approved for use in children; generic available.

Cons

Can cause excessive activation, even mania in extreme cases; frequent nausea and/or insomnia at initiation.

Overview

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) approved for the treatment of obsessive-compulsive disorder (OCD), including in children, and has a well-established safety record. Among SSRIs, fluvoxamine is often more sedating, which can be advantageous in patients who also struggle with insomnia or nighttime agitation. This property makes it a particularly appealing option for younger children with Fragile X

syndrome, who are often more sensitive to activating side effects of other SSRIs.

The only significant medical concern when using fluvoxamine is the potential for drug interactions. SSRIs are known to inhibit liver enzymes responsible for metabolizing other prescription medications — especially tricyclic antidepressants and some anticonvulsants — potentially resulting in elevated blood levels of those medications. Caution is advised when fluvoxamine is combined with such drugs.

Keep in mind that these medications all work gradually over a long period of time: most Fragile X families report noticeable effects from SSRIs only after 4–6 weeks of treatment, and the greatest effect typically occurs in 3–4 months. Expect to see a significant decrease in irritability, social and panic anxiety, obsessive-compulsive (O-C) symptoms, and temper tantrums. Aggression and self-injurious behavior (SIB) may be the first symptoms to respond, even before obvious mood improvement. Attention may also improve, although hyperactivity does not always decrease and may occasionally worsen if activation occurs.

If the desired response does not occur, a higher dose should be considered; however, time is more important than dose in determining success with SSRIs. Often, simply allowing more time for the medication to take effect yields better results. If one SSRI is not well tolerated or ineffective, it is sensible to try another. Response is highly individual and idiosyncratic: a poor response to one SSRI does not imply a poor response to the entire class.

Use in Fragile X

Fluvoxamine has been found especially useful for individuals with Fragile X syndrome who experience significant anxiety, obsessive-compulsive behaviors, or irritability. Its relatively sedating profile makes it a better tolerated option for younger children or those sensitive to activating side effects. Clinicians often favor fluvoxamine in early pharmacological trials for Fragile X patients with sleep disturbances or bedtime behavioral issues. Additionally, fluvoxamine has been shown to have a significant effect on sigma receptors, a relatively recently discovered pathway in cells which regulates inflammation. Fluvoxamine is the most potent sigma 1 receptor agonist of any available drug, and this likely confers potent anti-inflammatory and neuro-protective effects; this alone may make fluvoxamine the drug of choice in this class for Fragile X. As with all SSRIs, effects are gradual, and regular follow-up is important to optimize dosage and monitor for side effects.

Common Side Effects

Nausea → Take with food; Pepto-Bismol may be used; divided doses may reduce initial stomach upset; typically improves in 7–10 days.

Diarrhea → Usually transient; OTC remedies may be used if needed.

Sedation → Often beneficial at bedtime; residual daytime sedation usually improves in 3–7 days.

Tremor → Typically transient; may resolve in 1–2 weeks or be treated with a beta blocker.

Activation/restlessness/insomnia → May respond to dose reduction; morning dosing helps; clonidine may help if persistent.

Uncommon Side Effects

Headache → Temporary dosage reduction or divided doses often helpful; treatable with OTC headache medications.

Flushing/sweating: Generally transient → ensure adequate hydration.

Mania → If child becomes excessively elated, hyperactive, or experiences insomnia, discontinue fluvoxamine immediately. No taper is necessary. Symptoms usually resolve in a few days. Clonidine or, rarely, a mood stabilizer such as carbamazepine or valproic acid may be needed.

Dosage

Children: Start with 12.5 mg at bedtime. Titrate slowly at 3–4 week intervals to 25–100 mg/day as tolerated. Young children often do well on 50 mg/day or less. Teens may tolerate up to 200 mg/day.

Adults: Begin at 25 mg/day with food for 3–4 weeks. Increase gradually to 50–300 mg/day. Typical effective dose is around 100 mg/day.

Trintellix (vortioxetine)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅ ✅	$ $ $ $	👌 👌 👌

Drug Class

Serotonin Modulator and Stimulator (SMS) / Atypical SSRI.

Indications

Depression, anxiety, cognitive dysfunction associated with depression.

Pros

Fewer sexual side effects than traditional SSRIs, potential cognitive benefits, generally well tolerated.

Cons

Expensive, nausea common in early treatment, limited long-term data in pediatric use.

Overview

Trintellix (vortioxetine) is a newer antidepressant with a unique mechanism among selective serotonin reuptake inhibitors (SSRIs). In addition to inhibiting serotonin reuptake, it acts on multiple serotonin receptors as an agonist, partial agonist, or antagonist. This broad activity gives it potential benefits not only for mood symptoms but also for cognitive functioning, making it a useful choice for patients with depression and associated attention or executive function deficits.

Unlike older SSRIs, Trintellix is thought to enhance aspects of cognitive performance, including processing speed and memory. It also tends to cause fewer sexual side effects than medications like fluoxetine or sertraline. However, it can cause gastrointestinal side effects — particularly nausea — during the first week or two of treatment.

Use in Fragile X

While not studied extensively in Fragile X syndrome, Trintellix may be beneficial in individuals with prominent anxiety or depressive symptoms, especially when cognitive slowing is a concern. The medication's relative lack of sedation and its mild stimulating effects may make it a useful alternative to more sedating antidepressants. However, cost and insurance coverage may be barriers, and experience in pediatric and developmentally delayed populations remains limited.

Common Side Effects

Nausea: Very common, especially early in treatment; usually improves within 1–2 weeks.

Headache: Typically mild and transient.

Dry mouth → Can usually be managed with hydration and sugar-free gum.

Uncommon Side Effects

Dizziness: Usually resolves over time → consider bedtime dosing.

Sexual dysfunction: Lower incidence than with most SSRIs, but can still occur.

Agitation or restlessness: Rare → dose reduction or discontinuation may be required.

Dosage

Children and Adolescents: Limited data available; off-label use should begin with 5 mg once daily and increase cautiously.

Adults: Start at 10 mg once daily; increase to 20 mg/day as needed and tolerated.

Venlafaxine (Effexor)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅ ✅	$ $	👌 👌

Drug Class

Serotonin-Norepinephrine Reuptake Inhibitor (SNRI).

Indications

Aggression, anxiety, irritability, self-injurious behavior, obsessive-compulsive symptoms, attention deficit.

Pros

Broad spectrum of action, treats numerous symptoms of Fragile X.

Cons

Can cause excessive activation, even mania in extreme cases; frequent nausea at initiation; some people experience significant sedation; usually requires multiple dosing; no liquid or chewable formulation available.

Overview

Venlafaxine is an antidepressant which inhibits the reuptake of serotonin and norepinephrine, making it a pharmacologic cousin of clomipramine, but with a “cleaner” side effect profile and much lower toxicity. The original immediate-release formulation required dosing two to three times daily, which made compliance difficult, but this also allowed for rapid achievement of therapeutic blood levels and potentially quicker onset of benefits.

Effexor XR, the extended-release version, allows once or twice daily dosing with smoother drug absorption and fewer side effects. Although venlafaxine has proven highly effective for a broad range of mood and anxiety disorders (including OCD and treatment-resistant depression), its use in children is less well studied.

Use in Fragile X

Venlafaxine may be particularly helpful for Fragile X individuals due to its dual-action mechanism and serotonergic effects. It has shown promise in reducing irritability, mood lability, anxiety (social and panic), obsessive-compulsive symptoms, and perseverative behavior. While less data exists for its use in treating aggression or self-injurious behavior, its pharmacologic profile suggests it may be helpful in those areas too.

One notable side effect is a dose-related rise in blood pressure, though this is typically mild and asymptomatic in healthy children.

Common Side Effects

Blood Pressure Increase: typically mild and benign.

Nausea → Take with food; Pepto-Bismol may help; usually transient (5–7 days).

Sedation → Usually transient; may resolve with temporary dose reduction.

Tremor → Transient and benign; rarely needs treatment but a beta blocker can help.

Dry Mouth: Typically short-lived → sugar-free gum or candy may help.

Uncommon Side Effects

Activation or Restlessness → Dose reduction often resolves this; rarely needs clonidine or beta blocker.

Insomnia → Ensure last dose is taken at least 4–5 hours before bedtime.

Dosage

Adults: Start with ½ of a 37.5 mg tablet twice daily with food. Increase as tolerated to 37.5 mg two or three times per day. Maximum dose is 450 mg/day, though this is rarely needed. Effexor XR may allow for more convenient once or twice-daily dosing.

Children: Start with 18.75 mg (half of a 37.5 mg tablet) once daily with food. Monitor for side effects including nausea, sedation, or behavioral activation.
After 2–3 weeks, increase to 37.5 mg once daily if tolerated and symptoms persist. Some children may benefit from increasing to 37.5 mg twice daily (total 75 mg/day).
Doses above 75 mg/day in children should be used cautiously and only with specialist supervision.
Effexor XR (extended release) capsules may be opened and beads mixed with soft food for children who cannot swallow pills.

Bupropion (Wellbutrin)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅	$ $	👌

Drug Class

Dopamine and Norepinephrine Reuptake Inhibitor.

Indications

Attention deficit, hyperactivity, irritability/depression in Fragile X girls.

Pros

Generally few side effects, very mildly activating, non-sedating; may be especially effective in adults with ADHD; generic available.

Cons

Relatively high risk of seizures, especially in males with Fragile X or anyone with a seizure history; must be given multiple times daily (unless using SR/XL). Not effective for anxiety disorders; may actually worsen them.

Overview

Bupropion is an atypical antidepressant that primarily inhibits the reuptake of norepinephrine and dopamine, with minimal effect on serotonin. It is often considered for the treatment of major depression, ADHD, and nicotine dependence, but not for anxiety. Compared to SSRIs or TCAs, it is mildly stimulating and generally well tolerated, but carries a higher-than-average seizure risk, particularly at higher doses or in vulnerable populations.

Early promotional efforts suggested bupropion might be suitable for anxiety-related depression, but it is now widely accepted that it can actually worsen anxiety or panic disorders in a dose-dependent fashion. Because of this and the seizure risk, it is rarely appropriate for Fragile X males, who already have elevated seizure risk and prominent anxiety symptoms. However, it may be helpful in certain niche cases, especially among females with Fragile X whose clinical presentation includes depression, inattention, or mild hyperactivity, but not anxiety.

A sustained-release formulation (Wellbutrin SR) is preferred for its improved tolerability and potentially reduced seizure risk. Wellbutrin XL, which is taken once daily, is also available but may be less often used in Fragile X due to peak-level sensitivity.

Use in Fragile X

Bupropion is not commonly used in Fragile X syndrome due to its seizure risk and its tendency to exacerbate anxiety symptoms. However, it may offer benefit in full-mutation females who have minimal anxiety and a clinical profile dominated by inattention, hyperactivity, and depressive symptoms. In such cases, bupropion may serve as an alternative to stimulant medication or as an adjunct to an SSRI for improved attention and motivation. It should be avoided in males with Fragile X, in those with any history of seizures, or in individuals with high baseline anxiety.

Common Side Effects

Nausea → Take with food; usually transient.

Tremor → Benign; may respond to beta blocker or dosage reduction.

Agitation/restlessness/insomnia → Consider reducing dose or shifting timing; avoid dosing before bedtime.

Headache → Treat with any OTC analgesic.

Uncommon Side Effects

Constipation: Usually transient → any OTC remedy may help.

Seizures → Requires immediate discontinuation; risk minimized with SR/XL formulations and divided dosing.

Dosage

Adolescents and Adults: Start with 75 mg twice daily; increase to 75 mg three times daily if tolerated.
Maximum dose: 450 mg/day, given in 3–4 divided doses.
Wellbutrin SR may be taken twice daily.
Wellbutrin XL (once daily) is less commonly used in Fragile X due to potential for peak-related adverse effects.

Children: Not recommended because of the seizure risk.

Buspirone (BuSpar)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅✅✅	$ $	👌👌

Drug Class

Serotonin agonist.

Indications

Anxiety, aggression, obsessive-compulsive behavior, SIB.

Pros

Extraordinarily safe, non-sedating, very few side effects, often effective for aggression in only a few days.

Cons

Short-acting, so multiple daily doses are necessary (though recent experience indicates most people can take this medication twice a day); no chewable or liquid; not especially effective for panic anxiety.

Overview

Buspirone is a novel compound marketed for the treatment of generalized anxiety disorder in the general population. It has also shown some antidepressant and antiobsessional properties, though it is ineffective for panic disorder and likely ineffective for panic anxiety in Fragile X. In developmentally disabled populations, buspirone has particular value as a treatment for aggression, sometimes yielding dramatic improvement

within days. That said, response is highly individualized: many patients show no benefit, while others experience rapid and notable reductions in aggression—often at low doses.

Buspirone acts as a 5-HT1A agonist, stimulating serotonin receptors at both presynaptic and postsynaptic sites.

The drug is extremely safe and well tolerated. It does not provoke mania or cause significant activation, even at high doses, and has no known toxic interactions with other medications. However, it is not broadly effective for all Fragile X symptoms and is typically administered two or three times a day, which may limit feasibility.

Use in Fragile X

Buspirone is often used in Fragile X patients who cannot tolerate SSRIs or who experience excessive activation with other antidepressants. Its mild serotonergic effects make it more tolerable, and many individuals can benefit from its calming, anti-aggressive effects. It may also serve as an augmentation strategy for SSRIs, particularly when additional anti-obsessional effects are desired.

Common Side Effects

Dizziness/lightheadedness: usually transient and always benign → take with food to smooth absorption.

Nausea: transient and benign → take with food; Pepto-Bismol may help.

Uncommon Side Effects

Insomnia → take last dose 3–4 hours before bedtime.

Headache → any OTC remedy is fine; usually transient.

Dosage

Children: start with 2.5 mg twice a day (with breakfast and dinner) for at least one week; increase if needed to 2.5 mg three times a day. Can be increased to 10 mg three times a day, but higher doses are rarely necessary and may reduce efficacy.

Teens and Adults: start with 5 mg twice a day (with breakfast and dinner) for at least a week. Increase to 5 mg three times a day if needed. Further increases (up to 60 mg/day) can be made at one to two-week intervals. Some patients tolerate higher doses, but these rarely provide additional benefit.

Trazodone (Desyrel)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅✅	$	👌👌

Drug Class

Multiple mechanisms.

Indications

Most commonly used for non-specific treatment of insomnia and agitation; also effective for irritability, anxiety, and aggression.

Pros

Potent, rapid sedation without significant toxicity; an effective antidepressant in its own right; inexpensive (generic).

Cons

In practice, use is limited to low doses by sedation and orthostatic hypotension; no liquid or chewable available.

Overview

Trazodone is a novel antidepressant that is rarely used in general practice for its original purpose because it is simply too sedating. Most people cannot tolerate a full therapeutic dose during the day. However, this heavy sedation becomes an advantage when sedation is the goal. Trazodone provides powerful but safe sedation lasting about 8 hours and carries no risk of abuse, dependence, or overdose toxicity.

This medication is most commonly prescribed in the U.S. as a sleep aid for patients taking SSRIs, and it can play a similar role in Fragile X syndrome (FXS). Unlike benzodiazepines, which may cause disinhibition or confusion in Fragile X, or diphenhydramine (Benadryl), which carries anticholinergic and pro-convulsant risks, trazodone has a more favorable safety profile. Although not routinely used in general pediatric care, trazodone is often prescribed for individuals with developmental disabilities of all ages, especially as an alternative to antipsychotics for managing aggression, agitation, and insomnia.

Use in Fragile X

Trazodone offers several mechanisms of action that are particularly relevant to Fragile X. It enhances serotonin transmission, which is helpful for treating anxiety, irritability, and aggression. It simultaneously blocks the 5HT2 serotonin receptor which is associated with overactive Gq signaling, a pathway believed to be dysregulated in Fragile X. This receptor-blocking effect mirrors that of atypical antipsychotics like Abilify or Risperdal, offering similar therapeutic benefits without their higher cost or greater risk profile.

In addition, trazodone blocks alpha-1 adrenergic receptors, which are also linked to Gq signaling. Overactivity of this receptor may contribute to sleep disturbances and hyperarousal, both common in Fragile X. The sedating and alpha-1 antagonism properties of trazodone thus make it uniquely beneficial for addressing both behavioral and sleep-related symptoms.

Despite being one of the safest and most widely prescribed psychiatric medications, its use in Fragile X has been limited due to pediatrician unfamiliarity and overstated concerns about the risk of priapism. In reality, priapism is an extremely rare side effect. Trazodone is likely underutilized in Fragile X treatment, especially for individuals with severe agitation or aggression.

Common Side Effects

Residual daytime sedation → Reduce dosage; try taking one hour before bedtime rather than at bedtime. Adaptation usually occurs after several days.

Orthostatic hypotension (dizziness upon standing) → Lower the dose or split into smaller doses for daytime use.

Uncommon Side Effects

Priapism (persistent erection) → Stop medication immediately; seek medical attention if it doesn't resolve. Very rare but serious.

Nausea → Take with food.

Headache → Treat with any over-the-counter remedy.

Dosage

Children: 25 mg at bedtime (½ of the smallest tablet) for insomnia; may increase up to 100 mg if tolerated. For daytime treatment of agitation/aggression, begin with 25 mg three times daily; can increase to 50 mg TID in young children and up to 100 mg TID in older children and adolescents.

Adults: Start with 50 mg at bedtime for insomnia; may increase to 100–150 mg, up to a maximum of 300 mg. For agitation/aggression, begin with 50 mg TID, titrating up to 150–200 mg TID as needed and tolerated.

Sympatholytics

These medications are designed to counteract the effects of the sympathetic nervous system ("lytic" means "that which dissolves or severs") by various neurochemical means. While they are all marketed as treatments for high blood pressure, this effect can benefit many individuals with Fragile X who suffer from troublesome hyperarousal or overstimulation. These symptoms often manifest as hyperactivity, anxiety, mood lability, or even aggression.

Sympatholytics are broadly divided into two classes: those that act primarily in the brain to reduce "sympathetic outflow" and thereby lower circulating adrenaline levels (alpha-2 agonists), and those that act primarily in the periphery to block adrenaline receptors (beta blockers).

Clonidine is the prototypical alpha-2 agonist and remains one of the most commonly prescribed medications for children with Fragile X. Guanfacine, another medication in this class, is also being increasingly used by child psychiatrists for ADHD and hyperactivity in developmentally disabled populations. While clonidine has been more extensively studied in children, guanfacine is generally less sedating and has a longer duration of action, making it attractive for broader use.

Propranolol is the prototype beta blocker, though several others, such as atenolol, pindolol, and nadolol, have also been used in psychiatry. In adult psychiatry, beta blockers are generally considered ineffective as standalone treatments for most anxiety disorders, and some controlled studies have shown no benefit over placebo. However, they are occasionally helpful in cases of performance anxiety (e.g., stage fright or public speaking), likely by suppressing physical symptoms such as tremors and palpitations.

Notably, beta blockers have little or no direct action in the brain, which limits their utility in treating central anxiety symptoms that are common in Fragile X. One exception is pindolol, which appears to block presynaptic 5-HT1A receptors, potentially accelerating the effects of SSRIs. It may be a useful augmentation strategy in specific cases, though it is unclear whether other beta blockers share this property.

In child psychiatry, beta blockers are used more frequently, and small studies have suggested they may help with certain types of childhood anxiety. However, based on both clinical experience and literature review, these medications are not recommended as first-line treatments for anxiety in Fragile X. Their psychotropic effects are relatively weak, and they are not as benign as often believed, especially at high doses.

The case for beta blockers is somewhat stronger in the treatment of aggression. Multiple studies have reported modest benefits, though the effect size is generally small compared to other agents like SSRIs, anticonvulsants, or buspirone. For this reason, propranolol is included in this review for its potential use in managing aggression in Fragile X. Other

beta blockers, while numerous, can generally be considered equivalent in their mechanism and clinical impact.

In summary, while sympatholytics can be valuable tools for managing hyperarousal and aggression in Fragile X, their use should be tailored to individual needs. Alpha-2 agonists like clonidine and guanfacine offer the most promise, particularly for hyperactivity and sleep disturbance. Beta blockers, while occasionally useful, are best reserved for specific symptom clusters or as augmentation in carefully selected cases.

Clonidine (Oral Formulation)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅	$	👌 👌

Drug Class

Alpha agonist.

Indications

Hyperactivity, attention deficit, aggression, anxiety, insomnia.

Pros

Sedative properties can help with insomnia when administered at night; safe for long-term administration; much experience in treatment of developmental disorders; very inexpensive as generic tablets.

Cons

Sedation can be excessive; need to start with small (subtherapeutic) doses and increase gradually; can cause confusion and irritability at peak levels; rebound and withdrawal syndromes do occur if medication is missed or discontinued abruptly.

Overview

Clonidine is one of the most frequently used treatments for the behavioral disturbances seen in Fragile X, and it has much to recommend it. It is technically classified as a centrally acting alpha-2 adrenergic agonist, meaning that it stimulates the alpha-2 subclass of adrenaline receptors in the brain. These receptors are located primarily in the *locus ceruleus* — the so-called "fight or flight" center that regulates autonomic nervous

system arousal — and when activated, cause feedback inhibition of this system.

This mechanism not only explains clonidine's ability to lower blood pressure (for which it is marketed), but also accounts for its psychotropic effects in Fragile X. By toning down this "fight or flight" system, clonidine decreases "sympathetic outflow" and has a general calming effect. Since activation of the locus ceruleus is thought to underlie panic attacks, it's not surprising that inhibiting it may reduce anxiety, although clonidine has not proven effective for Panic Disorder in the general population.

The main practical limitation of clonidine is its initial sedative effect, which peaks about an hour after dosing and may cause dizziness, confusion, irritability, or loss of coordination. Fortunately, tolerance to these effects develops quickly, and starting at very low doses with gradual increases can minimize side effects. An elegant (though expensive) alternative is the clonidine patch (Catapres TTS), which provides steady release and avoids peak drug levels.

Use in Fragile X

In Fragile X individuals, clonidine can be expected to significantly decrease hyperactivity, hyperkinesis, and hyperarousal. These are often the root causes of inattention, aggression, and sensory-driven anxiety. When hyperarousal is effectively treated, attention and concentration typically improve. Clonidine is especially helpful for children with pronounced overstimulation or those whose anxiety manifests through extreme discomfort with eye contact or social interaction.

Aggression, too, often decreases, particularly when it is primarily driven by overstimulation rather than mood instability. Although insomnia is not usually a standalone target symptom, clonidine is commonly used as a sleep aid for hyperactive children, especially when stimulants contribute to poor sleep. At the appropriate dose, a bedtime dose of clonidine can result in pleasant, benign sedation with little or no morning "hangover."

Clonidine pairs well with other medications. It complements stimulants, offsetting side effects like insomnia, anxiety, or tics, while enhancing attention. In combination with SSRIs, clonidine helps address the physical symptoms of anxiety, while the antidepressants better target irritability, mood instability, and panic. This pairing — common in treating PTSD — is particularly effective in Fragile X, where both emotional and physiological arousal are often dysregulated.

Common Side Effects

Sedation → temporary dosage reduction usually helps; taking 2/3 of daily dose at bedtime may reduce daytime drowsiness; patch form minimizes this

Dry mouth: usually transient and benign → sugar-free candy or gum can help

Dizziness: often dose-related → reduce dose temporarily; monitor blood pressure periodically

Uncommon Side Effects

Urinary retention → discontinue and contact your physician.

Irritability or confusion: → reduce dose temporarily and increase more gradually; smaller, more frequent doses may help.

Dosage

Children:
Start with 1/4 of a 0.1 mg tablet at bedtime. After 3–5 days, increase to 1/4 tablet twice daily. Further increases in 1/4 tablet increments can be made at one-week intervals as tolerated, up to 0.3 mg per day.

Teens and Adults:
Start with 1/2 of a 0.1 mg tablet twice daily. After 3–5 days, increase to 0.1 mg twice daily. Increase in 1/2 tablet increments at one-week intervals as tolerated, up to a maximum of 0.6 mg per day.

Clonidine Patch (Catapres Transdermal Therapeutic System)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $ $	👌👌👌👌

See also previous entry on Clonidine.

Drug Class

Alpha agonist.

Indications

Hyperactivity, attention deficit, aggression, anxiety, insomnia.

Pros

Safe for long-term administration; much experience in treatment of developmental disorders; very convenient to administer; perhaps more effective than oral form, since chances of rebound are reduced; peak level side effects greatly reduced.

Cons

Sedation can be excessive, even with the patch; need to start with small (subtherapeutic) doses and increase gradually; rebound and withdrawal syndromes can occur if patch is removed, lost or discontinued abruptly; some children will chew on patch, causing overdose; much more expensive than generic tablets.

Overview

Catapres TTS is a skin patch designed to release clonidine into the bloodstream at a steady, controlled rate over 5–7 days. This is a generally superior way to administer clonidine, given the drug's high incidence of peak level side effects, and it is especially convenient in treating Fragile X children, who may not be fully compliant with oral medications. Clonidine is one of the most frequently used treatments for the behavioral disturbances seen in Fragile X, and it has much to recommend it.
See previous entry on Clonidine.

Use in Fragile X

The use of clonidine for behavioral treatment of Fragile X can be expected to result in a significant decrease in hyperactivity/hyperkinesis and hyperarousal.
See previous entry on Clonidine.

Common Side Effects

Sedation → temporary dosage reduction will usually help; patch form of drug will minimize this side effect; tolerance will develop to this side effect.

Dry mouth → usually transient and benign; sugar-free candy or gum helps.

Dizziness → temporary dosage reduction will help; blood pressure should be monitored.

Skin rash: happens in about 15–20% of all people treated → may require discontinuation; topical steroid spray can help.

Uncommon Side Effects

Urinary retention → discontinue and call your doctor.

Irritability/confusion → temporary dosage reduction, followed by more gradual increase, will help.

Dosage

Children: start with 1/2 of a TTS-1 patch at bedtime, increasing to one whole patch after 5–7 days (TTS-1 delivers 0.1 mg of clonidine per day); can go up to TTS-3 if needed.

Teens and Adults: start with a TTS-1 patch, increasing gradually and as tolerated to TTS-2 or 3; can go up to 0.6 mg per day (2 TTS-3's at a time) or more in some cases.

Special Notes on the Use of Catapres TTS Patches

When to change → expect to change patches every 3–5 days; apply new patches at night.

Where to place → place patch between the shoulder blades to prevent removal; use Tegaderm if needed.

How to keep it on → use adhesive overlays or Tegaderm for active children or swimmers.

Minimizing rebound → consider staggered application of two smaller patches.

Avoiding overdose: Each patch contains up to 25 times the daily dose of clonidine and can still hold nearly 2 mg of active drug after a week. **Never** allow a child to chew or swallow a patch, new or used. While designed to stay on during bathing, patches may detach during prolonged swimming. For extended water play, consider removing the patch and storing it securely. Check daily to ensure the patch is in place. If ingestion occurs, seek medical help immediately; early symptoms may include sedation, confusion, and dizziness. Prompt treatment prevents serious harm.

Guanfacine (Tenex)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $	👌👌

Drug Class

Alpha agonist.

Indications

Hyperactivity, attention deficit, aggression, anxiety, insomnia.

Pros

Less sedating and slightly longer acting than oral clonidine.

Cons

Sedation can still be excessive; need to start with small (subtherapeutic) doses and increase gradually; can cause confusion and irritability at peak levels; rebound and withdrawal syndromes do occur if medication is missed or discontinued abruptly; expensive.

Overview

Guanfacine is a centrally acting alpha-2 adrenergic agonist, closely related to clonidine. It stimulates alpha-2 receptors in the *locus ceruleus*, the part of the brain which modulates the sympathetic nervous system, reducing 'fight or flight' responses. This leads to a general calming effect and reduces hyperarousal. While primarily developed for blood pressure control, guanfacine has shown benefits in treating hyperactivity, impulsivity, aggression, and anxiety in individuals with Fragile X.

Compared to clonidine, guanfacine is longer-acting and less sedating, though initial sedation can still be problematic. Sedation, dizziness, and irritability may occur during titration, but tolerance develops quickly if dosed gradually. Though industry support for guanfacine waned after it went generic, it remains a useful and effective option in Fragile X, especially for children who are sensitive to clonidine's effects.

Use in Fragile X

Guanfacine can reduce hyperactivity and hyperarousal — key symptoms in Fragile X — leading to better attention and concentration. It may also reduce aggression, especially when triggered by overstimulation. It is often used in combination with stimulants, where it can mitigate stimulant-related side effects like anxiety, insomnia, or irritability. Guanfacine also complements SSRIs, as it provides calming effects without directly enhancing mood. While no longer the newest drug in the toolkit, guanfacine continues to offer a valuable treatment strategy, particularly for individuals who do not tolerate other medications well.

Common Side Effects

Sedation → temporary dosage reduction will usually help; take 2/3 of total daily dose at bedtime.

Dry mouth: usually transient and benign → sugar-free candy or gum helps.

Dizziness: temporary dosage reduction will help; blood pressure should be monitored, though this medication rarely causes orthostatic hypotension.

Tolerance develops rapidly to these side effects, so the key is to start with very low doses and increase gradually.

Uncommon Side Effects

Urinary retention → discontinue and call your doctor

Irritability/confusion → temporary dosage reduction, followed by more gradual increase, will help; smaller and more frequent doses will minimize this side effect

Dosage

Children: start with 1/4 of a 1 mg tablet at bedtime, increasing to 1/4 tab twice a day after 3–5 days; can be increased in 1/4 tablet increments at one-week intervals as tolerated to achieve best effect, up to 4 mg per day

Teens and Adults: start with 1/2 of a 1 mg tablet twice a day, increasing to 1 mg twice a day after 3–5 days; increase in 1/2 tablet increments at one-week intervals as tolerated to achieve best effect, up to 6 mg per day

Intuniv (Guanfacine Extended Release)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $ $	👌👌👌

Drug Class

Alpha-2A Adrenergic Agonist.

Indications

ADHD, impulsivity, aggression, hyperarousal.

Pros

Non-stimulant, once-daily dosing, useful in sleep and anxiety.

Cons

Sedation, blood pressure effects, may take weeks to see benefits.

Overview / Pharmacology

Intuniv is an extended-release formulation of guanfacine, a medication originally used to treat hypertension. It works by stimulating alpha-2A receptors in the brain, reducing sympathetic nervous system activity and promoting calm focus. It has been approved for ADHD and has growing off-label use for irritability and aggression in neurodevelopmental conditions.

Use in Fragile X

Intuniv is often used in Fragile X syndrome to target hyperarousal, impulsivity, and sleep difficulties. It can be especially helpful when stimulant medications are not tolerated or worsen anxiety. Sedation is common at first but often subsides with time.

Common Side Effects

Sleepiness, fatigue, dry mouth.

Uncommon Side Effects

Dizziness, low blood pressure, irritability.

Dosage

Children: Start at 1 mg at bedtime; increase weekly in 1 mg steps to 2–4 mg/day.

Adults: Similar titration up to 4–6 mg/day, typically once daily.

Kapvay (Clonidine Extended Release)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $ $	👌👌👌

Drug Class

Alpha-2A Adrenergic Agonist.

Indications

ADHD, severe hyperactivity, sleep disturbance, tics.

Pros

Non-stimulant, calming, may help sleep onset.

Cons

Sedation, potential for rebound hypertension, twice-daily dosing.

Overview / Pharmacology

Kapvay is an extended-release form of clonidine, another blood pressure medication repurposed for ADHD and behavioral dysregulation. Like Intuniv, it reduces central sympathetic activity. It tends to be more sedating than guanfacine but is also more effective for sleep-related concerns.

Use in Fragile X

Kapvay is sometimes used in Fragile X when other medications are poorly tolerated or when insomnia and extreme hyperactivity are prominent. It can be beneficial at bedtime or as a daytime calming agent, though dose timing and withdrawal must be managed carefully.

Common Side Effects

Sleepiness, fatigue, dry mouth.

Uncommon Side Effects

Low blood pressure, mood changes, constipation.

Dosage

Children: Start at 0.1 mg at bedtime; titrate every 3–7 days up to 0.2–0.4 mg/day in divided doses.

Adults: Doses up to 0.4–0.6 mg/day.

Propranolol (Inderal)

Effectiveness	Safety	Cost	Convenience
😊	✅✅	$	👌👌

Drug Class

Beta blocker.

Indications

Hyperactivity, anxiety, aggression, self-injurious behavior.

Pros

Inexpensive, available in many pill sizes and formulations.

Cons

Less effective than other agents for treating anxiety; sometimes effective for aggression or SIB at very high doses.

Overview

Propranolol is a beta-adrenergic blocker commonly prescribed for cardiovascular issues, but it also has psychiatric applications. While often used for anxiety disorders, its effectiveness in this area is inconsistent, particularly in generalized or panic anxiety. However, it remains useful as an adjunct treatment for specific symptoms like tremor, restlessness, and akathisia caused by other medications, including stimulants, SSRIs, and antipsychotics. In these roles, propranolol is usually administered at low doses, is well tolerated, and has minimal side effects even with long-term use. Other beta blockers, such

as **nadolol**, **atenolol**, and **pindolol**, may have similar clinical effects and can be considered interchangeable for most off-label psychiatric uses.

Use in Fragile X

In Fragile X syndrome, propranolol has been explored as a treatment for hyperactivity, anxiety, aggression, and self-injurious behavior (SIB). While not as effective as alpha-agonists like clonidine or guanfacine for core symptoms such as hyperarousal or attention deficits, propranolol may have a role—especially for individuals who exhibit behavioral symptoms tied to physiological overarousal (e.g., flushing, tachycardia). It is sometimes used at high doses for aggression or SIB, though rarely as monotherapy. Its greatest value may lie in targeted use: either for managing side effects from other drugs or as a secondary option in more complex medication regimens.

Common Side Effects

Fatigue/Lethargy → temporary dosage reduction indicated.

Decreased exercise tolerance → avoid taking one hour before vigorous exercise; caused by artificial slowing of heart rate (bradycardia).

Dizziness → fewer, smaller doses may work better; blood pressure should be monitored after dosage increases.

Uncommon Side Effects

Difficulty breathing: beta blockers can cause bronchospasm, a tightening of the lower airways → **no one with asthma should take a beta blocker**.

Dosage

Children: start with 10-20 mg three times a day; for treatment of aggression, dose will be increased steadily, in 20-60 mg increments, up to 200-300 mg per day, depending on body weight.

Teens and Adults: start with 20-40 mg three times a day, increasing by 60 mg/day every 3-4 days for desired effect; doses of more than 600 mg per day have been reported, but are not recommended for Fragile X individuals.

Mood Stabilizers

This class of medications encompasses several chemically distinct drugs that share a common clinical purpose: stabilizing mood and reducing affective lability. These agents are widely used in treating Bipolar Disorder, a condition marked by mood swings between mania and depression, and they have also proven helpful in managing emotional and behavioral instability in individuals with developmental disorders, including Fragile X syndrome. In the treatment of Fragile X, these drugs are not entirely equivalent and should not be considered interchangeable; special uses and contraindications will be noted.

The most well-established mood stabilizer is lithium, which has been a mainstay in the treatment of Bipolar Disorder for decades. It is most effective in individuals with clear-cut manic and depressive episodes but is less helpful for the rapid, frequent mood shifts often seen in Fragile X. Lithium requires regular monitoring of blood levels, thyroid, and kidney function, and it carries toxicity risks at only slightly elevated doses, which makes it less appealing for use in Fragile X populations unless classic bipolar symptoms are prominent.

Two anticonvulsants, carbamazepine and valproic acid, have demonstrated significant mood-stabilizing properties and are often the preferred first-line treatments for mood instability in Fragile X. Carbamazepine may be particularly effective in cases of rapid cycling, and valproic acid has broad applicability for mood stabilization and irritability. Both require routine monitoring due to rare but serious side effects, such as blood dyscrasias (carbamazepine) or liver toxicity (valproic acid), but they are generally well tolerated and can be especially beneficial when a co-occurring seizure disorder is present.

In summary, mood stabilizers — particularly the anticonvulsant class — are important tools for treating mood swings, irritability, aggression, and affective dysregulation in Fragile X. Careful selection, dosing, and monitoring can help maximize benefit while minimizing risks.

Lithium (Eskalith, Lithobid, Lithonate)

Effectiveness	Safety	Cost	Convenience
😊😊😊😊	✅	💲	👌👌

Drug Class

GSK3 inhibitor.

Indications

Mania, aggression, irritability.

Pros

Relatively few side effects; effective mood stabilizer without significant sedation; very inexpensive; liquid form available.

Cons

Potentially toxic; requires careful monitoring, including frequent blood levels.

Overview

Lithium was the first mood stabilizer to enter widespread use and remains the gold standard for treating Bipolar Disorder (Manic-Depressive Illness). It is a naturally occurring mineral rather than a synthetic drug, and its therapeutic effects were discovered accidentally. Though its exact mechanism remains unclear, lithium is believed to modulate neurotransmitters like serotonin and to regulate intracellular signaling pathways that influence mood.

Clinically, lithium is known for its effectiveness in individuals with classic Bipolar

Disorder characterized by prolonged manic and depressive episodes. It is less effective in rapid-cycling mood disorders, where mood shifts are more frequent and abrupt, a pattern often seen in developmental disorders such as Fragile X. As a result, its use in that population has been somewhat limited.

Lithium's primary drawback is its narrow therapeutic index: doses only slightly higher than therapeutic can be toxic. Careful monitoring of blood lithium levels is required, particularly during initiation and dose adjustments. Long-term use also necessitates regular monitoring of thyroid and kidney function, as lithium can impair both. Thyroid function, in particular, should be tracked through routine TSH testing. Fortunately, once a stable dose is reached, the frequency of testing can usually be reduced.

Although often perceived as a "toxic" drug, this concern is somewhat overstated. Lithium toxicity is usually reversible and easy to detect early. With proper monitoring, lithium is safe, even over the long term, and has relatively few psychiatric side effects. Common issues like fatigue or lethargy can usually be addressed with dosing adjustments or thyroid supplementation when needed.

Use in Fragile X

Historically, lithium has not been widely embraced as a first-line treatment for Fragile X syndrome. Its perceived toxicity has limited its appeal, and the challenges of routine blood monitoring in this population have made it even less attractive to many clinicians.

However, lithium has been shown to inhibit a specific intracellular signaling pathway (through the enzyme GSK3) known to be overactive in Fragile X. In animal models, including Fragile X knockout mice and fruit flies, lithium treatment reverses key cognitive and synaptic abnormalities. Most impressively, initial human clinical trials have also demonstrated meaningful improvements in core Fragile X deficits.

This growing body of evidence suggests that lithium may be particularly effective in treating Fragile X. Its long track record, low cost, and wide availability further add to its appeal. The greatest hurdle remains practical: consistent blood draws for lithium and thyroid monitoring can be challenging in children or adults with sensory issues or behavioral difficulties. Nevertheless, for those who can tolerate the monitoring regimen, lithium may represent a uniquely powerful treatment option, capable of addressing both behavioral symptoms and underlying biological mechanisms.

Drug Interaction Warning

NSAIDs (non-steroidal anti-inflammatory drugs such as Motrin, Advil, ibuprofen, Naprosyn, Aleve) can significantly increase lithium levels if taken regularly. Occasional single doses are generally safe.

Common Side Effects

Nausea/diarrhea → take with food; usually transient.

Tremor: usually mild and related to peak levels → try dosing at bedtime or use beta blockers (e.g., propranolol).

Frequent urination → ensure adequate fluid intake; consult a physician if excessive.

Uncommon Side Effects

Sedation or lethargy → take full dose at bedtime; assess thyroid function if persistent.

Edema (swelling) → minor swelling may be benign; otherwise, contact a healthcare provider.

Clumsiness/incoordination: may signal neurotoxicity → check serum lithium level promptly.

Dosage

Lithium must be dosed according to blood levels. Start low and titrate gradually based on serum lithium levels.

Formulations include:
Lithium carbonate: 150 mg, 300 mg tablets/capsules; 450 mg sustained-release tablet.
Lithium citrate: liquid form, can be mixed with juice and is relatively palatable.

Carbamazepine (Tegretol)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $	👌

Drug Class

Anticonvulsant mood stabilizer.

Indications

Mania, aggression, irritability, self-injurious behavior.

Pros

Approved for use in children, safe for long-term administration, available in chewable tablets and suspension.

Cons

Difficult to dose properly (children develop more rapid metabolism after 1–2 months), multiple daily doses needed, therapeutic drug monitoring required.

Overview

Carbamazepine is one of the most commonly prescribed anticonvulsants in the U.S. and is widely used to treat seizure disorders, mood disorders, and aggression. Originally developed as an anticonvulsant, it was later discovered to have mood-stabilizing properties. It has proven effective in psychiatric conditions such as Bipolar Disorder, Schizoaffective Disorder, drug withdrawal syndromes, and aggression across diverse patient populations. Carbamazepine is thought to stabilize the electrical activity in the limbic system and offers an alternative mechanism distinct from SSRIs. Though once

assumed to help only those with abnormal EEGs, it is now known that patients with normal EEGs can also benefit.

Use in Fragile X

Carbamazepine has been used extensively to treat aggression and mood instability in developmentally disabled populations, including Fragile X. Its psychotropic effects in Fragile X may be somewhat modest, but some individuals experience clear improvement. The medication is generally well tolerated and has few cognitive side effects.

Because it induces liver enzymes, it may require dose adjustments over time. It has largely fallen from favor due to the need for therapeutic drug monitoring and the availability of newer alternatives like oxcarbazepine (Trileptal), which are often easier and safer to manage.

Common Side Effects

Sedation: usually transient→ 2/3 of dose can be given at night.

Clumsiness/incoordination: transient→ adjust dose as needed.

Rash→ may require discontinuation; consult your physician.

Uncommon Side Effects

Nausea→ take with food.

Dizziness: transient→ smaller divided doses can help.

Excessive bruising: may signal bone marrow suppression → stop immediately and call your doctor.

Dosage

Children: usually start with 100 mg twice a day (chewable or suspension), titrating upward in 100 mg increments at 1–2 week intervals to maintain therapeutic levels (4–12 mcg/mL).

Adults: start with 100 mg three times a day, increasing by 100 mg weekly until levels are therapeutic. Higher doses may be considered if well tolerated and needed after 4–6 weeks.

Valproic Acid / Valproate (Depakene, Depakote)

Effectiveness	Safety	Cost	Convenience
😊😊😊	✅✅	$ $	👌

Drug Class

Anticonvulsant mood stabilizer.

Indications

Mania, aggression, irritability.

Pros

Approved for use in children; safe for long-term administration.
Available in “sprinkles” form (Depakote Sprinkle capsules), which are easy to mix with soft foods.

Cons

Therapeutic drug monitoring (blood levels) required; multiple daily doses (2–3 times a day); may cause dysphoria, fatigue, or lethargy.
Risk of serious liver toxicity (rare but significant).

Overview

Valproic acid is one of the most widely used anticonvulsants in the United States and is frequently prescribed for seizure disorders. Its mood-stabilizing properties were discovered after its approval as an anticonvulsant and have since been validated in a variety of psychiatric contexts, including Bipolar Disorder, Schizoaffective Disorder, and aggression in developmentally disabled populations.

Its exact mechanism remains uncertain, but it appears to increase levels of GABA, an inhibitory neurotransmitter. Though chemically unrelated to carbamazepine, valproic acid is used similarly in psychiatric settings. Compared to lithium or carbamazepine, valproate's psychotropic effects may be weaker in some Fragile X patients. Still, it can be an effective treatment, particularly in cases involving manic features.

Valproic acid requires careful monitoring due to a rare risk of severe liver toxicity, especially in young children or those with mitochondrial disorders. Blood tests for therapeutic levels and liver function are essential during treatment. Common side effects include sedation, fatigue, and gastrointestinal complaints, while more serious side effects like excessive bruising or swelling warrant immediate medical attention.

Use in Fragile X

Valproic acid is commonly used in Fragile X individuals who also experience seizures, and it may have modest benefits for mood stabilization, especially in those with manic or highly irritable presentations. However, its overall effect on Fragile X behavioral symptoms appears somewhat limited, especially when compared with carbamazepine or lithium.

While basic science interest in valproate has grown due to its influence on gene expression through histone acetylation, clinical relevance to Fragile X remains minimal. A small clinical trial in Fragile X patients showed some behavioral benefit consistent with mood stabilization, but no evidence of FMRP production or gene reactivation. Therefore, while helpful as a general mood stabilizer, valproic acid should not be considered a targeted treatment for Fragile X syndrome.

Common Side Effects

Nausea/Vomiting: Usually transient → take with food.

Sedation: Often improves over time → take 2/3 of dose at night if needed.

Fatigue/Lethargy → May require dosage adjustment or discontinuation.

Dysphoria → May defeat therapeutic intent; dosage adjustment or discontinuation may be needed.

Uncommon Side Effects

Excessive Bruising: Possible early sign of toxicity → call physician immediately.

Edema (Swelling): May indicate toxicity → seek medical attention.

Tremor: Typically mild and transient.

Headache → Prefer NSAIDs like ibuprofen over acetaminophen due to liver considerations.

Dosage

Children: Start with 125 mg twice daily (Depakote sprinkles); titrate to therapeutic serum level (50–100 mcg/mL).

Adults: Start with 250 mg twice daily; adjust based on tolerance and therapeutic response. Some behavioral benefits may occur below the typical anticonvulsant range.

Antipsychotics

Antipsychotics are among the most powerful tools in modern psychiatry. They were originally developed to treat schizophrenia and related psychotic disorders, and their introduction in the 1950s marked the birth of psychopharmacology. The first-generation, or "typical," antipsychotics such as Thorazine and Mellaril revolutionized psychiatric care by offering a biomedical treatment for severe mental illness. But their initial promise soon gave way to overuse, especially in developmental disability (DD) populations, where they were prescribed broadly for behavioral issues. In many cases, their primary effect was simply sedation. Tragically, long-term use often led to irreversible drug-induced movement disorders, such as tardive dyskinesia.

This early pattern of overprescription carries a cautionary lesson for today. Although typical antipsychotics are now rarely used in children, they've been succeeded by a newer class: atypical antipsychotics. These agents, such as risperidone and aripiprazole, were originally developed for schizophrenia but are now frequently prescribed for children and adults with autism spectrum disorders, intellectual disabilities, and Fragile X syndrome. Their use surged after risperidone received FDA approval in 2006 for the treatment of irritability in autism, based on a large and well-conducted clinical trial published in 2002.

These newer medications offer real advantages: they are generally better tolerated, cause less sedation, and carry a lower risk of movement disorders compared to their predecessors. Many also appear to have broader benefits, such as reducing aggression, self-injurious behavior (SIB), and mood lability. However, they are not without risk. Atypical antipsychotics have been associated with weight gain, metabolic changes, hormonal effects (like elevated prolactin), and rare but serious side effects such as neuroleptic malignant syndrome. Unusual reactions, such as urinary incontinence in younger patients, have also been reported. And while side effect profiles are improved, long-term safety in Fragile X and related conditions is not fully understood.

In Fragile X syndrome, antipsychotics should not be considered first-line treatments for common symptoms like anxiety or hyperactivity. They may be appropriate when aggression, SIB, or severe mood dysregulation presents a danger or severely impairs functioning, but they should only be used after other interventions have failed or proven intolerable. Clinicians should resist the urge to reach for these medications simply because they are FDA-approved or widely used. Broad indications and pharmaceutical marketing have contributed to their popularity, but treatment should always be tailored to the individual based on symptom targets, side effect risk, and long-term goals rather than just a diagnostic label.

Many of the atypical antipsychotics are now available as inexpensive generics, while some of the latest entries into this drug class are still expensive proprietary drugs.

Important Safety Information for Antipsychotics

All antipsychotic medications, including both typical and atypical classes, carry important safety considerations. Patients and caregivers should be aware of the following potential risks and side effects:

Increased Risk of Death in Elderly Patients with Dementia-Related Psychosis: Elderly patients treated with antipsychotics for dementia-related psychosis are at increased risk of death compared to those receiving placebo. Antipsychotics are not approved for treating dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS is a rare but potentially fatal condition. Symptoms include high fever, muscle rigidity, confusion, shaking, excessive sweating, changes in pulse or blood pressure, and muscle pain or weakness. Treatment should be stopped immediately if NMS is suspected.

Heart Rhythm Changes (QT Prolongation): Some antipsychotics can affect the heart's rhythm, which may lead to serious complications. Individuals with a history of cardiac problems should use caution and consult their healthcare provider. Be sure to disclose all medications and supplements to your doctor.

Tardive Dyskinesia (TD): TD is a serious movement disorder involving involuntary movements of the face, tongue, or limbs. The risk increases with higher doses and longer use, though it can occur at low doses or after short-term treatment. TD may be permanent, although symptoms may lessen or resolve if treatment is stopped early.

High Blood Sugar and Diabetes (Primarily with Atypical Antipsychotics): Cases of elevated blood sugar, new-onset diabetes, and diabetic complications have been reported—most often with atypical antipsychotics. Risk is higher in individuals who are overweight or have a family history of diabetes. Regular monitoring of blood glucose is advised.

Hyperprolactinemia (Elevated Prolactin Levels): Antipsychotics may increase levels of the hormone prolactin. This can lead to side effects such as missed menstrual periods, breast milk production, breast development in males, and erectile dysfunction. The clinical impact of prolonged prolactin elevation remains unclear.

Seizure Risk: Antipsychotics should be used with caution in individuals who have a seizure disorder or are at increased risk for seizures. Dose adjustments or alternative medications may be necessary.

Extrapyramidal Symptoms (EPS): EPS are movement-related side effects including restlessness, tremors, rigidity, and muscle stiffness. These symptoms may require dose adjustment or additional treatment.

Heat Sensitivity and Dehydration: Antipsychotics may impair the body's ability to regulate temperature. Use caution during physical activity or in hot weather and ensure adequate hydration.

Common Side Effects: The most frequently reported side effects include restlessness, drowsiness, and extrapyramidal symptoms (e.g., tremor, stiffness, or involuntary movements).

Risperidone (Risperdal)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅ ✅	$	👌 👌 👌

Drug Class

Atypical antipsychotic.

Indications

Mania, aggression, self-injurious behavior (SIB), irritability, psychosis.

Pros

Very effective, easy to administer (once daily), relatively non-toxic, few side effects.

Cons

Can be sedating in some cases; can increase incontinence in some cases; can cause weight gain and metabolic syndrome (insulin resistance).

Overview

Risperidone is a newer antipsychotic medication that has dramatically changed the treatment of psychosis and severe behavioral disturbances. It was the first in a class of drugs known as "atypical antipsychotics," which largely replaced older medications like Thorazine, Haldol, and Mellaril. These newer agents are generally safer, better tolerated, and more versatile, particularly when it comes to mood and behavioral symptoms.

Originally approved for schizophrenia, risperidone has proven effective in treating agitation, aggression, and delusional symptoms in diverse populations including those

with Alzheimer's disease and developmental disorders. Notably, risperidone became the first atypical antipsychotic to be FDA-approved for the treatment of irritability in autism, based on a large, well-controlled clinical trial published in 2002. This marked a significant milestone in pharmacologic treatment for developmental disorders and has since led to widespread prescribing.

Compared to older antipsychotics, risperidone is far less likely to cause irreversible movement disorders and often has more favorable effects on cognition and social functioning. It is also considered to have more intrinsic antidepressant activity than some of its peers, although it may be less effective than others (e.g., olanzapine) for pure mania.

Use in Fragile X

In Fragile X syndrome and related developmental disorders, risperidone is generally used to address more severe forms of aggression, self-injury, mood dysregulation, or psychotic features. It is not typically a first-line treatment for mild irritability or anxiety, but it can be highly effective when other medications have failed or when symptoms are severe enough to present safety concerns.

Risperidone can promote mood stabilization, reduce aggression, and eliminate psychotic symptoms (though frank psychosis is rare in Fragile X). These effects are usually seen within 1–2 weeks, though maximal benefit may take 6–8 weeks. As with all antipsychotics, close monitoring is essential, especially when initiating or adjusting doses.

The 2006 FDA approval for autism-related irritability increased risperidone's use dramatically. At the same time, the drug became available in generic form, making it more accessible. However, widespread adoption has brought renewed attention to class-wide safety concerns such as metabolic effects, movement disorders, and hormonal side effects that require thoughtful monitoring and patient education.

Common Side Effects

Sedation: usually transient → bedtime dosing may reduce impact.

Muscle stiffness (extrapyramidal symptoms) → may require dosage reduction; typically reversible.

Orthostatic hypotension: dizziness when standing → improved with bedtime dosing or lower dose.

Uncommon Side Effects

Restlessness (akathisia) → treatable with propranolol; may also respond to bedtime dosing

Nausea: generally mild → taking with food helps.

Dosage

Children: start at 0.25–0.5 mg at bedtime; titrate every 1–2 weeks by 0.5 mg as needed. Doses above 2 mg/day are rarely necessary in young children.

Teens and Adults: start with 0.5 mg twice daily; titrate upward to a maximum of 2 mg twice daily if tolerated. Entire daily dose may be given at bedtime to reduce side effects.

See above for important safety information for all antipsychotics

Olanzapine (Zyprexa)

Effectiveness	Safety	Cost	Convenience
😊😊	✅	💲	👌👌👌

Drug Class

Atypical antipsychotic.

Indications

Mania, aggression, self-injurious behavior (SIB), irritability, psychosis.

Pros

Effective, easy to take, relatively non-toxic, few side effects except weight gain.

Cons

Significant weight gain is common, especially in younger patients; can cause metabolic syndrome (insulin resistance).

Overview

Olanzapine is a newer antipsychotic medication that has significantly advanced the treatment of schizophrenia and other psychotic disorders. Like risperidone, it belongs to the atypical antipsychotic class and has replaced many of the older agents such as Haldol and Thorazine. It is known for its lower risk of causing extrapyramidal symptoms and its broader efficacy in mood and behavioral disturbances, including those seen in Alzheimer's disease and developmental disorders. Compared to risperidone, it may be better suited for patients with bipolar-type symptoms but tends to cause more weight gain, especially in children.

Use in Fragile X

Olanzapine can be very effective in treating severe aggression, SIB, and mood instability in Fragile X syndrome. In Fragile X and similar conditions, olanzapine is generally reserved for more severe behavioral issues. Due to its metabolic side effects, including substantial weight gain, altered lipid profile, and risk of diabetes, it is typically considered a second or third-line treatment. Weight gain tends to be more pronounced in younger children, and so treatment should be approached cautiously.

Potentially most distressing of all, treatment with olanzapine and some other atypical antipsychotics can cause diabetes (in some cases) without obvious weight gain. For this reason, in younger people with Fragile X, and especially in children under 12, it is strongly recommended to reserve olanzapine for use as a treatment of last resort. Try the other drugs in this class first.

When used, effects begin to appear in 1–2 weeks, with maximal benefits emerging over 6–8 weeks.

Common Side Effects

Sedation: usually transient → bedtime dosing may reduce impact.

Muscle stiffness (dystonia) → may require dosage reduction;

Orthostatic hypotension (dizziness upon standing); typically reversible → improve with bedtime dosing or dose reduction.

Weight gain: common, especially in children → may require switching medications.

Uncommon Side Effects

Restlessness (akathisia) → may improve with propranolol or bedtime dosing.

Nausea: mild → taking with food can help.

Dosage

Children: start with 1.25 mg (half of a 2.5 mg tablet) at bedtime; increase by 1.25 mg every 1–2 weeks as needed.

Teens and Adults: start with 2.5 mg at bedtime; increase gradually up to 15 mg/day if needed.

Quetiapine (Seroquel)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅ ✅	$	👌 👌 👌

Drug Class

Atypical antipsychotic.

Indications

Mania, aggression, self-injurious behavior (SIB), irritability, psychosis.

Pros

Very effective, easy to take, relatively non-toxic, few side effects; sedation can be useful as a sleep aid.

Cons

Sedating; can cause weight gain and metabolic syndrome (insulin resistance).

Overview

Quetiapine is one of the newer atypical antipsychotic medications that represents a major advance in the treatment of schizophrenia and other psychoses. It is also widely used to treat agitation and delusional symptoms in dementia, often with cognitive benefits. Atypical antipsychotics like quetiapine are replacing older drugs (e.g., Thorazine, Haldol) due to improved safety and broader therapeutic effects. Quetiapine can reduce aggression, psychosis, and mood instability in various developmental conditions. Compared to risperidone or olanzapine, it causes less weight gain and is less likely to cause muscle stiffness, though it may lead to greater sedation.

As of 2025, quetiapine (Seroquel) remains the most prescribed antipsychotic in the U.S., accounting for over 28% of prescriptions. Though FDA-approved for schizophrenia and bipolar disorder, much of its use is off-label, especially for insomnia. It is widely used as an expensive sleep aid, despite clinical guidelines advising against this practice due to rare but serious risks.

Use in Fragile X

In Fragile X syndrome, quetiapine is reserved for severe behavioral disturbances including aggression, SIB, and mood dysregulation. It is not a first-line option but may be useful when calming sedation is needed along with antipsychotic effects. Benefits usually begin within 1–2 weeks, peaking around 6–8 weeks. While its sedative properties can be helpful, quetiapine should be used cautiously due to risks like tardive dyskinesia (TD), neuroleptic malignant syndrome (NMS), and metabolic syndrome, even at low, off-label doses used for sleep.

Common Side Effects

Sedation: usually transient → bedtime dosing may reduce impact.

Muscle stiffness (dystonia) → dosage reduction is indicated; hold dose until resolved.

Orthostatic hypotension → improved with nighttime dosing; reduce dose if needed.

Uncommon Side Effects

Restlessness (akathisia) → treatable with propranolol; bedtime dosing may help.

Nausea: mild → take with food.

Dosage

Children: Start with 25 mg at bedtime; titrate every 1–2 weeks by 25 mg to optimal effect. Usual range: 100–300 mg/day in divided doses.

Teens and Adults: Start with 25 mg twice daily; increase every 1–2 weeks up to 300 mg twice daily. Higher doses rarely offer more benefit.

Aripiprazole (Abilify)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊 😊	✅ ✅ ✅	$	👌 👌 👌

Drug Class

Atypical antipsychotic.

Indications

Mania, aggression, self-injurious behavior (SIB), irritability, psychosis.

Pros

Very effective, easy to take, relatively non-toxic, few side effects; less likely to cause weight gain than other atypical antipsychotics.

Cons

Can still cause weight gain and metabolic syndrome (insulin resistance) in some individuals.

Overview

Aripiprazole is among the newer atypical antipsychotics and represents a significant advance in the treatment of schizophrenia, bipolar disorder, and other psychiatric conditions. It is used across a wide spectrum of disorders including psychosis, mood instability, and behavioral dysregulation. It is now also being increasingly prescribed for agitation and delusional symptoms in patients with dementia. Not only does aripiprazole appear to treat these symptoms, it often results in improved cognitive functioning as well.

Like others in its class, aripiprazole has largely replaced older "typical" antipsychotics (e.g., Haldol, Thorazine, Mellaril) due to its improved safety profile. It is significantly less likely to cause extrapyramidal symptoms (involuntary movements) and may have added benefits in improving social function and cognitive clarity.

Use in Fragile X Syndrome

In individuals with Fragile X, aripiprazole has been used effectively for managing severe aggression, self-injury, and mood instability. While not a first-line agent for mild symptoms, it is particularly helpful when behaviors pose a safety risk or are unresponsive to other treatments. The drug's partial agonist mechanism at dopamine D2 receptors is unique, allowing it to modulate dopamine transmission by enhancing it where it's low (e.g., improving attention) and reducing it where it's high (e.g., reducing psychosis or agitation).

Because of this balancing effect, aripiprazole is often considered ideal when stimulant medications (e.g., methylphenidate) are also used, as it does not antagonize their effects in the way that many other antipsychotics might. Clinical experience suggests that aripiprazole may offer broader benefits in Fragile X than other medications in its class, including fewer side effects and better tolerability.

Pharmacology Notes

Aripiprazole is a **partial dopamine D2 agonist**, which allows it to modulate, rather than block, dopamine transmission. It also affects serotonin receptors (5-HT1A and 5-HT2A), contributing to its antidepressant and anxiolytic effects. The drug has a long half-life (about 75 hours), so steady-state levels take up to two weeks to achieve — and similarly take time to clear when discontinued. When switching from another antipsychotic, a crossover strategy is often recommended to avoid gaps in coverage. This effect takes about 1-2 weeks to emerge but is not maximal for at least 6-8 weeks; once again, a bit of patience is required.

Common Side Effects

Sedation: Usually transient → improved with bedtime dosing and gradual titration.

Orthostatic hypotension: Dizziness when standing → reduced with nighttime dosing or dosage adjustment.

Uncommon Side Effects

Restlessness (akathisia) → May improve with bedtime dosing; often treated with propranolol.

Muscle stiffness (dystonia) → Dose adjustment or temporary pause may be required.

Nausea → Taking with food typically helps.

Dosage

Children: Start at 2.5 mg at bedtime; increase by 2.5 mg every 1–2 weeks as needed. Typical dose: 5–10 mg/day.

Teens and Adults: Start at 5 mg at bedtime; increase gradually up to 20 mg/day if needed. Doses above 20 mg rarely add benefit and increase side effect risk.

Rexulti (Brexpiprazole)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅ ✅	$ $ $ $	👌 👌 👌

Drug Class

Atypical Antipsychotic

Indications

Irritability, aggression, mood dysregulation, psychosis.

Pros

Mild side effect profile, once-daily dosing, lower risk of akathisia than aripiprazole.

Cons

Expensive, limited pediatric data, potential weight gain.

Overview / Pharmacology

Rexulti is a newer antipsychotic closely related to aripiprazole (Abilify), classified as a dopamine D2 partial agonist. It was originally developed as a more tolerable option with fewer side effects. Rexulti works by modulating dopamine and serotonin systems, enhancing mood and cognition while reducing psychotic and manic symptoms.

Use in Fragile X

Though not widely studied in Fragile X syndrome, Rexulti's mild sedation and relatively low risk of extrapyramidal symptoms make it a potentially useful option when mood or behavioral symptoms do not respond well to other treatments. It may be especially helpful in cases requiring antipsychotic support without heavy sedation.

Common Side Effects

Weight gain, sleepiness, mild restlessness.

Uncommon Side Effects

Akathisia, dizziness, increased appetite, insomnia.

Dosage

Children (off-label): Start with 0.25–0.5 mg daily; increase weekly by 0.25–0.5 mg as needed.

Adults: Start at 0.5–1 mg daily; titrate up to 2–4 mg/day.

Vraylar (Cariprazine)

Effectiveness	Safety	Cost	Convenience
😊 😊 😊	✅ ✅	💲 💲 💲 💲	👌 👌 👌

Drug Class

Atypical antipsychotic.

Indications

Bipolar disorder, schizophrenia, adjunctive treatment for depression.

Pros

Effective for mood stabilization and depression; low risk of weight gain; long half-life (missed doses less impactful).

Cons

Expensive; may cause restlessness or insomnia; not approved for use in children.

Overview / Pharmacology

Vraylar is an atypical antipsychotic that acts as a partial dopamine D3/D2 receptor agonist with preferential binding to D3 receptors, which may enhance cognition and motivation. It has antidepressant properties and is approved for bipolar I disorder, schizophrenia, and as an add-on treatment for depression. It has a long half-life, which allows for more stable blood levels but also means side effects can linger.

Use in Fragile X

There are no clinical trials in Fragile X, but Vraylar may be an option for patients with prominent mood swings, aggression, or apathy, especially when other antipsychotics have failed. Its favorable metabolic profile and mood-enhancing properties are appealing, but cost and availability can be limiting.

Common Side Effects

Restlessness (akathisia), insomnia, nausea, headache.

Uncommon Side Effects

Tremor, anxiety, extrapyramidal symptoms (mild), constipation.

Dosage

Start at 1.5 mg daily; titrate to 3–6 mg/day as tolerated. Doses above 6 mg/day are not generally recommended.

Miscellaneous Medications

Baclofen

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅✅	$	👌👌

Drug Class

GABA-B Agonist / Muscle Relaxant

Indications

Spasticity (especially in cerebral palsy, MS, or spinal cord injury).
Aggression and self-injury (off-label).
Anxiety (off-label).
Behavioral dysregulation in developmental disorders (off-label).

Pros

Widely available and inexpensive; may reduce irritability, aggression, and self-injury.
Long clinical history in neurology and developmental medicine.

Cons

Sedation and fatigue are common; can worsen hypotonia (low muscle tone).
Withdrawal from high doses can be serious.
Limited formal research in Fragile X.

Overview / Pharmacology

Baclofen is a centrally acting muscle relaxant that functions primarily as a GABA-B receptor agonist. It was originally developed for the treatment of spasticity in conditions like cerebral palsy and multiple sclerosis. Unlike benzodiazepines — which enhance

GABA-A transmission and are more sedating and dependence-forming — baclofen acts more selectively on the GABA-B system and tends to have milder anxiolytic effects.

Fragile X syndrome is associated with an imbalance between excitatory (glutamatergic) and inhibitory (GABAergic) signaling, and baclofen's mechanism may help restore this balance. In addition to its approved uses, baclofen has been prescribed off-label for behavioral challenges in developmentally disabled populations, including aggression, self-injury, and hyperarousal. Some case reports and small studies suggest that baclofen may dampen excessive arousal and impulsivity in selected patients.

Use in Fragile X

Although baclofen is not FDA-approved for any psychiatric indication, it has been used in Fragile X syndrome to target self-injury, agitation, and muscle tension when these co-occur. Its calming effects may help reduce sensory overload and hyperreactivity. However, care must be taken to avoid excessive drowsiness or worsening of hypotonia, which is already a concern in Fragile X.

There is additional interest in baclofen as a low-cost GABAergic modulator, particularly given the unavailability of arbaclofen (STX209), a more targeted GABA-B agonist that showed promise in clinical trials for Fragile X and autism spectrum disorders. Regular (racemic) baclofen consists of 50% R-baclofen (arbaclofen) and 50% S-baclofen. While some clinicians attempt to approximate arbaclofen's effect by adjusting the baclofen dose, the presence of S-baclofen may lead to additional side effects or reduced efficacy in some individuals.

Overall, baclofen remains a widely accessible option that may benefit selected Fragile X patients, especially when behavioral dysregulation is compounded by motor tension or spasticity, but it is best used with individualized monitoring and a clear therapeutic goal.

Common Side Effects

Sedation: Most common side effect → may improve with bedtime dosing.

Fatigue or weakness: Can limit daytime functioning, especially early in treatment.

Dizziness → May improve with slow titration.

Uncommon Side Effects

Nausea: Usually mild → may improve with food.

Confusion or disorientation: Dose-related; rare but possible, especially at higher doses.

Worsened hypotonia → mportant to monitor in individuals already prone to low muscle tone.

Withdrawal symptoms: Abrupt discontinuation after chronic use can result in rebound spasticity, agitation, or seizures → requires tapering.

Dosage

Children: Start with 5 mg once or twice daily; increase by 5 mg every 3–5 days to effect. Maximum dose rarely exceeds 40 mg/day.

Teens and Adults: Start with 5–10 mg two to three times daily; target dose often 30–60 mg/day in divided doses.

Note: Extended-release formulations are available for once-daily use but are typically reserved for adults with spasticity.

Naltrexone (ReVia, Trexan)

Effectiveness	Safety	Cost	Convenience
😊😊	✅✅	$	👌👌👌

Drug Class

Opioid antagonist.

Indications

Self-injurious behavior (SIB).

Pros

Non-sedating, once-daily dosing, few side effects, effective for specific SIB subtypes.

Cons

Lacks pediatric formulation, limited evidence base.

Overview

Naltrexone is an opioid antagonist originally developed to treat opioid and alcohol dependence. It works by blocking mu-opioid receptors, preventing both exogenous and endogenous opioids from producing their usual effects. More recently, it has been used off-label to treat certain forms of severe self-injurious behavior (SIB), particularly in developmentally disabled individuals.

Use in Fragile X and SIB

In some individuals with SIB, especially those with institutionalization histories or high pain thresholds, the behavior may be reinforced by endogenous opioid release. Naltrexone blocks this effect, restoring normal pain perception and reducing reinforcement from the behavior. In such cases, it can lead to rapid reduction in SIB.

However, this pattern is relatively rare in Fragile X syndrome. Most Fragile X individuals engage in SIB as a response to anxiety, overstimulation, or sensory overload, rather than for reinforcement or pain modulation. In these cases, naltrexone is generally ineffective and may even worsen behavior. Clinical trials have reflected these mixed results.

Clinical Considerations

Naltrexone is well tolerated and does not cause sedation, cognitive dulling, or dependence. Mild liver enzyme elevations have been reported in rare cases, usually at high doses, so liver function monitoring is advisable. Care must be taken to avoid opioid medications during treatment, as naltrexone will block their effects and may precipitate withdrawal.

Common Side Effects

Nausea → Take with food.

Uncommon Side Effects

Precipitated opioid withdrawal → Avoid if patient is on any opioid medication.

Mild liver enzyme elevation → Monitor LFTs periodically.

Fatigue (rare): Usually transient.

Dosage

Children and Adults: Start at 25–50 mg by mouth once daily. Some may benefit from 100 mg every other day or daily, but higher doses are not typically needed.

Folic Acid

Effectiveness	Safety	Cost	Convenience
😊	✅✅	$	👌👌

Drug Class

Essential Nutrient.

Indications

Attention deficit, hyperactivity.

Pros

Inexpensive; unlikely to cause adverse psychiatric effects.

Cons

Ineffective in studies; difficult to obtain in therapeutic doses; may cause medical side effects.

Overview

Folic acid is a vitamin essential for many cellular biochemical reactions. Early studies hypothesized a link between folic acid deficiency and Fragile X syndrome due to chromosome expression in folate-deprived cells. However, clinical trials have shown no statistically significant benefit in Fragile X.

Some anecdotal reports suggest improvements in attention and behavior, which may relate to weak psychostimulant-like activity. However, high doses can cause zinc and B6

malabsorption, leading to diarrhea and other issues. Folic acid also lowers seizure threshold, raising concerns in Fragile X patients already prone to seizures.

Leucovorin (folinic acid) has also been promoted as a more potent form of folate but is expensive and lacks supporting evidence. Therefore, it is not recommended.

Interestingly, FRAXA-funded research by Dr. Iryna Ethell suggests folic acid may reduce zinc absorption, which in turn could reduce activity of matrix metalloproteinases (MMPs) — enzymes linked to immature synaptic development in Fragile X. This unintended zinc depletion could partly explain the perceived benefit reported by some parents.

Use in Fragile X

Despite no strong clinical evidence, folic acid is often used as a first treatment in younger children due to its safety and low cost. Ongoing parent reports and basic research raise the possibility of subtle benefit via MMP suppression, although this is not well studied. Until further research is available, folic acid may be used with cautious optimism in Fragile X, preferably at modest doses without zinc co-supplementation.

Common Side Effects

Diarrhea → reduce dose, split dosing, or try fiber supplements.

Uncommon Side Effects

Malabsorption of zinc or B6 → consider vitamin supplementation if used long-term.

Dosing Guidance

Start with 1–2 mg twice daily. Increase as tolerated to 5 mg twice daily. Some patients tolerate up to 30–40 mg/day.

Pharmacists must often compound a special suspension for higher doses, since the largest commercial tablet is only 1 mg.

Dr. Mike's Unvarnished Opinion

🤔 A relic of early Fragile X treatment, but still oddly compelling. Doesn't work for most but might do something for a few. Cheap, safe, and occasionally helpful but don't expect miracles.

Appendix A: Medications No Longer Recommended

Since the previous edition of this guide (2009), the following medications are no longer recommended for individuals with Fragile X syndrome.

Pemoline (Cylert): Withdrawn for liver toxicity.

Nefazodone (Serzone): Liver failure risk; discontinued in many countries.

Thioridazine (Mellaril): Dangerous cardiac side effects.

Geodon (ziprasidone): Rarely used; cardiac arrhythmia risk.

Neurontin (gabapentin): No benefit for Fragile X symptoms.

Paroxetine (Paxil): Discontinuation syndrome concerns; safer alternatives exist.

Olanzapine (Zyprexa): Severe weight gain; high metabolic risk.

Lamotrigine (Lamictal): Limited benefit in Fragile X; may be used rarely in seizure or mood instability.

Haloperidol (Haldol): High risk of motor side effects; replaced by safer alternatives.

Clonazepam (Klonopin): Risk of sedation, tolerance, and dependence; not recommended long-term.

Appendix B: Newly Added Medications

The following medications have been added to this guide since the previous edition (2009).

Vyvanse

Class: Stimulant

Vyvanse is a prodrug stimulant with smoother effects. A useful tool in the right patient.

Trintellix

Class: Antidepressant

Novel SSRI with cognitive enhancement. Fancy and expensive but may be worth it.

Rexulti

Class: Antipsychotic

Next-gen option related to Abilify. A 'Goldilocks' choice for tough cases.

Intuniv

Class: Alpha-agonist

Extended-release guanfacine. A smoother ride than clonidine.

Kapvay

Class: Alpha-agonist

Extended-release clonidine. Old drug, new trick.

baclofen

Class: GABA-B agonist

Could target some core Fragile X issues.

Topiramate

Class: Mood stabilizer

Effective but dumbs people down. Better as backup.

Vraylar

Class: Antipsychotic

Mood and behavior support. Strong tool with balance.

Jornay PM

Class: Stimulant

Evening-timed Ritalin. Covers early morning symptoms.