

A Medication Guide For Fragile X

by Michael R. Tranfaglia MD

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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, caretakers 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.

Additional copies of this guide can be ordered from FRAXA Research Foundation.

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About FRAXA Research Foundation

FRAXA Research Foundation is a national nonprofit organization which supports medical research aimed at finding a treatment or a 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 contact:

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Yesterday, today, and tomorrow

It is tempting to say that the field of psychopharmacology is enjoying explosive growth in knowledge and capability; however, we seem to have stalled. After a period of exciting expansion in 1990's, with many new drugs and new drug classes entering the market, the new century has brought an era of retrenchment. The FDA approved only 16 new drugs in all of 2007, in all specialties---a tiny number by recent historical standards, and the Feds are only getting more conservative. Pharmaceutical companies have responded by playing it safe: reformulating old drugs and developing more "me-too" medications which don't offer any real advantage over existing agents.

Meanwhile, neuroscience research has continued to make remarkable progress in understanding the inner workings of the brain. Basic mechanisms of disease are being elaborated for some of our most feared afflictions. Targets for drug development are being identified at a furious and unprecedented pace, even as fewer and fewer new drugs actually make it to the market. The gap between drug research and the availability of new medications has never been greater. So, there is much promise, and much potential, in the future of drug development. But there is also enormous frustration on all fronts.

While new treatments for neuropsychiatric disease continue to be developed, albeit at an agonizingly slow pace, we have also continued to gain experience with available medications. In some cases, we have discovered new uses for some very unlikely old drugs. In the treatment of fragile X, there has been remarkable progress in the development of new drugs which may well alter the course of the disease itself. These drugs are entering clinical trials in patients with fragile X now, and may be available in the next few years. Perhaps even more exciting, the same research which has identified these new drugs for fragile X has also pointed us to existing medications which appear to do much more for people with fragile X than we might have thought.

This updated version of the popular Medication Guide for Fragile X will attempt to bring the reader up to speed on developments in many different fields. Necessarily, it will avoid excessively technical descriptions, since most readers will not have a medical or scientific background, but some precision is required, and some technical terms must be used. It is valuable to consider the historical perspective, so for this updated edition all the old text will remain in place and unchanged (except in the case of gross errors, such as typos) and updates will be added and noted obviously. This is intended to allow the reader to understand how things have changed in the past few years, and to give some idea of how much things might change in the next few years. By retaining the old text, it will also allow the reader to judge how accurate this book has been in the past. This author believes it has stood up remarkably well over time---far better than other similar works---and that this should be documented.

This new version will also contain more content reminiscent of newspaper columns, or even editorials; while the Medication Guide has always aimed to provide insights into the process of the prescription of medications for behavioral problems, these opinion pieces are designed to give the reader further insight into the thought processes doctors use to choose medications. These processes can seem baffling to the outsider; indeed, they are not always rational. However, the insider (i.e. this author) is often aware of many factors affecting these decisions which are not obvious to parents seeking treatment for their children. Knowledge is power, and the more parents understand, the better they can navigate this often confusing world of behavioral medicine.

Trends in Psychiatry

The medical field is just like any other kind of human endeavor: subject to fads and herd mentality. While we'd all like to think that doctors rely only on science and only care about the best available evidence, doctors are people, too. Like everyone else, doctors are heavily influenced by what other people think, and the opinions of their medical peers are very important in determining practice patterns. In addition, doctors must function in an environment where information is usually insufficient. We don't know enough about how any part of the body works, yet all these parts can have problems, and doctors are expected to fix them when they do. Filling in these knowledge gaps is more art than science, and in this artistic facet of medicine, most doctors seek the consensus of their peers---medicine is a field for creative renegades only on TV.

So, each medical specialty has its own trends, which vary over time and by geographic region. This is by no means peculiar to psychiatry; all areas of medicine experience this same phenomenon, but here we are concerned with the effect of psychiatric fads on treatment of people with developmental disorders.

Major Tranquilizers: The Original Fad

The field of psychopharmacology didn't really exist until the first antipsychotic drugs became available in the 1950's. The first generation of antipsychotics, like Thorazine and Mellaril, revolutionized psychiatry by allowing direct biomedical treatment of psychosis. These "major tranquilizers" were powerful drugs with a wide range of effects (good and bad) which could actually treat schizophrenia and other major thought disorders for the first time. Unfortunately, the enthusiasm for these drugs was a bit overdone, and many people who were never psychotic were prescribed antipsychotics anyway. Why? As an old professor of mine used to say, "When all you have is a hammer, everything starts to look like a nail!" Nowhere did this megatrend of the 50's cause more problems than in the medical management of developmental disorders. Enormous numbers of people with DD were prescribed major tranquilizers for a wide range of symptoms. In some cases, the drugs had genuine benefits, but in many others, the main effect was non-specific sedation. Decades later, the chickens finally came home to roost, as thousands of people with developmental disorders were diagnosed with irreversible, drug-induced movement disorders.

Nowadays, these older antipsychotics are rarely used, and seldom prescribed to children. However, we may be seeing a similar phenomenon in our time. The newest generation of antipsychotics, usually called "atypical antipsychotics", are being prescribed in vast quantities to children and adults with developmental disorders. In part, this is because this class of drugs represents a significant advance compared to the older antipsychotics, though some critics argue that the differences in practice are not that great, and the real push is coming from pharmaceutical companies. Indeed, while the new drugs are more easily tolerated by patients, and they appear to be somewhat more effective in their primary indication, the treatment of schizophrenia, they are not the "silver bullet" many had hoped for. Risperdal (risperidone) became the first atypical antipsychotic actually

marketed for the treatment of autism after a large and well-done study showed efficacy in treating the irritability and behavior problems associated with autism. The multicenter trial described below led to FDA approval of Risperdal for this indication, the first formal approval of any treatment for autism.

N Engl J Med. 2002 Aug 1;347(5):314-21.

Risperidone in children with autism and serious behavioral problems.

McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D; Research Units on Pediatric Psychopharmacology Autism Network.

University of California, Los Angeles, USA.

BACKGROUND: Atypical antipsychotic agents, which block postsynaptic dopamine and serotonin receptors, have advantages over traditional antipsychotic medications in the treatment of adults with schizophrenia and may be beneficial in children with autistic disorder who have serious behavioral disturbances. However, data on the safety and efficacy of atypical antipsychotic agents in children are limited. **METHODS:** We conducted a multisite, randomized, double-blind trial of risperidone as compared with placebo for the treatment of autistic disorder accompanied by severe tantrums, aggression, or self-injurious behavior in children 5 to 17 years old. The primary outcome measures were the score on the Irritability subscale of the Aberrant Behavior Checklist and the rating on the Clinical Global Impressions - Improvement (CGI-I) scale at eight weeks. **RESULTS:** A total of 101 children (82 boys and 19 girls; mean [\pm SD] age, 8.8 \pm 2.7 years) were randomly assigned to receive risperidone (49 children) or placebo (52). Treatment with risperidone for eight weeks (dose range, 0.5 to 3.5 mg per day) resulted in a 56.9 percent reduction in the Irritability score, as compared with a 14.1 percent decrease in the placebo group ($P < 0.001$). The rate of a positive response, defined as at least a 25 percent decrease in the Irritability score and a rating of much improved or very much improved on the CGI-I scale, was 69 percent in the risperidone group (34 of 49 children had a positive response) and 12 percent in the placebo group (6 of 52, $P < 0.001$). Risperidone therapy was associated with an average weight gain of 2.7 \pm 2.9 kg, as compared with 0.8 \pm 2.2 kg with placebo ($P < 0.001$). Increased appetite, fatigue, drowsiness, dizziness, and drooling were more common in the risperidone group than in the placebo group ($P < 0.05$ for each comparison). In two thirds of the children with a positive response to risperidone at eight weeks (23 of 34), the benefit was maintained at six months. **CONCLUSIONS:** Risperidone was effective and well tolerated for the treatment of tantrums, aggression, or self-injurious behavior in children with autistic disorder. The short period of this trial limits inferences about adverse effects such as tardive dyskinesia.

This would seem to be good news, and in most ways it is. A commonly used treatment for autism spectrum disorders was shown to be efficacious in autistic children; this is good evidence that this drug and other atypical antipsychotics treat some of the most difficult symptoms of developmental disorders. However, all drugs have side effects, and

antipsychotics have more than most. Some of these are well known and well described. For example, a number of movement disorders, some irreversible, can occur with these medications. Fortunately, newer drugs are less likely to cause these problems, especially at the lower doses usually prescribed in developmental disorders. However, they seem to have some special problems of their own, like pronounced weight gain in younger patients, and unusual side effects such as this:

J Child Adolesc Psychopharmacol.

Risperidone-induced enuresis in two children with autistic disorder.

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INTRODUCTION: Risperidone appears to be effective in treating behavioral problems in children with autistic disorder. Although increased appetite, weight gain, and sedation are among the most common side effects, risperidone-induced enuresis is rarely reported. **METHOD:** We will present two cases with risperidone-induced enuresis, and discuss our findings in the context of current literature. **RESULTS:** Two children aged 11 and 10 years, diagnosed with autism and mental retardation, have developed new-onset diurnal and nocturnal enuresis respectively on their first and second weeks of risperidone monotherapy (1.5 and 1 mg/day). They did not experience sedation, and their medical history and workup were unremarkable. As enuresis did not resolve spontaneously, we decided to substitute risperidone with olanzapine. Enuresis ceased rapidly after discontinuation of risperidone with no emergence when patients were treated with olanzapine 5 mg/day for a period of 6 months and 1 year, respectively. **DISCUSSION:** Although the pathophysiology of antipsychotic-induced enuresis remains unclear, a number of mechanisms including alpha(1)-adrenergic blockade, dopamine blockade, and antimuscarinic effects has been proposed. Olanzapine has lower alpha(1)-adrenergic and dopaminergic blockade properties, thus changing risperidone to olanzapine may be an alternative modality in risperidone-induced enuresis when antipsychotic treatment is crucial. Clinicians should be more vigilant about screening for this side effect, especially in younger population with developmental disabilities.

Urinary incontinence is not usually associated with treatment with older antipsychotics, yet the newer drugs can cause this with surprising frequency in younger patients with DD.

By itself, this isn't a show-stopper, but this illustrates an important point. When a drug which is useful, but perhaps not the first choice in most cases, becomes the only drug actually officially approved for that indication, it suddenly becomes the first choice of many risk-averse doctors. Thus, Risperdal became the first choice for the treatment of all autism spectrum disorders, in the eyes of many physicians. That could be a big problem in the end, with atypical antipsychotics becoming more popular than their first-generation cousins ever were. While we'd like to think that these are simply better drugs, and their popularity is well-deserved, we may not know the whole story. People with MRDD suffer from a wide range of symptoms, and many are better treated with other classes of

medications. Risperdal and other atypical antipsychotics may be the first choice for some of these symptoms, but they're certainly not the first choice for most.

Newer Drugs Worth Noting:

Minocycline

Research sponsored by FRAXA Research Foundation has shown that the available antibiotic **minocycline** may be an especially effective treatment for the core deficits of fragile X. Preliminary results were presented at the recent conference, “The Shared Neurobiology of Fragile X Syndrome and Autism” at the University of Southern California, June 11-13, 2007. This work has just recent been published:

J Med Genet. 2008 Oct 3.

Minocycline Promotes Dendritic Spine Maturation and Improves Behavioral Performance in the Fragile X Mouse Model.

Bilousova T, Dansie L, Ngo M, Aye J, Charles JR, Ethell DW, Ethell IM.

University of California Riverside, United States.

BACKGROUND: Fragile X syndrome (FXS) is the most common single-gene inherited form of mental retardation, with behaviors at the extreme of the autistic spectrum. Subjects with FXS and Fragile X mental retardation gene knock out (Fmr1 KO) mice, an animal model for FXS, have been shown to exhibit defects in dendritic spine maturation that may underlie cognitive and behavioral abnormalities in FXS. Minocycline is a tetracycline analog that has been used in clinical trials for stroke, Multiple Sclerosis and several neurodegenerative conditions. **METHODS:** We evaluated the effects of minocycline on dendritic spine development in the hippocampus of young Fmr1 KO mice, and in primary cultures of hippocampal neurons isolated from those mice. Cognitive effects of minocycline in young WT and Fmr1 KO mice were also evaluated using established behavioral tests for general cognition, activity and anxiety. **RESULTS:** Our studies demonstrate that minocycline promotes dendritic spine maturation both in cultures and in vivo. The beneficial effects of minocycline on dendritic spine morphology are also accompanied by changes in the behavioral performance of 3-week-old Fmr1 KO mice. Minocycline-treated Fmr1 KO mice show less anxiety in the elevated plus-maze and more strategic exploratory behavior in the Y-maze as compared to untreated Fmr1 KO mice. Our data suggest that these effects of minocycline may relate to its inhibitory action on MMP-9 expression and activity, which are higher in the hippocampus of Fmr1 KO mice. **CONCLUSION:** These findings establish minocycline as a promising therapeutic for the treatment of Fragile X mental retardation.

Essentially, fragile X is caused by the absence of a single protein, FMRP. FMRP normally regulates the production of a number of critical proteins in and around the dendrites of neurons in response to synaptic activity. It is a key mediator of synaptic plasticity, and dysregulation of synaptic plasticity is thought to be the basis of fragile X syndrome. In the absence of FMRP (as in fragile X syndrome,) there is excessive production of a discrete set of synaptic proteins, usually in response to activation of group

I metabotropic glutamate receptors (mGluRs,) and our research has targeted these over-expressed proteins for potential therapeutic intervention. In particular, FRAXA-supported scientists have found that an extracellular enzyme called Matrix Metalloproteinase 9 (MMP-9) is significantly over-expressed in fragile X. MMP-9 is involved in tissue remodeling (including dendritic growth) and its over-expression in fragile X may also account for the universally observed soft tissue laxity.

The neuronal abnormalities of fragile X (long, thin dendritic spines) can be duplicated by artificially over-expressing MMP-9. Likewise, stimulation of mGluRs increases MMP-9 and induces long, thin spines. Blockade of mGluRs in fragile X mice decreases MMP-9 and normalizes dendritic spines; we are currently working with several pharmaceutical companies to develop mGluR5 antagonists, but these are not yet available. However, it has been known for some time that minocycline potently inhibits MMP-9 at usual antibiotic doses, and crosses the blood brain barrier quite efficiently. In the fragile X mouse model, this same research project has shown that minocycline normalizes dendritic spines, reduces MMP-9 levels to normal, and (most significantly) treats behavioral abnormalities like anxiety and seizure susceptibility.

Coincidentally, a study of the treatment of regressive autism with minocycline was recently initiated at NIH, based on a completely different hypothesized mechanism of action---the theory that regressive autism is caused by an inflammatory and/or autoimmune process, and the known anti-inflammatory effects of minocycline. Anti-inflammatory and neuro-protective effects are also the basis for the use of minocycline in rheumatoid arthritis, MS, ALS, and several other neurodegenerative conditions. The dose ranges in studies addressing neurodegenerative conditions have usually been well above typical antibiotic doses, but the regressive autism study is utilizing a typical antibiotic dose, treating children as young as 3 years of age. In yet another interesting coincidence, an Orphan Drug Designation was recently granted by the FDA for the development of minocycline as a treatment for pediatric obsessive-compulsive disorder; most fragile X patients display significant obsessive-compulsive symptoms.

The animal studies described previously represent impressive proof of principle, and have prompted the organization of fragile X clinical trials. In the meantime, there has been some experience with open, off-label use of minocycline as an add-on treatment for fragile X, and it has been markedly positive to date in subjects ranging in age from 5 to 48. Minocycline is ordinarily not recommended for patients under 8 years of age because of the risk of permanent tooth staining, though the autism trial mentioned above is treating patients as young as 3, and some studies suggest that the risk of enamel deposits is not as great as generally thought. The usual dose of minocycline is 50 mg PO qD or BID in younger patients, and 100 mg PO qD or BID in adults, and these are the doses used to date in fragile X subjects. Improved language utilization, decreased anxiety and repetitive/perseverative behaviors, decreased mood lability, and generally improved cognition have been reported in initial, uncontrolled use of minocycline. These effects are usually readily apparent within the first 2-3 weeks of treatment, though one would expect that longer-term treatment would be required to yield true developmental enhancement. Significant improvement in connective tissue abnormalities (such as flat feet and aortic root dilation) have been reported with extended treatment. It is worth noting that mice in

the Ethell study were treated with minocycline for the first 4 weeks of their lives. This is the equivalent of human treatment for the first 2-3 years of life, and it is reasonable to assume that treatment later in life would require an even longer duration to achieve optimal results. Fortunately, minocycline has an excellent track record of safety in long-term use (typically for acne) in millions of teenagers worldwide. While rare (approx. 1:10,000) side effects such as severe autoimmune responses and elevated intracranial pressure have been reported, minocycline is clearly a much safer drug than any antipsychotic or any anticonvulsant on the market today. Clinicians rarely hesitate to employ those agents where appropriate, so we must now focus on clinical demonstration of efficacy in treating fragile X, and the first formal clinical trials are now under way.

This is intended to serve as an explanation of the rationale for prescribing minocycline as an off-label treatment for fragile X. It should not be considered full prescribing information or a formal recommendation, since pivotal proof of efficacy studies remain to be done. However, such studies are unlikely to be completed and published for at least 2-3 years; since minocycline is an available agent with a benign side-effect profile, it is likely that many fragile X families will entertain the possibility of a minocycline trial in the interim. Hopefully, this information is useful, along with the usual medical references, in weighing the risks and benefits of this developing treatment strategy in consultation with a trusted physician.

Dr. Mike's unvarnished opinion: seems too good to be true, but it really works!

Provigil (modafinil)

One of the great challenges in the treatment of fragile X is that most affected children are quite hyperactive and have poor attention, yet most of the typical ADHD medications carry serious liabilities for this patient group. As noted in the discussion of stimulants, all the various amphetamine and methylphenidate formulations can cause significant psychiatric side effects in kids (and adults) with fragile X. Irritability, mood lability, increased anxiety, and aggression are all frequent adverse effects of stimulant treatment in people with fragile X. While the frequency of these side effects is apparently greater in more affected individuals, just about anyone with fragile X is at an increased risk compared to the general population.

This leaves us searching for alternatives to conventional stimulants, and Provigil may be a useful alternative. Modafinil is chemically unrelated to amphetamines or methylphenidate, and has a somewhat different spectrum of pharmacologic activity. It has been used (off-label) in a large number of fragile X patients to enhance attention and decrease hyperactivity.

Modafinil

From Wikipedia, the free encyclopedia

Modafinil (Provigil) is a stimulant-like drug manufactured by Cephalon, and is approved by the U.S. Food and Drug Administration (FDA) for the treatment of narcolepsy, shift work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea. Modafinil, like other stimulants, increases the release of monoamines but also elevates hypothalamic histamine levels, leading some researchers to consider Modafinil a "wakefulness promoting agent" rather than a classic amphetamine-like stimulant (as evidenced by the difference in c-fos distribution caused by modafinil as compared to amphetamine). Although modafinil is thought to be effective in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD), in 2006 it was specifically rejected by the FDA for use by children for that purpose after Cephalon was rebuffed in its effort to introduce modafinil as a children's drug under the trade name, Sparlon. Cephalon's own label for Provigil now discourages its use by children for any purpose. Modafinil has been shown to be effective in the treatment of depression, cocaine addiction, Parkinson's Disease, schizophrenia, and disease-related fatigue. By law, however, Cephalon is not allowed to market Modafinil for conditions other than those officially approved by the FDA.

Modafinil and its chemical precursor Adrafinil were developed by Lafon Laboratories, a French company acquired by Cephalon in 2001. Modafinil is the primary metabolite of adrafinil, and, while their activity is similar, adrafinil requires a higher dose to achieve equipotent effects.

Indications

In the United States, modafinil is approved by the U.S. Food and Drug Administration for the treatment of narcolepsy, obstructive sleep apnea/hypopnea and shift work sleep disorder. In some countries, it is also approved for idiopathic hypersomnia (all forms of excessive daytime sleepiness where causes can't be established).

Off-label use

Modafinil is widely used off-label to suppress the need for sleep. It is also used off-label in combating general fatigue unrelated to lack of sleep such as in treating ADHD and as an adjunct to antidepressants (particularly in individuals with significant residual fatigue). There is a disagreement whether the cognitive effects modafinil showed in healthy non-sleep-deprived people are sufficient to consider it to be a "cognitive enhancer." The researchers agree that modafinil improves some aspects of working memory, such as digit span, digit manipulation and pattern recognition memory, but the results related to spatial memory, executive function and attention are equivocal. Some of the positive effects of modafinil may be limited to "lower-performing" individuals or to the individuals with lower IQ. There is also evidence that it has neuroprotective effects. Modafinil may be also an effective and well-tolerated treatment in patients with seasonal affective disorder/winter depression.

ADHD

As of February 2007, there are at least seven English-language articles on randomized clinical trials in humans in the Medline database addressing the use of modafinil for the treatment of attention deficit/hyperactivity disorder (ADHD). Some studies have shown the use of modafinil in the treatment of ADHD is associated with significant improvements in primary outcome measures. Cognitive function in ADHD patients was also found to improve following modafinil treatment, in some studies. Studies for ADHD report insomnia and headache were the most common adverse effects, seen in approximately 20% of treated individuals. These studies were not adequate to demonstrate that the beneficial effects of modafinil are maintained with chronic administration. Additional large, long-term studies using flexible titration methods to establish safety and efficacy and head-to-head comparisons between modafinil and stimulants are needed to determine the role of modafinil in the treatment of ADHD.

In December 2004, Cephalon submitted a supplemental new drug application (sNDA) to market Sparlon, a brand name of tablets containing higher doses of modafinil for the treatment of ADHD

in children and adolescents ages 6 through 17. However, in March 2006, the FDA advisory committee voted 12 to 1 against approval, citing concerns about a number of reported cases of skin rash reactions in a 1000-patient trial, including one which was thought to be likely a case of Stevens-Johnson syndrome. Final rejection occurred in August 2006, although subsequent follow-up indicated that the skin rash reaction was not Stevens-Johnson syndrome. Cephalon then decided to discontinue development of the Sparlon product for use in pediatric cases, though there is potential for use in treating Adult ADHD.

Modafinil is relatively contraindicated for patients with a history of cardiac events. However, one 2005 case report positively describes transitioning a 78 year old with "significant cardiac comorbidity" from methylphenidate (5 mg b.i.d.) to modafinil; however, this was in the setting of severe treatment resistant depression, not ADHD. Thus, Modafinil's physiologic (and political) advantages over conventional ADHD therapies should not be dismissed out of hand, but rather discussed individually with a physician, neurologist or psychiatrist.

Side-effects

The most common side-effects observed with modafinil, as compared to placebo, when prescribed in the recommended doses for the approved indications, are as follows:

Common Headache (34% vs 23%); Nausea (11% vs 3%)

Less common Nervousness (7% vs 3%); Insomnia (5% vs 1%), Anxiety (5% vs 1%); Dizziness (5% vs 4%)

Infrequent Chest pain (3% vs 1%); Hypertension (3% vs 1%); Tachycardia (2% vs 1%); Vasodilatation (2% vs 0%); Dry mouth (4% vs 2%); Paresthesia (2% vs 0%); Pharyngitis (4% vs 2%); Anorexia (4% vs 1%)

In 2007, the FDA ordered Cephalon to modify the Provigil leaflet in bold-face print of several serious and potentially fatal conditions attributed to modafinil use, including TENS, DRESS syndrome, and most seriously, Stevens-Johnson Syndrome (SJS).

Additionally, gastrointestinal distress, which may be alleviated by taking the drug after a meal, aggressiveness and skin irritation have been reported, but are rare. Most side-effects subside after a few weeks without reducing the dose. Only headaches and anxiety have been shown to be proportional to dose, and these may benefit from a temporary reduction or dividing the dose. A single case of premature ventricular contractions appeared causally linked to administration of modafinil.

Modafinil may have an adverse effect on hormonal contraceptives, lasting for a month after cessation of dosage. Modafinil toxicity levels vary widely among species. In mice and rats, the median lethal dose LD50 of modafinil is approximately or slightly greater than 1250 mg/kg. Oral LD50 values reported for rats range from 1000 mg/kg to 3400 mg/kg. Intravenous LD50 for dogs is 300 mg/kg. In clinical trials on humans, taking up to 1200 mg/day for 7 to 21 days or one-time doses up to 4500 mg did not appear to cause life-threatening effects, although a number of adverse experiences were observed, including excitation or agitation, insomnia, anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, and diarrhea. As of 2004, FDA is not aware of any fatal overdoses involving modafinil alone (as opposed to multiple drugs, including modafinil). Consequently, oral LD50 of modafinil in humans is not known exactly. However, it appears to be higher than oral LD50 of caffeine.

The experience with Provigil (modafinil) in fragile X patients has been quite positive overall: the medication is clearly better tolerated than typical stimulants, and it does seem

to be effective in enhancing attention. This may simply be the result of lower potency; modafinil is not a potent psychostimulant, and the usual starting dose of 100 mg is easy for most people to tolerate. Of course, higher doses may be required for best effect, and larger/older individuals may require up to 400 mg/d to obtain the best effect. Modafinil is relatively long-acting, so it can often be given once a day; however, it can be dosed in the morning and mid-day to reduce the side effects of large single doses (such as headache and GI upset.) One major disadvantage is cost: Provigil is very expensive, and Cephalon has been raising prices steadily as off-label use has increased. For this reason, some insurance plans will not cover the off-label use of this drug.

Dr. Mike's unvarnished opinion: overpriced, but useful if you need a stimulant-lite.

Trileptal (oxcarbazepine)

Trileptal is essentially a new, improved version of Tegretol (carbamazepine.) It is very closely related to carbamazepine chemically, but does not cause the worst kind of carbamazepine toxicity: suppression of white blood cells. For this reason, blood levels are not required for people taking Trileptal---a major advantage in the case of fragile X and other developmental disorders. Unlike Tegretol, which is dosed to achieve a particular blood level, the dose of Trileptal can simply be titrated upward for best effect, within the limits of tolerability. This makes Trileptal a natural choice for people with fragile X who require treatment for a seizure disorder, and Trileptal appears to be just as good at treating the complex-partial seizures which are frequently seen in fragile X. Most of the other side effects of Trileptal are the same as those seen with Tegretol, but these meds generally cause less sedation and weight gain than other anticonvulsants, and they do not seem as likely to cause irritability and other behavioral problems as many other anticonvulsants. Trileptal is generally thought to have the same mood-stabilizing effects as Tegretol, and so it is often used to treat Bipolar Disorder and other psychiatric conditions. Thus, Trileptal may be prescribed to people with fragile X for purely psychiatric reasons, in the absence of any seizure disorder. While the efficacy of anticonvulsants in the psychiatric treatment of people with fragile X is somewhat suspect, in the opinion of this author, Trileptal does seem to be a genuine improvement, and may be a worthwhile treatment for fragile X.

This medication is usually initiated at a relatively low dose, 100-200 mg twice a day in children, 200-400 mg twice a day in older individuals, then increased gradually up to a maximum of 2400 mg/d in divided doses (can be given 3 or 4 times a day to minimize acute side effects) to achieve the desired effect. The most serious side effect encountered with this medication, like Tegretol, is low sodium in the bloodstream (hyponatremia.) This is medically significant, though not usually life threatening, and can manifest as a sudden increase in confusion or lethargy, sometimes with swelling in the ankles; often this hyponatremia is not symptomatic and is only detected on a blood test. The risk of this adverse effect increases with higher doses and with older patient age. Very low sodium can cause seizures and delirium. Drug discontinuation or fluid restriction typically results in rapid resolution of this form of hyponatremia.

Like Tegretol (carbamazepine), though to a somewhat lesser extent, Trileptal will induce certain liver enzymes which metabolize other drugs. Your pharmacist can alert you to which medications might need dose adjustment, but the most significant effects seen in psychiatric treatment occur with antipsychotics. Most of the older and newer (atypical) antipsychotics will be metabolized more rapidly by patients who are taking either of these drugs. In some cases, this effect can be striking, with a decrease of the drug's blood level by as much as 90%. This happens because carbamazepine and oxcarbazepine induce some liver enzymes, and this process occurs over a few weeks. If a patient is taking an antipsychotic, then starts taking one of these drugs, for whatever reason, that individual can experience a loss of efficacy of the antipsychotic over the course of 1-4 weeks. This can be very perplexing if the prescribing physician is unaware of this mechanism, and it is easy to mistakenly conclude that the second medication (i.e. Tegretol or Trileptal) made the patient's condition worse. This is not, strictly speaking, true. The anticonvulsant simply lowered the level of the antipsychotic, necessitating upward dose titration of the antipsychotic.

To complicate things even further, carbamazepine and oxcarbazepine induce their own metabolism, so the doses of these medications usually require adjustment after the process levels out, usually at the 4-6 week mark. So, if an individual with fragile X is treated with Trileptal for several weeks with good results, then appears to suffer a recurrence of symptoms, this may be why. A simple dose increase, which is really only getting back to the previously effective blood level, should set things straight.

Dr. Mike's unvarnished opinion: useful in any situation where you might use Tegretol.

Newer Drugs Not Worth Noting

While new drugs are being introduced all the time, many are not especially useful in treating fragile X, or they have no particular advantage over existing drugs. Space doesn't allow for discussion of every medication on the market, especially with the recent brand and formulation proliferation in the psychiatric marketplace.

However, some drugs simply need to be avoided, and these do deserve a special mention. *Please note: if you or a family member is currently prescribed one of these medications, do not stop it simply because you've read my negative opinions---talk to your doctor!*

Geodon (ziprasidone)

Geodon is an atypical antipsychotic which has never really caught on, mainly because every now and then it causes someone's heart to stop suddenly (in technical terms, it causes Q-T prolongation, disrupting the electrical signals within the heart.) It is an effective drug, with antipsychotic and mood-stabilizing properties, though this (rare) side effect has kept it from widespread use, and it is hardly ever used in pediatric patients. On the plus side, it causes very little weight gain, though it probably has no advantage over Abilify in this regard. It can be difficult to dose in adults, with a highly non-linear dose-response relationship, and it is every bit as expensive as its atypical antipsychotic classmates. For these reasons, there has been little experience using this drug in the treatment of developmental disorders, and so this is not a drug to be recommended for use in fragile X.

Dr. Mike's unvarnished opinion: an OK antipsychotic, but hard to justify its use in fragile X, especially with all the alternatives available. Might be worth a try in adults with weight problems.

Lamictal (lamotrigine)

Lamictal is an anticonvulsant drug, and it may be effective in controlling seizures in some patients with fragile X. However, it is much more commonly used in the US to treat psychiatric disorders. In fact, it has been officially approved by the FDA for the treatment of Bipolar Disorder, and this indication has turned a little-used seizure med into a blockbuster drug for its maker, Glaxo. As an anticonvulsant, it does not appear to be especially effective in fragile X (though it may be an essential part of an effective combination, so please do not stop this medication based on this information!) It can cause severe and potentially fatal allergic reactions, so it must be monitored very carefully, with only small, incremental dose increases. Because this is such a popular treatment in psychiatry generally, it seems inevitable that it will be tried in fragile X patients for purely psychiatric (as opposed to neurologic) reasons. Indeed, a study has already been done in autism:

Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial.

Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW.

The Center for Autism and Related Disorders, Kennedy Krieger Institute, Baltimore, Maryland, USA.

In autism, glutamate may be increased or its receptors up-regulated as part of an excitotoxic process that damages neural networks and subsequently contributes to behavioral and cognitive deficits seen in the disorder. This was a double-blind, placebo-controlled, parallel group study of lamotrigine, an agent that modulates glutamate release. Twenty-eight children (27 boys) ages 3 to 11 years (M = 5.8) with a primary diagnosis of autistic disorder received either placebo or lamotrigine twice daily. In children on lamotrigine, the drug was titrated upward over 8 weeks to reach a mean maintenance dose of 5.0 mg/kg per day. This dose was then maintained for 4 weeks. Following maintenance evaluations, the drug was tapered down over 2 weeks. The trial ended with a 4-week drug-free period. Outcome measures included improvements in severity and behavioral features of autistic disorder (stereotypies, lethargy, irritability, hyperactivity, emotional reciprocity, sharing pleasures) and improvements in language and communication, socialization, and daily living skills noted after 12 weeks (the end of a 4-week maintenance phase). We did not find any significant differences in improvements between lamotrigine or placebo groups on the Autism Behavior Checklist, the Aberrant Behavior Checklist, the Vineland Adaptive Behavior scales, the PL-ADOS, or the CARS. Parent rating scales showed marked improvements, presumably due to expectations of benefits.

This study was reasonably well done, with a modest-sized group of subjects, and showed absolutely no effect from the drug. Often there are numerical advantages seen in the drug-treated group in studies of this type, but these may not reach statistical significance; in this case there was no difference of any kind. It just doesn't do anything useful for the kinds of symptoms seen in autism spectrum disorders (including fragile X.) Thus, its use in psychiatric treatment of fragile X cannot be recommended, given the potentially serious side effects (not to mention its high cost and extreme difficulty of use.)

Dr. Mike's unvarnished opinion: a weak psychotropic agent with particular disadvantages in treating fragile X; the psychiatric niche (bipolar depression) really doesn't apply to the vast majority of people with developmental disorders.

Neurontin (gabapentin)

Neurontin is one of the least useful drugs in history, and the subject of one of the sorriest scandals in modern pharmaceutical history. Unfortunately, some doctors still haven't figured out that they were scammed, and a few persist in prescribing this drug for various inappropriate indications. Thus, a caveat is in order. A brief history, via Wikipedia:

Gabapentin is best known under the brand name Neurontin manufactured by Pfizer subsidiary Parke-Davis. A Pfizer subsidiary named Greenstone markets generic gabapentin. In December

2004, the FDA granted final approval to a generic equivalent to Neurontin made by Israeli firm Teva.

Neurontin is one of Pfizer's best-selling drugs, and was one of the 50 most-prescribed drugs in the United States in 2003. However, in recent years, Pfizer has come under heavy criticism for its marketing of Neurontin, facing allegations that, behind the scenes, Parke-Davis marketed the drug for at least a dozen supposed uses for which the drug had not been FDA approved.

By some estimates, so-called off-label prescriptions account for roughly 90% of Neurontin sales. While off-label prescriptions are common for a number of drugs and are perfectly legal (if not always appropriate), marketing of off-label uses of a drug is strictly illegal. In 2004, Warner-Lambert agreed to plead guilty and pay \$430 million in fines to settle civil and criminal charges regarding the illegal marketing of Neurontin for off-label purposes, and further legal action is pending. The courts of New York State, for example, have refused to certify a class of injured parties who took Neurontin for off-label use, finding that they had failed to state that they had any injury.

The University of California, San Francisco (UCSF) has archived and studied the documents made public by this case, which opens a unique window into pharmaceutical marketing and their illegal promotion. However, Pfizer maintains that the illegal activity originated in 1996, well before it acquired Parke-Davis (through its acquisition of Warner-Lambert) in 2000. Several lawsuits are underway after people prescribed gabapentin for off-label treatment of bipolar disorder attempted or committed suicide.

In fact, Neurontin was very heavily marketed (illegally) to psychiatrists (including this author) by its manufacturer as a new treatment for Bipolar Disorder, with no evidence to support its use. At one point, Neurontin was probably the single most commonly prescribed drug for Bipolar Disorder, and its use was widespread for many other off-label indications. Eventually, FDA pressure led the company to do some actual research, which showed that Neurontin was *slightly less effective than placebo* in treating Bipolar Disorder! So why did anyone ever prescribe this dud? Because it's *sooo* well tolerated (again, from Wikipedia):

Gabapentin's most common side effects in adult patients include dizziness, drowsiness, and peripheral edema (swelling of extremities); these mainly occur at higher doses, in the elderly. Also, children 3–12 years of age were observed to be susceptible to mild-to-moderate mood swings, hostility, concentration problems, and hyperactivity. Although rare, there are several cases of hepatotoxicity reported in the literature.

Clinical experience in fragile X shows gabapentin to be rather ineffective in its primary indication (epilepsy) and entirely useless as a psychiatric treatment. Indeed, most fragile X patients treated with Neurontin exhibit markedly worse behavior. This typically manifests as behavioral disinhibition---decreased impulse control, defiant and unruly behavior, etc. Aggression, irritability, and mood lability (already a problem) usually get much worse when Neurontin is introduced. Now, to be fair, gabapentin probably does have some role in the treatment of certain chronic pain conditions---it's not complete garbage---but it is not a useful psychotropic, period.

As a litmus test for psychopharmacologists, you could not do better than simply asking how much Neurontin that doctor has used (this author has never written a single prescription or recommended it to any patient---ever.) Any psychiatrist who still uses this

medication is not worth seeing; if any doctor recommends Neurontin to you or a family member for a psychiatric purpose, run away and don't look back. (*You may have noticed that I feel strongly about this; the misrepresentation of Neurontin by Big Pharma and the wholesale, unthinking acceptance of a worthless drug by the psychiatric profession represent embarrassing low points for both.*)

Dr. Mike's unvarnished opinion: in case it's not obvious, I don't really like Neurontin very much.

Pristiq (desvenlafaxine)

One way that pharmaceutical companies can extend the lives of their older drugs which are about to go off-patent is to introduce a new formulation of the old drug (controlled release or CR, and extended release or XR versions are popular for this reason.) Another way is to come out with a purified stereo-isomer of the chemical compound (for example, Lexapro is S-citalopram, the "left-handed" version of citalopram; Celexa is a mix of R and S-citalopram.) Yet a third way is to find the active metabolite of the compound, and market that as a new drug. Thus, Pristiq is the active metabolite of venlafaxine (previously known by the brand name Effexor, then Effexor XR.) It's always easier and cheaper for the company to invest in this kind of project, since they know the basic compound is safe, effective, and likely to be approved by the FDA---after all, it's the same drug patients have already been taking for year of general-market use, with only minor modifications.

In some cases, these minor modifications make the drug much better---Effexor XR has a much longer duration of action than the very short-acting, three-times-a-day regular Effexor. But in some cases, there is essentially no difference, other than the much bigger price tag. Paxil CR was introduced as a patent-extender for the mediocre also-ran SSRI Paxil; but Paxil is already slowly absorbed and long acting, so there is no compelling rationale for Paxil CR (at least not from the patient's point of view!) Likewise, Pristiq is being heavily promoted by its manufacturer as having fewer side effects and greater efficacy and ease of use than its predecessor, Effexor. However, there is no reason to think that Pristiq is any better than Effexor XR, since anyone taking this will have mainly desvenlafaxine (Pristiq) in their system.

In addition, venlafaxine in all its various forms is probably not the best drug for people with fragile X---its dual mechanism of action is highly touted for its potential effectiveness, but carries a much higher side effects burden. Essentially, venlafaxine increases levels of two neurotransmitters, norepinephrine and serotonin, while many other popular drugs focus on just serotonin. This may be a genuine advantage in treating depression, but not fragile X. The extra norepinephrine can cause extra agitation and activation, and dual mechanism antidepressants are much more likely to trigger mania than those with a single neurotransmitter mechanism (ie SSRIs.) It also causes physical side effects, like hypertension, which is rarely seen with SSRIs. Most importantly, the added mechanism of action, with all its extra side effects, makes it nearly impossible to get the high levels of serotonin necessary for treatment of obsessive-compulsive symptoms. One of the major reasons why SSRIs became the first practical treatments for

OCD is because it is easy to tolerate very high doses of these drugs, and high doses are required for the best effect (which is still just a partial effect.) High doses of SSRIs, in the “anti-obsessional” dose range, have been shown to be optimal for the treatment of autism spectrum disorders, and clinical experience in fragile X patients indicates that the same is true in this case. It is a rare patient who can tolerate a dose of Effexor or Pristiq high enough to treat OCD, so these medications have limited usefulness in fragile X.

Dr. Mike’s unvarnished opinion: a waste of time and money; the kind of drug that gives the pharmaceutical industry a bad name.

Available Without a Prescription

L-acetyl carnitine (or acetyl-L-carnitine, ALCAR)

In an odd twist of fate, the one drug with the best track record in fragile X clinical trials has never shown any efficacy in fragile X preclinical animal models. L-acetyl carnitine (LAC), otherwise known as ALCAR or acetyl-L-carnitine, is a naturally occurring substance which is widespread throughout our bodies. It is involved in many cellular and metabolic processes, including energy metabolism, and it is usually involved in the production of the neurotransmitter acetylcholine. As a natural product it is available without a prescription, usually sold with other supplements and “nutraceuticals.” Research on LAC in fragile X has been confined entirely to Italy, where stimulant medications are difficult to obtain, and where this supplement is considered a substitute for stimulants in the treatment of hyperactivity. The original studies which form the basis for this treatment strategy are summarized below:

Rev Neurol. 2001 Oct;33 Suppl 1:S65-70

L-acetylcarnitine treatment on fragile X patients hyperactive behaviour

Calvani M, D'Iddio S, de Gaetano A, Mariotti P, Mosconi L, Pomponi MG, Tabolacci E, Torrioli MG, Vernacotola S, Neri G.

Departamento Científico, Sigma-Tau S.p.A., Rome, Italy.

Hyperactivity is a significant problem for almost all young males affected by fragile X syndrome (FXS), the most common inherited disease causing mental retardation. Therapeutical approaches are actually based on Central Nervous System (CNS) stimulants lacking a well defined rationale and efficacy while they further decrease the patient's limited attention span. A pilot study on 17 fragile X male treated with L-acetylcarnitine (LAC) over one year, showed a significant reduction of their hyperactivity behaviour tested by the Conners Abbreviated Parent-Teacher Questionnaire. LAC use in FXS patients derives from the hypothesis that the biochemical and physiological properties this substance has may preserve brain activity. LAC is a small, hydrosoluble molecule that easily diffuses in the extracellular space and enters any cell in the nervous system through specific transporters. Different cerebral areas use this molecule differently to metabolize glucose and lipids to provide for ATP and neurotransmitters synthesis. The acetyl group LAC carriers represents a key metabolic signaling element possibly mediating its effect in the CNS. The exogenous administration of LAC may affect brain activity in FXS by: I) modulation of fuel partitioning for energy production, which at the mitochondrial level is associated with the Krebs's cycle metabolic role in neurotransmitter synthesis; II) remodelling of lipid membrane in terms of LAC actively determining the production of polyunsaturated fatty acids; III) preferential effect on the attention component of the cholinergic system which relies on its peculiar modality of communication in the CNS. Based on the above premises an explorative, double-blind, placebo controlled, multicenter study is ongoing. A total population of 160 children from

nine European centers will be enrolled. The objective of this study is to determine the effect of LAC on the hyperactive behaviour of FXS children as evaluated by the administration of the Conners Abbreviated Parent Questionnaire.

Am J Med Genet A. 2008 Apr 1;146(7):803-12.

A double-blind, parallel, multicenter comparison of L-acetylcarnitine with placebo on the attention deficit hyperactivity disorder in fragile X syndrome boys.

Torrioli MG, Vernacotola S, Peruzzi L, Tabolacci E, Mila M, Militerni R, Musumeci S, Ramos FJ, Frontera M, Sorge G, Marzullo E, Romeo G, Vallee L, Veneselli E, Cocchi E, Garbarino E, Moscato U, Chiurazzi P, D'Iddio S, Calvani M, Neri G.

Cattedra di Neuropsichiatria Infantile, Università Cattolica, Rome, Italy.

Attention deficit hyperactivity disorder (ADHD) is a frequent behavioral problem in young boys with fragile X syndrome (FXS), and its treatment is critical for improving social ability. The short-term efficacy of stimulant medications like methylphenidate (MPH) is well established in children with ADHD. FXS boys treated with MPH have improved attention span and socialization skills; however their mood becomes unstable at higher doses. Therefore, alternative pharmacological treatment of ADHD symptoms is desirable. A recent study showed that carnitine has a beneficial effect on the hyperactive-impulsive behavior in boys with ADHD without side effects. Our previous placebo-controlled trial indicated that L-acetylcarnitine (LAC) reduces hyperactivity in FXS boys. The objective of this study was to determine the efficacy of LAC in a larger sample of FXS boys with ADHD. The study design was randomized, double blind placebo controlled, parallel, and multicenter (with eight centers involved in Italy, France, and Spain). Sixty-three FXS males with ADHD (aged 6-13 years) were enrolled; 7 patients dropped out, 56 completed the one-year treatment, and 51 were included in the statistical analysis. Both groups improved their behavior, showing that psychosocial intervention has a significant therapeutic effect. However, we observed a stronger reduction of hyperactivity and improvement of social behavior in patients treated with LAC, compared with the placebo group, as determined by the Conners' Global Index Parents and the Vineland Adaptive Behavior Scale. Our results show that LAC (20-50 mg/kg/day) represents a safe alternative to the use of stimulant drugs for the treatment of ADHD in FXS children.

Overall, LAC showed a rather weak effect on hyperactivity at a typical dose of 500 mg twice a day; other studies of LAC in ADHD populations have been equivocal. The studies also used rather atypical methodology, and the actual results do not appear to justify some of the conclusions stated in the original articles. It is also possible that dosing was sub-optimal in some cases. The researchers have commented that they believe some individuals could have benefited from a higher dose than that allowed by the study protocol, as 500 mg 3 times a day is commonly utilized in the general population when taking this supplement. This might appear to be a potentially useful strategy for fragile X

children who suffer primarily from hyperactivity, prior to consideration of a stimulant trial (or other treatment for ADHD symptoms.) However, direct clinical experience with LAC treatment in the US has not been especially encouraging---if there is any effect at all with this supplement, it is much weaker than that which can be obtained with other (prescription) treatments. Side effects are typically mild or non-existent, so a trial of LAC is relatively risk-free (and inexpensive.) Given the putative mechanism of action (enhancement of cellular energy metabolism) it may eventually turn out that combinations of LAC with antioxidants such as vitamin E may be required for best effect.

Dr. Mike's unvarnished opinion: probably doesn't do much, at least not by itself. "A 21st century folic acid!"

Taurine

Recent research in the fragile X mouse model suggests that the nutritional supplement and naturally occurring amine, taurine, may have a therapeutic role in fragile X:

Adv Exp Med Biol. 2009;643:191-8.

Taurine improves cognitive functions in a mouse model of fragile X syndrome.

El Idrissi A, Boukarrou L, Dokin C, Brown WT.

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Increased seizure susceptibility is a feature of the mouse model for fragile X that has parallels in the hyperarousal and prevalence of seizures in the fragile X syndrome. Our investigation of the basis for the increased seizure susceptibility of the fragile X mouse indicated a reduction in GABA(A) receptor expression and increased expression of glutamic acid decarboxylase (GAD), the enzyme responsible for GABA(A) synthesis. Taurine-fed mice also show these GABAergic alterations. However, unlike fragile X mice, taurine-fed mice show a significant increase in memory acquisition and retention. This discordance implies that there may be divergent events downstream of the biochemical changes in the GABAergic system in these two mouse models. To investigate the divergence of these two models we fed taurine to fragile X mice. Our preliminary data shows that taurine supplementation to fragile X mice resulted in a significant improvement in acquisition of a passive avoidance task. Since taurine is an agonist for GABA(A) receptor, we suggest that chronic activation of GABA(A) receptors and the ensuing alterations in the GABAergic system may have beneficial effects in ameliorating the learning deficits characteristic of the fragile X syndrome.

However, there have been no clinical trials of any kind in fragile X subjects, and clinical use has been very limited. This author has consulted on a small number cases in which children with fragile X in the 6-10 range were prescribed taurine (obtained from local vitamin shops) at doses of 500 mg 2-3 times per day. More than half the families reported positive effects, primarily enhanced attention, with decreased anxiety and hyperactivity,

and elected to stay on the supplement long-term. None of the families reported any significant adverse effects.

How could taurine be of benefit in fragile X? The most likely effect is as an enhancer of inhibitory neurotransmission; it is thought that fragile X involve an excess of excitatory neurotransmission, and a relative deficit in inhibitory activity. Most inhibitory neurotransmission is mediated by gamma amino butyric acid (aka GABA) and taurine appears to act as a GABA agonist (and may even act as an inhibitory neurotransmitter in its own right.) In addition, chronic taurine administration may enhance levels of the hormone somatostatin, which appears to be low in fragile X (at least, in the knockout mouse.) Taurine has many functions in the body, many of which are still poorly understood, and exogenously applied taurine has wide-ranging effects. However, it does appear to be quite safe, and as a “natural product” its use is not regulated by the FDA. This is the same compound found in some “energy” drinks like Red Bull (along with large amounts of caffeine, sugar, and many other ingredients---so their use is not recommended.)

From Wikipedia:

Taurine crosses the blood-brain barrier and has been implicated in a wide array of physiological phenomena including inhibitory neurotransmission, long-term potentiation in the striatum and hippocampus, membrane stabilization, feedback inhibition of neutrophil/macrophage respiratory burst, adipose tissue regulation and possible prevention of obesity, calcium homeostasis, recovery from osmotic shock, protection against glutamate excitotoxicity and prevention of epileptic seizures. It also acts as an antioxidant and protects against toxicity of various substances (such as lead and cadmium). Additionally, supplementation with taurine has been shown to prevent oxidative stress induced by exercise.

There is also evidence that taurine is beneficial for adult human blood pressure and possibly, the alleviation of other cardiovascular ailments (in humans suffering essential hypertension, taurine supplementation resulted in measurable decreases in blood pressure). In a recent 2008 study, taurine has been shown to reduce the secretion of apolipoprotein B100 and lipids in HepG2 cells. High concentrations of serum lipids and apolipoprotein B100 (essential structural component of VLDL and LDL) are major risk factors of atherosclerosis and coronary heart disease. Hence, it is possible that taurine supplementation is beneficial for the prevention of these diseases. In a 2003 study, Zhang et al. have demonstrated the hypocholesterolemic (blood cholesterol-lowering) effect of dietary taurine in young overweight adults. Furthermore, they reported that body weight also reduced significantly in the taurine supplemented group. These findings are consistent with animal studies. Taurine has also been shown to help people with congestive heart failure by increasing the force and effectiveness of heart-muscle contractions.

Taurine levels were found to be significantly lower in vegans than in a control group on a standard American diet. Plasma taurine was 78% of control values, and urinary taurine 29%.

According to animal studies, taurine produces anxiolytic effect and may act as a modulator or anti-anxiety agent in the central nervous system.

Taurine is necessary for normal skeletal muscle functioning. This was shown by a 2004 study, using mice with a genetic taurine deficiency. They had a nearly complete depletion of skeletal and cardiac muscle taurine levels. These mice had a reduction of more than 80% of exercise capacity compared to control mice. The authors expressed themselves as "surprised" that cardiac function was largely normal (given various other studies about effects of taurine on the heart).

Studies have shown that taurine can influence (and possibly reverse) defects in nerve blood flow, motor nerve conduction velocity, and nerve sensory thresholds in experimental diabetic neuropathic rats. In another study on diabetic rats, taurine significantly decreased weight and decreased blood sugar in these animal models. Likewise, a 2008 study demonstrated that taurine administration to diabetic rabbits resulted in 30% decrease in serum glucose levels.^[41] According to the single study on human subjects, daily administration of 1.5g taurine had no significant effect on insulin secretion or insulin sensitivity. However it is possible that an effect may occur at higher dosages. There is evidence that taurine may exert a beneficial effect in preventing diabetes-associated microangiopathy and tubulointerstitial injury in diabetic nephropathy.

Dr. Mike's unvarnished opinion: could be useful; certainly seems better than L-acetyl carnitine! (And there's no reason you couldn't use both together.)

Vitamin E

A recent study suggests that alpha tocopherol (vitamin E) could have therapeutic effects in fragile X:

Neuropsychopharmacology. 2009 Mar;34(4):1011-26.

Alpha-tocopherol protects against oxidative stress in the fragile X knockout mouse: an experimental therapeutic approach for the Fmr1 deficiency.

de Diego-Otero Y, Romero-Zerbo Y, el Bekay R, Decara J, Sanchez L, Rodriguez-de Fonseca F, del Arco-Herrera I.

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Fragile X syndrome is the most common genetic cause of mental disability. The mechanisms underlying the pathogenesis remain unclear and specific treatments are still under development. Previous studies have proposed an abnormal hypothalamic-pituitary-adrenal axis and high cortisol levels are demonstrated in the fragile X patients. Additionally, we have previously described that NADPH-oxidase activation leads to oxidative stress in the brain, representing a pathological mechanism in the fragile X mouse model. Fmr1-knockout mice develop an altered free radical production, abnormal glutathione homeostasis, high lipid and protein oxidation, accompanied by stress-dependent behavioral abnormalities and pathological changes in the first months of postnatal life. Chronic pharmacological treatment with alpha-tocopherol reversed pathophysiological hallmarks including free radical overproduction, oxidative stress, Rac1 and alpha-PKC activation, macroorchidism, and also behavior and learning deficits. The restoration of the oxidative status in the fragile X mouse emerges as a new and promising approach for further therapeutic research in fragile X syndrome.

Now, there are a few problems with this putative therapeutic intervention. First off, vit E has been used extensively in many children and adults with fragile X, and the results have been decidedly underwhelming. Second, the doses used in this animal study are far greater than any that could be administered to actual humans; this is a problem with anti-oxidant strategies in general--they often require doses which simply aren't practical (for

example, the experiments which have shown that red wine confers all sorts of health benefits, as long as you consume the equivalent of 100 bottles of red wine per day.) Third, there just isn't any evidence of oxidative damage in human fragile X brains, nor is the course of the disease consistent with this type of mechanism.

Based on actual clinical experience, it is not possible to recommend this approach, but it is a benign treatment strategy.

Dr. Mike's unvarnished opinion: couldn't hurt, but don't expect much.

A Medication Guide
For
Fragile X

(2009 revision of original version written 2004)

Introduction

Recent dramatic advances in the field of psychopharmacology have made possible treatments which were inconceivable ten years ago. Many conditions previously viewed as intractable are now almost trivially simple to treat. Along with these advances in treatment have come much better understanding of the basic neuronal processes involved in psychiatric disorders, and the prospect of far more advanced therapies to come.

Fragile X syndrome is by far the leading cause of inherited mental retardation around the world; it is, arguably, the most common serious genetic disease in humans; it is also a complex and highly variable neuropsychiatric disorder. Many individuals with Fragile X, especially females, exhibit less overt developmental delay, but still suffer from subtler dysfunction of attention or socialization which may be every bit as treatable as more severe behavioral disturbances. Much of the attention given to the psychopharmacology of Fragile X is devoted to treatment of more severely affected individuals; it should not be inferred that these individuals are the only ones "bad enough" to need medications or to respond to them: all medical treatments are more successful in treating the mild-to-moderately ill patient who can best tolerate the treatment and heal on his own in conjunction with it.

This manual is intended as an aid for parents seeking or considering drug treatment of the behavioral and psychiatric sequelae of Fragile X syndrome. It is designed to enhance parents' ability to make informed decisions about their children's medical treatment. It is not meant to be a "how-to" book of psychopharmacology, nor can it ever take the place of a qualified physician. In a perfect world this manual would not be necessary: All physicians would have a good working knowledge of Fragile X, every child would be thoroughly evaluated and closely followed for psychiatric as well as physical problems, and the time would be invested in educating patients and families about their treatment. However, in the real world things just don't always work out this way. So, the following discussion is meant to acquaint the non-medical caretaker with the facts relevant to the psychopharmacology of Fragile X syndrome.

A note about references: since the vast majority of the readers of this book will not have access to a medical library, no attempt is made at conventional referencing; instead, abstracts of pertinent articles will be provided as a service to the reader; further references are available in the cited articles. Many of the references are from autism research, an unfortunate indication of the paucity of research on the psychopharmacology of Fragile X syndrome. Nevertheless, most of the major principles learned from autism and mental retardation research can be applied to the treatment of Fragile X.

Who Should Be Treated?

Of course, this is a matter of clinical judgement in any individual case. However, since parents so often ask this question, it is worth considering a few general guidelines.

The presence of symptoms which are likely to respond to currently available medications is usually considered a prerequisite. The severity of these symptoms is not as important a factor as one might otherwise assume: many of the symptoms which respond to psychopharmacologic treatment do so whether mild, moderate, or severe. In practice, however, most people think of medications as a "last resort" and consider their use only when other interventions (i.e. behavioral or educational) fail. Thus, most often we see more serious symptoms when evaluating for medication treatment, even though these treatments will work at least as well for mild or moderate symptoms.

When there is a specific treatment for Fragile X syndrome itself, one that actually helps to compensate for the underlying biochemical defects, we might recommend that all children receive that treatment, much the way all juvenile diabetics are prescribed insulin. Since no such specific treatment for Fragile X exists, however, we must treat the parts of the whole that we can treat, more like treating the pulmonary infections of cystic fibrosis with antibiotics--a life-saving treatment, but one that does not affect the underlying disease process at all. We (psychopharmacologists) refer to these treatable symptoms as "target symptoms", and some familiarity with this concept is essential for parents who want to be fully informed about their child's treatment. A large part of this manual is therefore devoted to discussion of just what we are attempting to treat when medicating a Fragile X patient.

Age is certainly an important factor in the clinical decision to prescribe. Most physicians feel terribly uncomfortable medicating preschool children, and it is quite rare that any child under 3 is ever prescribed psychotropic medication, even with a precise molecular diagnosis like Fragile X in hand. In part, this may be because very little research is done on young children, so doctors do not have the kind of hard evidence of safety and efficacy that they would like to have before prescribing. In addition, since the ultimate goal of medication is to enhance function, impairment is sometimes hard to define concretely until a child starts school, and is required to function outside the home. Parents should always keep in mind that psychotropic medications are supposed to enhance function--this is the only valid reason for their use, and should always be the primary goal of treatment.

Since the symptoms of Fragile X typically seem to change with age, sometimes even with the seasons, treating this condition can be like shooting at a moving target. Anxiety is especially prominent around ages 2-4 for many fra(x) boys; hyperactivity develops (sometimes abruptly) in the 4-10 year age range, often ending (sometimes just as abruptly) with puberty or the adolescent growth spurt. Aggression and "catastrophic reactions" can occur at any age, but seem to intensify in adolescence; this is one of the more common reasons for Fragile X males to be hospitalized or institutionalized. Aggression is also a readily treatable symptom and a clear-cut indication for medication. Irritability often worsens in winter in northerly latitudes, in some cases requiring only seasonal treatment. The point is that Fragile X usually changes over time, and no one should recommend treating all Fragile X individuals alike, or maintaining one individual on a fixed medication regimen indefinitely.

Since most parents would prefer to try non-medical alternatives if possible, it is entirely reasonable to attempt behavior modification or sensory integration techniques before considering medications. However, no outcome studies of these methods have been conducted, so no advice can be given about relative efficacy or length of treatment necessary. Also, these methods can certainly be used with medications; in other types of psychiatric disorders the combination of medication and other therapies invariably proves more effective in rigorous studies than either treatment alone. It is probably a safe assumption that the same is true for Fragile X syndrome. A good rule of thumb is that if specific symptoms have not improved measurably after six months of treatment (i.e. in PT, OT, SI) evaluation for medication should at least be considered.

The fact is that nearly all Fragile X males will be prescribed psychotropic medication at some point in their lives; in the Age of Prozac, many Fragile X females will be given a trial of medication as well; this need not be considered a tragedy. Psychotropic medication was never meant to be a substitute for anything. It should not be used instead of psychotherapy, OT, PT, speech therapy, special education-- or love, affection, individual attention, family, community, etc. But the judicious use of these agents to treat this devastating neuropsychiatric illness can greatly enhance all other aspects of a person's life, so withholding treatment can be as great a sin as overmedicating. Approaching the topic with an open mind and enough information is key to optimal treatment.

Keeping these things in mind, let's assume that you have made the decision to seek consultation about medication.

Who Should Treat ?

What kind of specialist should parents consult? The true experts in this area are ultra-specialists called neuropsychiatrists. They are psychiatrists who have done fellowship training in Child Psychiatry, then gone on to further training in treatment of patients with developmental disorders and brain injury. They will almost certainly have a fair amount of experience in treating individuals with Fragile X, and will be quite astute psychopharmacologists. They are also exceedingly rare, and are hardly ever found outside of major medical centers. (Not to be confused with neuropsychologists, who are not medical doctors, but have doctoral degrees in psychology. Psychologists cannot prescribe medications, although they may be involved in treatment by performing psychometric testing.)

Child psychiatrists are somewhat easier to find (there are about 3000 total in the US) but can be quite variable in their approach to a Fragile X child. Some specialize in psychotherapy and have little training in psychopharmacology or developmental disorders. Others are well versed in psychopharmacology and experienced in treating developmentally disordered patients. How do you find out which is which? Be sure to ask specifically ahead of time.

Developmental pediatricians are experts in the medical care of children with developmental disorders and can be quite astute in treating behavioral problems as well. However, some do not prescribe psychotropic medications, preferring to refer to another specialist. Others may not feel comfortable prescribing some of the medications reviewed in this text. Having a single physician manage most of your child's care is a good idea, so developmental pediatricians can be especially valuable; once again, ask ahead of time to gauge the doctor's "comfort level" in working with Fragile X syndrome.

Pediatric neurologists are often called upon to treat behavioral problems associated with Fragile X syndrome, and some are quite sophisticated in the treatments they utilize, while others feel comfortable only with relatively simple regimens like stimulant trials or clonidine administration. Most are, of course, quite expert in the use of anticonvulsants, both for seizure disorders and behavioral control. The key here is to ask about the prospective physician's experience in treating a broad range of behavioral problems, like mood disorders, aggression, anxiety, self-injurious behavior, etc.

Someone from one of the four sub-specialties mentioned above should be able to help, but if you live in a rather remote area you may have little choice--there may be only primary care doctors in the area. Since it is not a good idea to rely on any doctor who is located too far from home, you (the parent) then will likely assume the responsibility of arranging for some type of consultation between your family doctor or pediatrician and a suitable specialist. The specialist can assist in diagnosing the problem and initiating treatment, with the primary care doctor taking care of follow-up and maintenance.

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.

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 in regard 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 fra(x) girl (full-mutation female). However, given the variability of expression of Fragile X, it is possible that some girls will actually 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 neuropsychiatric 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 the medications virtually every parent has heard of: Ritalin, Dexedrine, and Cylert (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 Dexedrine, 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.

Cylert is a far less-restricted, schedule IV drug which avoids most of these hassles, but is much less commonly used, for a variety of reasons to be discussed later.

Since all of 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 the enhancement of 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. 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 the aforementioned 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/Hyperkinesia

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 actually 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--a part which, if electrically stimulated, 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.

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 anyhow; 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, just that they are often not enough. Remember that medications and non-medical therapies work together well, and that not only will medication 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--to 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 really even 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.

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 my 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, Fragile X children 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 Prozac, Zoloft, Paxil, 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, as we described in a previous section, they can enhance attention and concentration. The older antidepressants (this term is a confusing misnomer, since these medications have many uses) 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 are increasingly favoring 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 still in progress.

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** (including caffeine) will invariably exacerbate anxiety in a dose-dependent fashion; they can often be used in 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 cost, since they can cause severe side effects and do very little to relieve anxiety. Nevertheless, some backward clinicians still believe that mentally retarded individuals require the strongest possible "tranquilization" to keep their behavior in check, and thus these drugs are still widely prescribed to non-psychotic individuals, despite a lack of any evidence of efficacy.

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 actually 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, since 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--"losing touch with reality".

The neurobiology of mania is not well understood, despite the fact that 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 the course of 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, Cylert, etc.--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 FMR-1 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 fra(x) children does not qualify (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 antiobsessional 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 all the 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 recently done in the "neuropsych" (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. Therefore, it looks likely that violent behavior is biologically similar whether directed at self or others--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 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 Prozac (fluoxetine, an SSRI antidepressant) 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 all of these symptoms. Psychiatry has simply begun to understand the important role this one neurotransmitter plays in all of 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 coincidentally, 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 actually demonstrated any link to serotonergic dysfunction.

In both of the 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 is 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.

Most recently, severe aggression is being treated more and 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 likely to emerge as the treatment of choice for severe behavioral problems in Fragile X, autism, and general developmental disorders.

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Thompson T, Hackenberg T, Cerutti D, Baker D, Axtell S

Opioid antagonist effects on self-injury in adults with mental retardation: response form and location as determinants of medication effects.

John F. Kennedy Center, Peabody College, Vanderbilt University, Nashville, TN 37203.

Am J Ment Retard 1994 Jul;99(1):85-102

ABSTRACT:

The opioid antagonist naltrexone was administered to 8 adults with severe or profound mental retardation and extensive histories of self-injurious behavior. Five-minute behavioral samples were observed randomly out of every hour from 8 a.m. through 3 p.m., Monday through Friday, for four 2-week phases (baseline, placebo, 50 mg, and 100 mg). During naltrexone administration, there were fewer days with frequent head-banging and self-biting, whereas there were more days on which blows to the head or self-biting were infrequent. Self-injurious participants slept 1.38 hours less per night during baseline, which was unaffected by naltrexone.

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Ricketts RW, Goza AB, Ellis CR, Singh YN, Singh NN, Cooke JC 3d

Fluoxetine treatment of severe self-injury in young adults with mental retardation.

Southwest Institute for Developmental Disabilities, Abilene, Texas.

J Am Acad Child Adolesc Psychiatry 1993 Jul;32(4):865-9

ABSTRACT:

Dysfunction of the serotonergic system has been implicated in the development and maintenance of self-injury in some persons with mental retardation. Several preliminary reports have suggested that fluoxetine, a drug that blocks the reuptake of serotonin, may decrease self-injury in these individuals. Of the 44 cases of self-injury treated with fluoxetine and previously reported in the literature, 42 demonstrated a beneficial response to the drug. We report four additional cases of adults with mental retardation whose self-injury was treated with fluoxetine. Each of these individuals benefited from fluoxetine to some extent, with average decreases in self-injury ranging from 20% to 88% when compared with baseline levels. These findings, combined with those from previously published case studies, emphasize the need for well-controlled studies to more adequately assess the effects of fluoxetine on self-injury.

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 bed time. 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--they sleep less in the winter--and 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.

Recently, 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.

Update 2008: 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 “G_q”. The best known G_q pathway involved in fragile X is the one linked to mGluR5, and this is certainly 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 G_q 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 insomnia, 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:

Biol Psychiatry. 2008 Mar 15;63(6):629-32. Epub 2007 Sep 14

Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study.

Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA.

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BACKGROUND: Prazosin, a central nervous system (CNS) active alpha-1 adrenoreceptor antagonist, has reduced nightmares and sleep disturbance in placebo-controlled studies of combat-related posttraumatic stress disorder (PTSD). We evaluated objective sleep parameters and PTSD symptoms in a placebo-controlled prazosin trial for civilian trauma-related PTSD. **METHODS:** Thirteen outpatients with chronic civilian trauma PTSD, frequent nightmares, and sleep disturbance participated in a randomized placebo-controlled crossover trial of prazosin. Sleep parameters were quantified at home with the REMView (Respironics, Pittsburgh, Pennsylvania). The PTSD symptoms were quantified with the Clinician Administered PTSD Scale (CAPS) "recurrent distressing dreams" and "disturbed sleep" items, a non-nightmare distressed awakenings scale, the PTSD Dream Rating Scale (PDRS), the PTSD Checklist-Civilian (PCL-C), and the Clinical Global Impression of Improvement (CGI-I). **RESULTS:** Prazosin compared with placebo significantly increased total sleep time by 94 min; increased rapid eye movement (REM) sleep time and mean REM period duration without altering sleep onset latency; significantly reduced trauma-related nightmares, distressed awakenings, and total PCL scores; significantly improved CGI-I scores; and changed PDRS scores toward normal dreaming. **CONCLUSIONS:** Prazosin reductions of nighttime PTSD symptoms in civilian trauma PTSD are accompanied by increased total sleep time, REM sleep time, and mean REM period duration in the absence of a sedative-like effect on sleep onset latency.

Thus, sleep may be disturbed in fragile X and in PTSD by similar mechanisms (though acquired in very different ways,) and may be treated with a similar (available, generic) drug. Clinical trials of prazosin to treat sleep disturbance in fragile X have not been done, and clinical experience is quite limited. However, this is a promising emerging treatment strategy, with several medications available in this class, on the market today.

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 caretakers 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 particular 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 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 prophylaxis 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

In an effort to simplify rapid comparison of a wide array of different 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, more than \$5 per day for usual doses



expensive, in the \$2-4 per day range



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 Listed by Generic Name

GENERIC NAME	brand name	brief description
amphetamine/ dextro- amphetamine	<i>Adderall</i>	see dextroamphetamine; an essentially equivalent medication, slightly different preparation
aripiprazole	<i>Abilify</i>	newer atypical antipsychotic, used for treating more severe agitation and aggression; also a potent mood stabilizer and antimanic agent
atomoxetine	<i>Strattera</i>	newer treatment for ADHD; a non-controlled compound unrelated to stimulants, similar in mechanism of action to desipramine
bupropion	<i>Wellbutrin</i>	novel antidepressant; ineffective for anxiety disorders, but used increasingly for ADHD; higher-than-average seizure risk
buspirone	<i>BuSpar</i>	novel anxiolytic with some (weak) anti-obsessional, antidepressant, and anti-aggressive activity
carbamazepine	<i>Tegretol</i>	anticonvulsant and mood-stabilizer commonly prescribed for behavior disorders in the neuropsychiatric population
citalopram	<i>Celexa, Lexapro</i>	selective serotonin re-uptake inhibitor (SSRI); used to treat a wide range of mood disorders, anxiety disorders, impulse control disorders, and attentional problems
clomipramine	<i>Anafranil</i>	tricyclic antidepressant with potent serotonin re-uptake inhibition; spectrum of activity similar to venlafaxine and SSRIs
clonazepam	<i>Klonopin</i>	benzodiazepine anxiolytic and anticonvulsant, may have weak mood-stabilizing and anti-obsessional effects
clonidine	<i>Catapres</i>	centrally-acting alpha-2 agonist, commonly used for hyperactivity/hyperarousal
desipramine	<i>Norpramin</i>	tricyclic antidepressant; used in ADHD and anxiety disorders
dextro- amphetamine	<i>Dexedrine, Dextrostat</i>	a commonly used psychostimulant
fluoxetine	<i>Prozac</i>	selective serotonin re-uptake inhibitor (SSRI); used to treat a wide range of mood disorders, anxiety disorders, impulse control disorders, and attentional problems

fluvoxamine	<i>Luvox</i>	selective serotonin re-uptake inhibitor (SSRI); used to treat a wide range of mood disorders, anxiety disorders, impulse control disorders, and attentional problems
folic acid	<i>none</i>	commonly used, weak psychostimulant
guanfacine	<i>Tenex</i>	centrally-acting alpha-2 agonist, commonly used for hyperactivity/hyperarousal
imipramine	<i>Tofranil</i>	tricyclic antidepressant; used in ADHD and anxiety disorders
lithium	<i>Eskalith, Lithobid, Lithonate</i>	mood-stabilizer, commonly used to treat Bipolar Disorder; moderately effective in treatment of aggression
methylphenidate	<i>Ritalin, Concerta, Metadate</i>	a commonly used psychostimulant; Concerta and Metadate are long-acting, time-release formulations
naltrexone	<i>ReVia</i>	a long-acting, orally administered opioid antagonist; used in treatment of SIB
nefazodone	<i>Serzone</i>	new antidepressant; a less-sedating derivative of trazodone, works via a novel serotonergic mechanism
nortriptyline	<i>Pamelor</i>	tricyclic antidepressant; used in ADHD and anxiety disorders
olanzapine	<i>Zyprexa</i>	novel antipsychotic; probably more effective and certainly safer than older drugs in this class
paroxetine	<i>Paxil</i>	selective serotonin re-uptake inhibitor (SSRI); used to treat a wide range of mood disorders, anxiety disorders, impulse control disorders, and attentional problems
pemoline	<i>Cylert</i>	a less commonly prescribed, long-acting psychostimulant
propranolol	<i>Inderal</i>	beta blocker; sometimes used to treat children with anxiety disorders
quetiapine	<i>Seroquel</i>	newer atypical antipsychotic, used for treating more severe agitation and aggression; also a potent mood stabilizer and antimanic agent
risperidone	<i>Risperdal</i>	novel antipsychotic; probably more effective and certainly safer than older drugs in this class
sertraline	<i>Zoloft</i>	selective serotonin re-uptake inhibitor (SSRI); used to treat a wide range of mood disorders, anxiety disorders, impulse control disorders, and attentional problems
thioridazine	<i>Mellaril</i>	low-potency, highly sedating antipsychotic; used in thought disorders and mania

trazodone	<i>Desyrel</i>	powerfully sedating antidepressant, used primarily to treat sleep disorders; also helpful for decreasing agitation in some cases
valproic acid	<i>Depakote</i>	anticonvulsant and mood-stabilizer commonly prescribed for behavior disorders in the neuropsychiatric population
venlafaxine	<i>Effexor</i>	novel antidepressant with serotonin and norepinephrine re-uptake inhibition; spectrum of activity similar to SSRIs, but may be useful in treatment-resistant cases

Medications Listed by Brand Name

BRAND NAME	generic name
<i>Abilify</i>	aripiprazole
<i>Adderall</i>	amphetamine/dextro-amphetamine
<i>Anafranil</i>	clomipramine
<i>BuSpar</i>	bupirone
<i>Catapres</i>	clonidine
<i>Celexa</i>	citalopram
<i>Cylert</i>	pemoline
<i>Depakote</i>	valproic acid
<i>Desyrel</i>	trazodone
<i>Dexedrine</i>	dextro-amphetamine
<i>Effexor</i>	venlafaxine
<i>Eskalith</i>	lithium
<i>Inderal</i>	propranolol
<i>Klonopin</i>	clonazepam
<i>Lexapro</i>	s-citalopram
<i>Lithonate, Lithobid</i>	lithium

<i>Luvox</i>	fluvoxamine
<i>Mellaril</i>	thioridazine
<i>Norpramin</i>	desipramine
<i>Pamelor</i>	nortriptyline
<i>Paxil</i>	paroxetine
<i>Prozac</i>	fluoxetine
<i>ReVia</i>	naltrexone
<i>Risperdal</i>	risperidone
<i>Ritalin</i>	methylphenidate
<i>Seroquel</i>	quetiapine
<i>Serzone</i>	nefazodone
<i>Strattera</i>	atomoxetine
<i>Tegretol</i>	carbamazepine
<i>Tenex</i>	guanfacine
<i>Tofranil</i>	imipramine
<i>Wellbutrin</i>	bupropion
<i>Zoloft</i>	sertraline
<i>Zyprexa</i>	olanzapine

Stimulants

The psychostimulants, as a class, have been around for a long time. These were some of the first drugs to be used in psychiatry, and so physicians feel fairly comfortable with these medications--some would say too comfortable. In children, stimulants are by far the most commonly prescribed psychoactive medications, primarily for the treatment of attention deficit/hyperactivity disorder (ADHD). Stimulants are also used, with questionable effectiveness, as appetite suppressants to promote weight loss. They can be valuable for people with narcolepsy, since their stimulating properties can help narcoleptics stay awake and function through the day. Some adults with ADHD also seem to benefit from stimulant medication.

Currently, there is a bit of controversy about the frequency with which stimulants are used; many people (this author included) feel that these medications are overprescribed and that ADHD is overdiagnosed. It is likely that the ability to attend, as a biological trait, exists on a continuum: some individuals are designed to focus narrowly on the task at hand, while others are always open to input from the environment, and are thus "easily distractable". It is also likely that many children and adults nowadays are labeled as having ADHD when they simply are normal individuals at one end of the spectrum. Viewed this way, medicating these individuals constitutes cosmetic psychopharmacology.

This argument certainly does not apply to Fragile X, however. Children with Fragile X have a well-defined, single-gene disorder which causes attentional deficits along with other characteristic symptoms. They (along with a fair number of children who really do have neurologically-based ADHD) have symptoms which offer a clear-cut rationale for the use of psychostimulants to enhance attention. The only reasonable question is whether these medications work for children with Fragile X.

To answer this question we must first consider how these drugs work. Although the mechanism of action is by no means fully understood, the conventional wisdom is that psychostimulants work by promoting release of certain neurotransmitters, especially dopamine (but also norepinephrine, as well as other things secreted along with them). The primary effect of psychostimulants, the enhancement of attention and concentration, is thought to result from the increased release of dopamine in the frontal areas of the brain. But, of course, the drug is present in other areas, too, and exerts effects there as well. The areas of the brain which regulate level of arousal, blood pressure, heart rate and other "autonomic" functions are also stimulated, while the area controlling appetite is inhibited. Under normal circumstances, most people are much more sensitive to the primary effect of facilitating dopaminergic transmission in the frontal lobes, and at most therapeutic doses will experience an enhancement of attention, concentration, and overall cognitive performance (which is why these medications were initially touted as "smart drugs").

As attention and concentration (referred to by some as "focus") increase with increasing doses of a stimulant, physical activity tends to decline, accounting for the paradoxical decrease in hyperactivity (which is usually the objective of treatment). However, the primary and secondary effects of stimulants, enhancement of attention and reduction of hyperactivity, are known to occur at different dosages. Lower doses of a stimulant are likely to enhance attention optimally and improve cognitive performance, but may not control hyperactivity. Higher doses are likely to reduce hyperactivity, but may actually result in "overfocus", in which attention is focused so narrowly that actual cognitive performance declines. Still higher doses will cause psychiatric symptoms in virtually anyone, including irritability, aggression, anxiety, agitation, paranoia, or hallucinations. Fortunately,

for most people the dose required to cause trouble is much higher than usual therapeutic doses. However, the situation is somewhat different for Fragile X individuals.

Fragile X predisposes one to anxiety, aggression, and agitation. On an intuitive level, it seems obvious that care should be taken with any substance which could aggravate these. On a biochemical level, psychostimulants are "sympathomimetic": they mimic the effects of adrenaline in the central nervous system, heightening arousal as well as increasing heart rate and blood pressure. Since Fragile X individuals often have problems with hyperarousal, stimulants may make matters worse in some cases. Many Fragile X individuals are able to achieve significant improvements in attention and cognitive performance with low doses of stimulants, though, and any potential adverse effects are readily reversible should they arise. Therefore, a trial of a stimulant is rational and safe for a Fragile X individual with particular attentional problems, but should be done with caution. Dosages should be relatively low, and it cannot be expected that significant reduction of hyperactivity will occur, at least compared to the sometimes dramatic response seen in "garden variety" ADHD. Careful monitoring for emergence or exacerbation of anxiety or aggression **must** occur throughout treatment. *Many Fragile X parents are not informed of this risk, are unaware of the connection between stimulants and worsening of aggression or anxiety, and therefore continue administering the medication even when adverse psychiatric side-effects occur--despite the fact that these effects readily reverse upon discontinuation of the drug.*

Psychostimulant medications can cause uncommon, but serious, medical problems. Most worrisome is the development of motor tics. This can start as a subtle, almost undetectable twitch, and progress to severe involuntary muscle movement. It usually stops soon after the stimulant is discontinued or the dosage decreased, but sometimes is frighteningly persistent. The key is to catch the tics early on; more persistent tics usually occur following longer treatment in which early signs were ignored. This side-effect is usually dose related, so reducing the dose can be helpful and allow for uninterrupted treatment. Also, since most Fragile X children are treated with lower doses of stimulants, this may be less likely to occur in the first place (there are no reliable statistics on the frequency of this side-effect in Fragile X). Tics can also be treated with clonidine if they persist, or if the clinical judgment is made not to interrupt stimulant therapy.

Since they can be potent appetite suppressants, psychostimulants can cause some growth delays during long-term administration. Several studies have shown, however, that children will eventually catch up, even if the medication is continued. Often, "drug holidays" are taken during non-critical times (such as summer vacation) to expedite this process. In any case, growth charts should be carefully monitored for all children on stimulant medications, and significant growth delay is an appropriate reason for discontinuing the medication.

Specific side effects and their medical management are discussed in the individual reviews of medications.

Update 2008: The caveats concerning stimulants noted in this book have proven to be well founded, and just as frequently ignored as ever. Stimulants are nearly irresistible for all concerned, offering the promise of an instant fix for the disabling inattentiveness and the disruptive hyperactivity seen in nearly all children with fragile X. Teachers love stimulants because they help so many kids participate in class. Parents love them because they start working right away, and because they want their kids to get the most out of school. Pediatricians love them because they're easy to prescribe and have a long safety record. The only problem is that they don't work very well in kids with fragile X! At least half of all stimulant trials in fragile X kids end abruptly because of immediate psychiatric side effects---usually extreme irritability or increased aggression. Seizures and tics are also seen with

alarming frequency in this population following the start of a new stimulant medication. However, these are all fairly obvious and easily recognized, and when the drug is discontinued the adverse effects dissipate rapidly. Perhaps more concerning are the psychiatric side effects which develop insidiously over much longer time frames; I have consulted on many cases in which a fragile X child has an excellent initial response to a stimulant with no apparent side effects, only to have multiple problems emerge months or years later. Most commonly, obsessive-compulsive symptoms worsen over time, as mood deteriorates and tantrums increase. Because stimulants cause significant physiological dependence, everything gets worse if any attempt is made to discontinue the drug, and this is often seen as evidence the stimulant is working well and not to blame. In fact, this is only evidence that stimulants are potentially addictive, and demonstrates why they are highly controlled substances. The appropriate response is a gradual taper of the stimulant dose over the course of many months.

The entire field of Child Psychiatry appears to have come to the realization that excessive and indiscriminate use of stimulants has led to an increase in childhood Bipolar Disorder, Anxiety Disorders, and psychoses. Indeed, the current fad is for overdiagnosis of Bipolar Disorder, after ignoring for decades that this condition can present in childhood. So, the most important lesson is to be vigilant over the long term; most medications which work right away have serious side effects which develop much later.

methylphenidate (Ritalin)

effectiveness	safety	cost	convenience
😊😊	👉👈	\$\$	☯️☯️

indications: attention deficit, hyperactivity

pros: works almost immediately, usually well tolerated; enhances attention and concentration

cons: high incidence of psychiatric side effects; no liquid or chewable formulations available

use: Methylphenidate is the most commonly prescribed psychostimulant in the United States. It is unclear just why this is, since it has few clinical advantages and numerous disadvantages compared to other available stimulants. Methylphenidate is a synthetic analog of amphetamine which causes somewhat less euphoria and less cardiovascular stimulation, and is generally thought to be less abusable, though it is still a schedule II controlled substance. It can be quite effective in enhancing attention, concentration, and general cognitive performance in Fragile X children (male or female), but its use is ordinarily restricted to lower doses by the emergence of dose-related anxiety and irritability (especially in males). Since its duration of action is very short--about 3 hours--it must be given at least twice a day, and periods of *rebound* are quite common as the drug is wearing off. At these times, attention deficit and/or hyperactivity can be worsened. A Sustained Release preparation is available to counteract this effect, but it comes in only one size (20 mg) and is still relatively short-acting (about 6 hours); some children do not find the therapeutic effect of the Sustained Release tablet equivalent to the regular tablet. Newer formulations like Concerta and Metadate overcome some of these problems by extending the duration of action; these are preferable to standard (short-acting) formulations, and there are now enough different versions to allow significant choice of dosages.

common side effects

appetite suppression: give after meals to minimize this effect

behavioral rebound: more frequent doses or sustained release formulations should be used

insomnia: last dose of the day is too close to bed time--move to an earlier time

anxiety: dosage reduction (at least initially) is indicated

nausea: taking on a full stomach will greatly reduce this effect

headache: Tylenol is fine; temporary dosage reduction may help; usually transient

uncommon side effects

motor tics: dosage reduction or discontinuation; can be treated with clonidine

palpitations: dosage reduction is indicated

rash: immediated discontinuation is required

psychosis (hallucinations or delusions): immediate discontinuation is required

usual dosage

general: ordinarily, a total dose of 1.0 mg/kg/day is considered optimal for treating ADHD; a dose of 0.5-0.7 mg/kg/day is recommended for all individuals with Fragile X to minimize the risk of psychiatric side effects.

children: start with 2.5 mg (half tab) in morning, increasing as tolerated in 2.5 mg increments; doses over 30 mg/day are not recommended in Fragile X boys (36 mg Concerta may be well tolerated in some cases)

teens and adults: start with 5 mg morning and afternoon, increasing as tolerated up to 50-60 mg/day

Aman MG, Marks RE, Turbott SH, Wilsher CP, Merry SN

Clinical effects of methylphenidate and thioridazine in intellectually subaverage children.

Nisonger Center for Mental Retardation and Developmental Disabilities, Ohio State University, Columbus 43210-1296.

J Am Acad Child Adolesc Psychiatry 1991 Mar;30(2):246-56

Thirty children with subaverage IQs and psychiatric diagnoses of attention deficit disorder and/or or conduct disorder took part in a double-blind study of placebo, methylphenidate, and thioridazine, which were given for 3 weeks each. The results showed a consistent and highly significant effect of methylphenidate in reducing teacher ratings of problem behavior. Parent ratings showed no behavioral effects for the group as a whole. An attentional model of stimulant drug response was used to divide subjects according to a cognitive maturity domain presumed to reflect selective attention. When divided according to breadth of attention, mental age, and IQ level, higher functioning subjects were found to show a generally favorable response to methylphenidate on both teacher and parent rating scales, whereas children of low functional level typically showed an adverse or indifferent response. The present data suggest that mental age and IQ may be important determinants of drug response; below a given level, there was a greatly reduced likelihood of responding positively. Clinical response to thioridazine was substantially less than the response to methylphenidate, with significant improvements confined to conduct and hyperactivity problems on teacher ratings.

Update 2008: the convenience of methylphenidate formulations has improved tremendously in the past few years; a number of different time-release formulations of methylphenidate are now available. One of the more successful is an advanced osmotic pump delivery system marketed as Concerta. This capsule actually contains a small bag full of methylphenidate liquid; when ingested, the stomach fluids cause an influx of water through the semi-permeable outer capsule,

which squeezes the bag, pushing the drug out through a small hole at a controlled rate. Concerta is an expensive name-brand drug, but this delivery system is far better than the multiple daily doses of regular Ritalin which predictably yield a noticeable “roller-coaster effect.”

Please note that even the most advanced drug delivery system cannot overcome some of the adverse effects of the drug itself. Thus, fragile X patients treated with Concerta can still experience increased irritability, anxiety, and aggression. The risk of this adverse effect is still dose-dependent, and it is still inversely proportional to IQ.

One major limitation of time-release preparations is that they tend to be available in far fewer dosages, limiting the precision with which the dose can be adjusted. Fortunately, there have been many new “branded generic” time-release methylphenidate preparations released in the past few years, affording a wide range of options for individuals who respond well to methylphenidate, but need the dosage and timing of delivery adjusted. Newer time-release preparations include Focalin XR and Metadate CD; since these preparations all contain the same active drug, methylphenidate, there is little basic difference. However, individuals may respond much better to one preparation than another because of idiosyncratic factors such as drug absorption and metabolism, so some trial and error may be necessary to find the best medication.

Another interesting possibility is the new Daytrana patch---methylphenidate delivered transdermally. Unlike the clonidine patch, Daytrana patches are made to be worn for one day only, and the timing of drug delivery can be tailored quite precisely by altering when the patch is applied and when it is removed. The patch delivers methylphenidate through the skin at a constant rate, which is proportional to the surface area of the patch, and it comes in several sizes designed to deliver from 10-30 mg per day. In many ways, this is an ideal way to administer a stimulant to children with fragile X, since the drug is delivered at a slow, steady, controlled rate over a prolonged time. There are no peak levels to cause greater side effects, and no interdose troughs to cause behavioral rebound.

For all fragile X individuals, the risk of side effects seems to depend on the level of functioning---higher functioning people with fragile X (at any given age) have fewer psychiatric side effects from stimulants. The usual recommendation for dosing methylphenidate in the general population is up to 1 mg/kg/d total dose; in other words, a 50 kg (110 lb) child would usually get a maximum of 50 mg of methylphenidate through the course of the day. This author recommends, as a general rule-of-thumb, dosing methylphenidate in fragile X patients in direct proportion to IQ (this is not meant to validate the dubious concept of IQ, but this is useful shorthand for overall functioning.) Thus, a typical fragile X patient with an IQ of 50 (50/100 of normal) should probably receive no more than 0.5 mg/kg/d of methylphenidate (regardless of specific formulation.) A higher functioning individual with an IQ of 70 might be able to tolerate 0.7 mg/kg/d. A lower functioning individual with IQ lower than 40 or so probably shouldn't be treated with stimulants in the first place, and experience over the past 10 years has reinforced this clinical impression.

Many people with fragile X will still be unable to tolerate useful doses of methylphenidate; for those individuals, an alternative worth considering is Provigil (modafinil), a non-stimulant, schedule IV medication which generally has fewer side effects than methylphenidate or amphetamine.

dextroamphetamine (Dexedrine)

effectiveness	safety	cost	convenience
😊😊	👉👉	\$\$	☯️

indications: attention deficit, hyperactivity

pros: works almost immediately, usually well tolerated; enhances attention and concentration

cons: high incidence of psychiatric side effects; short acting, requires frequent dosing; no liquid or chewable formulations available

use: dextroamphetamine is the active form of amphetamine, and is the prototype of the stimulant class of medications. While it is somewhat longer-acting than methylphenidate, it still must be administered at least twice a day to be effective, and rebound symptoms are often prominent. Compared to methylphenidate, it tends to cause more euphoria, more cardiovascular stimulation, and more appetite suppression (although all of these are obviously dose-dependent). It is available in longer-acting "Spansules" which come in three different sizes (5, 10, and 15 mg), making dosing a bit more flexible. Differential response is highly variable--some individuals who respond poorly to methylphenidate will have a good response to dextroamphetamine, and vice versa.

common side effects

appetite suppression: give after meals to minimize this effect

behavioral rebound: more frequent doses or Spansule formulation should be used

insomnia: last dose of the day is too close to bed time--move to an earlier time

anxiety: dosage reduction (at least initially) is indicated

nausea: taking on a full stomach will greatly reduce this effect

headache: Tylenol is fine; temporary dosage reduction may help; usually transient

uncommon side effects

motor tics: dosage reduction or discontinuation; can be treated with clonidine

palpitations: dosage reduction is indicated

rash: immediate discontinuation is required

psychosis (hallucinations or delusions): immediate discontinuation is required

usual dosage

children: start with 2.5 mg in morning, increasing in 2.5 mg increments as tolerated to optimal effect; 2 or 3 doses are usually required to provide adequate coverage throughout the day; doses over 20-25 mg per day are not recommended for children with Fragile X

teens and adults: start with 5 mg twice a day, increasing in 5 mg increments as tolerated to optimal effect, up to 30-40 mg per day total; Spansules will likely have a more sustained, but also less potent effect.

Update 2008: Several new formulations of amphetamine have become available in the past few years, increasing the number of options for fragile X patients who respond better to amphetamine than methylphenidate. Adderall XR has become one of the most popular stimulant formulations, and a new pro-drug formulation, Vyvanse has been introduced. Vyvanse is metabolized into amphetamine, resulting in smoother plasma levels of the active drug. Once again, the basic pharmacology remains the same, and the same “IQ adjustment” recommended for methylphenidate is also recommended for amphetamine preparations (see methylphenidate section.)

Many people with fragile X will still be unable to tolerate useful doses of amphetamine; for those individuals, an alternative worth considering is Provigil (modafinil), a non-stimulant, schedule IV medication which generally has fewer side effects than methylphenidate or amphetamine.

pemoline (Cylert)

Update 2008: Pemoline has been withdrawn from the market because of rare hepatotoxicity; some speculate that Abbott Labs simply lost interest in a drug which never sold well in the US. Fortunately, other long-acting stimulants have come along to fill this niche.

effectiveness	safety	cost	convenience
😊😊	👉👉	\$\$	☯️☯️☯️

indications: attention deficit, hyperactivity

pros: long-acting stimulant, once-a-day dosing; chewable tablets, flexible dosages; fewer peak-level side effects and less rebound than Ritalin; less-controlled substance (refills allowed)

cons: delayed onset of action, takes longer to find optimal dose; insomnia more likely with long half-life; monitoring of liver function tests necessary (see below)

use: pemoline is a synthetic psychostimulant chemically unrelated to dextroamphetamine or methylphenidate; its much longer half-life of approximately 12 hours allows for once daily dosing, making it an especially convenient treatment option. Pemoline does not seem to have the abuse

potential of other stimulants, and is assigned by the DEA to schedule IV, which means that refills are allowed and prescriptions do not expire as rapidly as those for schedule II compounds. Another convenience feature is the availability of a scored, chewable tablet which most children (even with Fragile X) find quite acceptable. The main drawback in the use of pemoline is that the onset of action is often delayed; since the medication is long-acting, it accumulates over the course of several days after starting, so one must wait for the level of the medication in the body to equilibrate before deciding whether or not to increase the dose. Usually, the dose is increased at one week intervals, and since this process might need to be repeated several times before the optimal dose is found, it could easily take three or four weeks. This may not be such a disadvantage in treating children with Fragile X, however, since it is wise to "start low and go slow" in this case. Since some people treated with pemoline have experienced hepatotoxicity (a rare, but serious form of liver damage), monitoring of liver function tests (a simple blood test) is needed periodically during treatment, though not frequently. Pemoline is quite safe overall, and essentially all cases of elevated liver function tests resolve quickly if the medication is discontinued.

common side effects

insomnia: usually transient; temporary dosage reduction is often helpful

appetite suppression: usually transient--will resolve over time; give after breakfast

anxiety: dosage reduction (at least initially) is indicated

nausea: taking on a full stomach will greatly reduce this effect

headache: Tylenol is fine; temporary dosage reduction may help; usually transient

uncommon side effects

motor tics: dosage reduction or discontinuation; can be treated with clonidine

palpitations: dosage reduction is indicated

rash: immediate discontinuation is required

psychosis (hallucinations or delusions): immediate discontinuation is required

usual dosage

children: start with 18.75 mg (half a chewable 37.5 mg tab) each morning for the first week, increasing as tolerated in 18.75 mg increments at one week intervals; dose for children should not exceed 75 mg; most Fragile X children will have trouble tolerating more than 1.5 tablets per day (56.25 mg)

teens and adults: 37.5 mg after breakfast, increasing as tolerated to optimal effect; maximum dose for anyone is 112.5 mg; some older Fragile X individuals (especially females) can tolerate this without difficulty

atomoxetine (Strattera)

effectiveness	safety	cost	convenience
😊😊	👉👉	\$\$\$	👁️👁️👁️

indications: attention deficit, hyperactivity

pros: long-acting; flexible dosages; less rebound than Ritalin; not a controlled substance (refills allowed); should have distinct antidepressant effects

cons: delayed onset of action, takes longer to find optimal dose; high incidence of adverse effects (mainly psychiatric)

use: Strattera is a relatively new drug marketed specifically for the treatment of Attention Deficit Disorder; it is similar in its mechanism of action to desipramine and bupropion, and is not a stimulant or a controlled substance. This medication has been used quite a bit in the treatment of individuals with Fragile X, with mixed results. Some find it a useful alternative to stimulant medications, with the added benefit of enhanced antidepressant effects; however, it appears to cause significant behavioral side effects in about half of those treated, especially during the initial phases of treatment. This is probably to be expected, given its mechanism of action: atomoxetine is essentially an antidepressant medication marketed as a stimulant substitute. This means that it will take longer to start working (compared to a stimulant) and will generally cause most of its side effects during the first 2 weeks of treatment, while the body is still adjusting to the presence of the drug. If this different time course of side effects and response (compared to stimulants) is not adequately explained to patients and families, premature discontinuation of treatment may result, based on the assumption that the drug is ineffective. As with antidepressants, the therapeutic effects of atomoxetine will increase over time, while the side effects should decrease; this is the exact opposite of the experience with stimulants, which are effective immediately but then show development of tolerance, with side effects usually negligible at first but increasing with cumulative exposure over the course of months (presumably due to dopamine depletion with long-term use of higher doses.) Children appear to be more sensitive than adults to some of the side effects such as agitation and excessive activation (which is also the case with most antidepressants.)

common side effects

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

uncommon side effects

weight loss, allergic reactions, agitation, aggression

usual dosage

children: start with a low dose to avoid most common side effects---10 mg twice a day for 1-2 weeks, then increase as tolerated to 20-25 mg twice a day; allow 2-4 weeks for full effect (unlike stimulant meds); older and larger children/adolescents can take up to 80 mg/day





adults: can usually start with 25 mg twice a day, increasing as tolerated to 40 mg twice a day; allow 2-4 weeks for full effect before considering further dose increase; maximum dose quoted by

manufacturer is 150 mg/day, but doses above 120 mg/day should be used with caution in Fragile X individuals

doses should be reduced in anyone taking an SSRI, such as Prozac or Zoloft

Update 2008: Strattera continues to offer an attractive option for a non-stimulant treatment of attentional problems; unfortunately, results in the treatment of fragile X have continued to be mixed, at best. Most people with fragile X have difficulty tolerating higher doses of the drug, and lower doses are often ineffective. Overall, less than one third of Strattera trials in fragile X patients are successful---a rather high wash-out rate.

folic acid

effectiveness	safety	cost	convenience
			

indications: attention deficit, hyperactivity

pros: inexpensive; unlikely to cause adverse psychiatric effects

cons: ineffective; difficult to obtain; can cause significant medical side effects

use: folic acid is a vitamin which is essential for several critical biochemical reactions which occur in all human cells. Since the Fragile X chromosome was originally observed in cells which had been deprived of folic acid, one of the first specific attempts to treat Fragile X involved the use of folic acid supplements, on the theory that some sort of error in folic acid metabolism might cause Fragile X syndrome. Systematic studies of the use of folic acid in Fragile X have failed to demonstrate any statistically significant efficacy; however, anecdotal reports and testimonials from parents indicate that some children may benefit from folic acid. It is worth noting that folic acid, in the megadoses used to treat Fragile X, is not an entirely benign treatment. Doses of folic acid in this range can cause significant intestinal malabsorption, especially of zinc and pyridoxine (vitamin B₆), often leading to diarrhea. Folic acid also lowers the seizure threshold, and seizures have been reported in Fragile X boys on high doses of folic acid (though this is a high risk group anyway). Since it has now been conclusively shown that Fragile X does not involve any defect in folic acid metabolism, newer theories about the mechanism of action of folic acid in treating Fragile X have arisen. The conventional wisdom holds that folic acid acts as a weak psychostimulant, and that this is the basis of its reported effects. Some parents feel that it enhances their children's attention while ameliorating behavioral disturbances, but it is most certainly not a cure for Fragile X, or even a specific treatment. Some articles have promoted the use of Leucovorin (folinic acid), a more potent version of the vitamin which is marketed as an antidote to some forms of cancer chemotherapy (for "Leucovorin rescue"). There is no evidence that this medication works, either, and it is astronomically expensive; therefore, this treatment (Leucovorin/folinic acid) cannot be recommended.

common side effects

diarrhea: attempt dosage reduction; split dosing; fiber supplement

uncommon side effects

malabsorption: vitamin B₆, zinc supplements, multivitamins

usual dosage

start with 1-2 mg twice a day, increasing as tolerated to 5 mg twice a day; some children have been treated with 30-40 mg per day without ill effects; special formulation (usually a suspension) must be prepared by pharmacist with proper prescription--largest commercially available tablet is only 1 mg.

references:

Webb T, Crawley P, Bunday S

Folate treatment of a boy with Fragile-X syndrome.

University of Birmingham, Department of Clinical Genetics, Birmingham
Maternity Hospital, Edgbaston, England.

J Ment Defic Res 1990 Feb;34 (Pt 1):67-73

ABSTRACT:

A severely behaviourally disturbed three year old boy with the Fragile-X syndrome was treated with intermittent folate therapy over a period of 2 years. No behavioural improvement was noted in this time but variations between cultural regimes for the successful detection of the Fragile-X marker were observed.

Fisch GS, Cohen IL, Gross AC, Jenkins V, Jenkins EC, Brown WT

Folic acid treatment of Fragile X males: a further study.

NYS Institute for Basic Research/OMRDD, Staten Island.

Am J Med Genet 1988 May-Jun;30(1-2):393-9

ABSTRACT:

Investigations of the effect of high dose folic acid treatment of Fragile X syndrome in males has produced mixed results. However, no study had examined the possible drug effects of folic acid on non-Fragile X control males. Therefore, we examined the effect of folic acid on Fragile X males using non-Fragile X control males. Subjects were assigned randomly to an ABA or BAB design. Duration of either folic acid or placebo condition was 4 months. Folic acid or placebo was given in a double-blind fashion. At the end of each condition, the subjects' behavior was assessed. At the end of the study, parents were asked to complete a questionnaire. Using parents' responses, we examined 22 items on the Autistic Descriptors Checklist and two subscales from the Vineland Adaptive Behavior Scale which corresponded to areas of behavior parents' noted to have shown improvement. We did not find significant differences between Fragile X males and control males, within subjects, nor across folic acid and placebo conditions. Thus, our follow-up study confirms and extends our original findings, as well as those of other researchers: namely, that no dramatic changes in behavior result from high dose folic acid. Moreover, subtle improvements observed in earlier investigations were not confirmed.

Update 2008: Academic interest in folic acid treatment has essentially disappeared. Virtually all clinicians in the fragile X field have concluded that folic acid simply doesn't work, though reviews on the subject often note that some parents believe strongly that the treatment has helped their children. In addition, folic acid often serves as a gateway to drug treatment of fragile X---this is still a common first treatment for young children with fragile X. Oddly enough, recent evidence from basic research in fragile X disease mechanisms indicates that folic acid might actually have an unintended therapeutic action in people with fragile X. FRAXA-funded research by Dr. Iryna Ethell of the University of California at Riverside showed that dendritic spines, the tiny cell structures on the receiving end of neurotransmitter signals in the brain, are kept in an immature and poorly functioning state by excessive activity of enzymes called Matrix Metalloproteinases. These enzymes can be inhibited by certain medications, like minocycline, which can be therapeutic for fragile X. However, these same enzymes also depend on zinc ions inside the protein to give them biological

activity (that's the metal in the metalloproteinase); in a condition of zinc deficiency, MMP activity is impaired (which might be a good thing for someone with fragile X.) Indeed, it appears that zinc concentrations are regulated in the brain as one way of regulating activity of these enzymes. It so happens that high doses of folic acid administered orally impair the absorption of zinc. This is well known, so zinc supplements are routinely recommended for anyone taking more than the usual (ie 400 microgram/day) dose of folic acid. It is interesting to speculate whether zinc depletion may actually be a therapeutic mechanism of action of folic acid in fragile X, and whether we may be inadvertently defeating this therapeutic effect by co-administration of zinc supplements. Research on the role of zinc in neural function is still in its infancy, so it is still premature to recommend intentional zinc depletion for people with fragile X, but this may explain why some fragile X parents still swear by folic acid.

{If we really want to speculate even further, this could potentially explain why some parents of (non-fragile X) autistic children swear by chelation therapy. They may be doing it to eliminate mercury (which is highly unlikely to be a significant cause of autism), but in so doing, they may be unintentionally lowering zinc levels and suppressing MMP activity.}

Antidepressants

The term itself is a misnomer, since antidepressant medications are effective for treating much more than just clinical depression. It has long been recognized that most antidepressant medications are effective treatments for certain anxiety disorders, such as Panic Disorder and Generalized Anxiety Disorder. However, psychiatrists have also known that even though all antidepressants approved for use in the U.S. are equally effective in treating depression, there can be a huge disparity between different agents in treating some of these "off-label" indications.

For many years, there were only two classes of antidepressant medications available: the original monoamine oxidase inhibitors (MAOI's) and the tricyclic antidepressants (TCAs). While many derivatives of these original medications were developed during the 1960's and 1970's, nothing really new or more effective came along for more than two decades. This was particularly unfortunate, since neither of these classes are especially safe or pleasant to take; in fact, the MAOI's are not even reviewed here because they have such enormous potential for lethal interactions with certain foods and many over-the-counter drugs. Only highly compliant and well-educated patients should be considered for a trial of an MAOI, and even then, so many alternatives are available that the risk hardly seems worth taking. TCAs are still used, but mainly by patients on long term maintenance who started these medications before newer drugs were available. Otherwise, they are rapidly being supplanted by agents such as Prozac and Zoloft.

The first real advance in terms of enhanced efficacy came with the release of clomipramine (Anafranil) in the late 1980's. This was the first medication available in the US with proven efficacy in Obsessive-Compulsive Disorder, and it was quickly shown to be effective against a wide variety of anxiety disorders. However, clomipramine (basically an improved TCA) was soon eclipsed by the phenomenon of Prozac (fluoxetine), one of the most successful new medications of any kind, of all time. Fluoxetine has the effectiveness of clomipramine without all the side effects, and it has no toxic effects at any dose--so even massive overdoses are clinically insignificant. This is a very important advantage, since people with depression and anxiety disorders are, unfortunately, at high risk for suicide attempts. Even now, with most people taking the newer, non-toxic antidepressants there are still thousands of deaths each year in the US from intentional tricyclic overdose. No one has exact figures, but many children die each year from unintentional ingestion of TCAs. From a safety perspective alone this new class of antidepressants has been a major advance, but there are other advantages as well.

This newer class of antidepressants, called Selective Serotonin Reuptake Inhibitors (SSRIs), have the advantage of being very "clean" drugs. They only do one thing in the human body:: block the reuptake of the neurotransmitter serotonin at the synapse. This effectively enhances the flow of the body's own naturally occurring serotonin, while still leaving intact other regulatory mechanisms which prevent an individual from getting too much serotonin. Currently, this class includes fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa). The few side effects these medications do have are the result of increased serotonin transmission in other parts of the body, especially the gastro-intestinal system, which is also a major site of serotonin activity.

No one really anticipated that SSRIs would have such a broad spectrum of activity, but once they were available for widespread use, it became apparent that many conditions previously considered intractable were readily treated with these agents. They are now considered the first-line

treatment of choice for Major Depressive Disorder, Dysthymic Disorder, Pre-Menstrual Syndrome, Post-Partum Depression, Panic Disorder, Social Phobia, OCD, Post-Traumatic Stress Disorder, Body Dysmorphic Disorder, Bulimia, Compulsive Overeating (Binge Eating Disorder), a variety of paraphilias (fetishes), and disorders of impulse control such as Kleptomania, Pathological Gambling, Trichotillomania (compulsive hair-pulling), and Onychophagia (compulsive nail-biting). This is not to imply that a simple trial of an SSRI will be 100% effective in every patient with any of these conditions: some people have no response at all, and many obtain varying degrees of partial response. But before SSRIs were available, many people did not achieve any benefit at all from pharmacologic therapies, leading many experts to believe that some disorders were simply not treatable with medications. These new medications have changed our whole view of what is treatable and what is not.

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).

While this news is encouraging, the best may be yet to come. There has been a flurry of interest in development of new antidepressants which has resulted in a large number of novel compounds coming to the market in the last few years. Venlafaxine is a powerful new medication which not only duplicates the mechanism of action of clomipramine without its overwhelming side effects, but also shows great promise as a treatment for ADHD--making it potentially ideal as a treatment for Fragile X. Nefazodone is an improved version of trazodone which provides an immediate calming effect without excessive sedation; not only is this medication potentially useful for treatment of anxiety and agitation, but its selective blockade of the 5-HT₂ subclass of serotonin receptor may afford it particularly potent antiaggressive effects. Furthermore, nefazodone does not appear to cause excessive activation in children (at least not very often), giving it a potential advantage over SSRIs.

In addition to the new medications reviewed in this publication, many compounds are being actively investigated which offer even "cleaner" action, for example working only in the brain or a certain part of it, or working only on one subclass of receptor, rather than mimicking all the actions of a particular neurotransmitter. This is certain to benefit individuals with Fragile X, given the obvious involvement of mood-regulating mechanisms in this disorder.

Addendum (8/10/04): A number of ominous warnings have been issued by regulatory agencies in the US and Europe concerning potential emergence of suicidal behavior in children treated with SSRIs; this has naturally caused alarm and prompted many questions within the Fragile X community concerning the safety of these widely used medications. Since suicidal behavior is quite rare overall in Fragile X individuals---and none has been reported in association with SSRI treatment, this does

not appear to translate directly to treatment of Fragile X. However, this effect may be similar to the excessive activation and increased hyperactivity which is frequently reported in children with Fragile X who are treated with SSRIs. In any case, treatment should never be discontinued or altered based on press reports---always consult with your doctor first if there is any question about the safety of ongoing treatment.

reference:

Benign course in a child with a massive fluoxetine overdose.

Feierabend RH Jr Department of Family Medicine, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, USA.

J Fam Pract 1995 Sep;41(3):289-91

ABSTRACT: The selective serotonin reuptake inhibitors appear to have a much wider margin of safety than most other classes of antidepressants. Although there is limited experience with acute overdoses of fluoxetine alone, few serious adverse effects have been reported. There has been almost no experience, however, with significant fluoxetine overdoses in children. This report describes the accidental ingestion of as much as 43 mg/kg of fluoxetine by a 4-year-old child. In this case, serum blood levels of the drug and its major metabolite were consistent with a large ingestion and are among the highest reported in the medical literature. Toxic effects were relatively mild and consisted of a brief spell of unresponsiveness, sinus tachycardia, and moderate psychomotor agitation and dyskinesia. Supportive care was provided and the child recovered completely.

Update 2009: The safety and usefulness of SSRIs in people of all ages with fragile X seems beyond question at this point---no medically significant adverse effects have been described in fragile X patients, other than simple allergic reactions. There are no known cases of suicidal (or homicidal) behavior in anyone with fragile X associated with the use of this drug class. However, the issue of activation continues to present the greatest challenge in the use of this class of medications in children with fragile X; if anything, the sensitivity of younger children to the activating effects of SSRIs was underestimated by most early studies. Prepubertal fragile X children seem to be especially sensitive to this side effect, and their typical hyperactivity can be aggravated by this side effect. Starting at a low dose and increasing gradually, as tolerated, still seems to be the best (perhaps only) way to deal with this problem. This may limit the dose which can be utilized in any given case. Older children and adults with fragile X appear to be much less sensitive to SSRI-induced activation, and can usually tolerate quite high doses of SSRIs in the “anti-obsessional” range (often 2-3 times the typical dose for depression.)

As a class, SSRIs are still enormously useful in treating the anxiety, irritability, aggression, and obsessive-compulsive behaviors so commonly seen in fragile X. This class is also a mainstay of treatment for autism spectrum disorders generally, and fluoxetine is likely to be approved by the FDA for the treatment of autism in the near future.

J Clin Psychiatry. 2006 Mar;67(3):407-14.

Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability.

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BACKGROUND: Awareness of the impact and prevalence of autism spectrum disorders has significantly increased in recent years. Given the dearth of reliable interventions, there is great interest in demonstrating efficacy of the various treatment options. A growing body of evidence links autism spectrum disorders to abnormalities in serotonin function, and the selective serotonin reuptake inhibitors (SSRIs) have been utilized to target various symptoms of the disorders. This article reviews the available data on the efficacy and tolerability of SSRIs in individuals with autism spectrum disorders. Objectives for future research in this area will also be suggested.

DATA SOURCES AND STUDY SELECTION: The entire PubMed database including MEDLINE (1966-July 2005) was searched for English-language biomedical articles. Search terms included autism, autism spectrum disorder, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, pervasive developmental disorder, selective serotonin reuptake inhibitors, and sertraline. All clinical trials evaluating treatment outcomes associated with the use of SSRIs in managing symptoms of autism that were identified in the search were reviewed. All randomized controlled trials and open-label trials were included in this review. Case reports and case series were excluded.

DATA SYNTHESIS: We identified 3 randomized controlled trials and 10 open-label trials or retrospective chart reviews on the use of SSRIs in autism and autism spectrum disorders. The SSRIs that have been studied in autism spectrum disorders are citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline. Most studies demonstrate significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors. While side effects were generally considered to be mild, increased activation and agitation occurred in some subjects.

CONCLUSIONS: Although SSRIs may demonstrate therapeutic benefit in autism spectrum disorders, methodological weaknesses of many of the clinical trials suggest the need for additional randomized controlled trials. Furthermore, given the increased awareness of the dangers associated with SSRI-induced activation and agitation, the presence of these side effects in the autistic population warrants closer attention to dosage, titration, and subject selection issues.

fluoxetine (Prozac)

effectiveness	safety	cost	convenience
😊😊😊😊	👉👉👉	\$\$	😬😬😬😬

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

use: 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 drugs in this class, 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 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. 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, O-C 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 get worse if activation is excessive). If this response does not occur, a higher dose should be considered; however, time is more important than dose in using these medications, and often simply waiting will give the best result. If one SSRI is not well tolerated, or does not work, it is sensible to try another. Response to these medications (and many others) is highly individual and idiosyncratic--a poor response to one member of this class does not mean that all the others should be avoided.

common side effects

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

tremor: benign and transient--will improve 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 in the course of antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

dosage

children: start with 2-4 mg each morning with food; capsule contents are freely soluble in water, taste is well hidden in juices; liquid is available (but expensive) with 4 mg per ml; capsule contents can be mixed ahead of time with a known volume of juice to make an economical and stable solution, i.e. 20 mg of Prozac in 20 ounces of juice will give 1 mg of medication for each ounce of juice; *if this method is used, be sure to mark carefully and keep away from other children, (even though no serious toxicity will result from unintentional overdose)*; increase as tolerated for optimal effect in 3-4 week intervals to 5-20 mg per day; young children will rarely require more than 10 mg/day, some teens can metabolize 40 mg/day and tolerate this dose well.

adults: start with 10 mg per day with food for the first 3-4 weeks (10 mg capsule now available); if needed, increase to 20-40 mg/day for optimal effect; most people respond to 20 mg/day if given enough time.

references:

Birmaher B, Waterman GS, Ryan N, Cully M, Balach L, Ingram J, Brodsky M
Fluoxetine for childhood anxiety disorders.
Department of Psychiatry, University of Pittsburgh, School of Medicine,
Western Psychiatric Institute and Clinic, PA 15213.

J Am Acad Child Adolesc Psychiatry 1994 Sep;33(7):993-9

OBJECTIVE: The objective of this open study was to determine the efficacy and safety of fluoxetine for the treatment of children and adolescents with anxiety disorders. **METHOD:** Twenty-one patients with overanxious disorders, social phobia, or separation anxiety disorder, who were unresponsive to previous psychopharmacological and psychotherapeutic interventions, were treated openly with fluoxetine for up to 10 months. Patients with lifetime histories of obsessive-compulsive disorder (OCD) or panic disorder, or with current major depression, were excluded. Beneficial and adverse effects of fluoxetine were ascertained using the improvement and severity subscales of the Clinical Global Impression Scale (CGIS) in two ways: (1) independent chart reviews by two child psychiatrists and (2) prospective assessments by the treating nurses and the patients' mothers. **RESULTS:** Eighty-one percent (n = 17) of patients showed moderate to marked improvement in anxiety symptoms. The severity of anxiety as measured by the CGIS was also significantly reduced from marked to mild (effect size: 2.3). There were no significant side effects. **CONCLUSIONS:** These results suggest that fluoxetine

may be an effective and safe treatment for nondepressed children and adolescents with anxiety disorders other than OCD and panic disorder. Future investigations using double-blind, placebo-controlled methodologies are warranted.

Update 2009: Fluoxetine is as useful as ever, though younger children with fragile X do seem especially sensitive to its activating effects; start low and go slow! It is now available in generic form, and this may make it an especially economical alternative. Fluvoxamine (Luvox) may be less activating for most younger children (and is indicated for the treatment of OCD in children.) Neuropharm, a British pharmaceutical company which is also developing fragile X therapeutics, is developing an alternative formulation of fluoxetine as a treatment for autism. This formulation is currently undergoing large-scale Phase III clinical trials, the largest ever for an SSRI in the treatment of MRDD. Numerous other clinical trials have now established the safety and efficacy of fluoxetine in the treatment of many of these same symptoms in autism.

Neuropsychopharmacology. 2005 Mar;30(3):582-9.

A placebo controlled crossover trial of liquid fluoxetine on repetitive behaviors in childhood and adolescent autism.

Hollander E, Phillips A, Chaplin W, Zagursky K, Novotny S, Wasserman S, Iyengar R.

Seaver and New York Autism Center of Excellence, New York, NY 10029, USA.
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Repetitive behaviors are a core symptom domain in autism that has been linked to alterations in the serotonin system. While the selective serotonin-receptive inhibitor fluvoxamine has been shown to be effective in adults with autism, as yet no published placebo controlled trials with these agents document safety and efficacy in children with autism. This study examines the selective serotonin reuptake inhibitor liquid fluoxetine in the treatment of repetitive behaviors in childhood and adolescent autism spectrum disorders (ASDs). In total, 45 child or adolescent patients with ASD were randomized into two acute 8-week phases in a double-blind placebo-controlled crossover study of liquid fluoxetine. Study design included two randomized 8-week fluoxetine and placebo phases separated by a 4-week washout phase. Outcome measures included measures of repetitive behaviors and global improvement. Low-dose liquid fluoxetine (mean final dose: 9.9+/-4.35 mg/day) was superior to placebo in the treatment of repetitive behaviors by CY-BOCS compulsion scale. The effect size was in the moderate to large range, and the doses used were low. Liquid fluoxetine was only slightly, and not significantly, superior to placebo on CGI autism score partially due to a phase order effect. However, fluoxetine was marginally superior to placebo on a composite measure of global effectiveness. Liquid fluoxetine did not significantly differ from placebo on treatment emergent side effects. Liquid fluoxetine in low doses is more effective than placebo in the treatment of repetitive behaviors in childhood autism. Limitations include small sample size and the crossover design of the study. Further replication and long-term maintenance trials are needed.

citalopram (Celexa, Lexapro)

effectiveness	safety	cost	convenience
😊😊😊😊	👉👉👉	\$\$	😬😬😬😬

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

use: 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. 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, O-C 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 get worse if activation is excessive). If this response does not occur, a higher dose should be considered; however, time is more important than dose in using these medications, and often simply waiting will give the best result. If one SSRI is not well tolerated, or does not work, it is sensible to try another. Response to these medications (and many others) is highly individual and idiosyncratic--a poor response to one member of this class does not mean that all the others should be avoided.

common side effects

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

tremor: benign and transient--will improve 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 tapering--no medically 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 in the course of antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

Dosage

(numbers below are for Celexa; Lexapro dose is usually half as much)

children: start with 5 mg; increase as tolerated for optimal effect in 3-4 week intervals to 5-20 mg per day; young children will rarely require more than 10 mg/day, some teens can metabolize 40 mg/day and tolerate this dose well.

adults: start with 10 mg per day with food for the first 3-4 weeks; if needed, increase to 20-40 mg/day for optimal effect; most people respond to 20 mg/day if given enough time.

Update 2009: Celexa has gone generic, and a funny thing happened along the way. The company that, until very recently, made Celexa now says that the drug has lots of side effects that it really hadn't appreciated at first. Fortunately, this same company coincidentally has an "improved" version of citalopram called Lexapro (escitalopram, the S-isomer of the exact same compound.) Unfortunately, wonderful new Lexapro is an expensive name-brand-only drug, while crummy old citalopram (the drug formerly known as Celexa) is a cheap generic. Now, a cynic might say that this is a prime example of a drug company trying to extend its patent by introducing a "new" drug which is new in name only. In this case, the cynics are probably right. Celexa has few side effects, and Lexapro doesn't seem much better. A few patients who've tried both prefer Lexapro, but others prefer Celexa (or generic citalopram.) The point is that Celexa is still a good drug, and citalopram is a useful generic. The makers of Lexapro also claim that the newer version is 4 times as potent as the older citalopram; this does not appear to be true in clinical practice, where higher doses are often needed. In the treatment of fragile X, optimal doses of generic citalopram are typically around 40 mg/day in adults; for Lexapro, 20 mg or more is usually required.

sertraline (Zoloft)

effectiveness	safety	cost	convenience
😊😊😊😊	👉👉👉	\$\$	😬😬😬😬

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

use: 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. Sertraline was introduced to the US market four years after fluoxetine, and became an immediate success, partly because fluoxetine had an undeservedly bad reputation in the popular press, and partly because it has a slightly different side-effect profile, making it better tolerated for some people. Compared to other drugs in this class, sertraline causes more nausea and diarrhea, but somewhat less activation or restlessness. It also causes a very high rate of sexual dysfunction, and while this may not be a concern for most children, it can interrupt treatment of adults.

The only significant medical concern when using sertraline 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; sertraline seems less likely to cause this type of interaction than some other SSRIs, but caution should still be observed.

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, O-C 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. If this response does not occur, a higher dose should be considered; however, time is more important than dose in using these medications, and often simply waiting will give the best result. If one SSRI is not well tolerated, or does not work, it is sensible to try another. Response to these medications (and many others) is highly individual and idiosyncratic--a poor response to one member of this class does not mean that all the others should be avoided.

common side effects

nausea: take with food; Pepto-Bismol may be used; divided doses may result in less initial stomach upset; always transient--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--will improve 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 in the course of antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

dosage

children: start with 12.5 mg (1/4 tablet) each morning with food; this pill is rather bitter, but can be hidden in candy or applesauce or peanut butter to mask the taste; increase as tolerated for optimal effect in 3-4 week intervals to 25-75 mg per day; young children will rarely require more than 50 mg/day, some teens can metabolize 100-200 mg/day and tolerate this dose well.

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 people respond to 100 mg/day if given enough time.

Reference:

Sertraline Response in Adults With Mental Retardation and Autistic Disorder

Jessica A. Hellings, M.D., Lee Ann Kelley, M.D., William E Gabrielli, M.D., Ph.D., Earl Kilgore, Psy.D., and Priti Shah
(J Clin Psychiatry 1996;57:333-336)

Background:

Self-injury and aggression are common reasons for urgent psychiatric referral of persons with mental retardation and autistic spectrum disorders. Although the treatment prescribed for these problems has traditionally been neuroleptic medication, serotonin reuptake inhibitors such as sertraline may result in significant clinical improvement as well as fewer side effects.

Method

The authors administered sertraline in an open trial to nine consecutively admitted adult mentally retarded outpatients presenting with target behaviors of self-injury and/or aggression. Most patients (N = 6) were mildly or moderately mentally retarded by DSM-III-R criteria; five had comorbid autistic disorder. Prescribed dosages ranged from 25 mg to 150 mg daily, based on observed clinical responses. Clinical Global Impressions (CGI) ratings were made at baseline and again after sertraline treatment for at least 28 days.

Results

Sertraline led to improvement in CGI ratings of overall clinical severity in eight of nine subjects; mean + SD improvement in CGI ratings was 2.44 points +/- 1.67. Discontinuation of the treatment was necessary in only one patient, after 18 weeks of sertraline treatment, because of agitation and worsening of self-picking. Side effects were otherwise minimal.

Conclusion

These findings from a clinical sample suggest that sertraline is promising in the treatment of self-injury and aggression. Double-blind controlled studies of sertraline and other serotonin reuptake inhibitors in the treatment of self-injury and aggression in patients with mental retardation and with autistic disorder are warranted.

[editor's note: *Most of the patients treated with sertraline (Zoloft) demonstrated a meaningful reduction (though not complete elimination) of aggressive or self-injurious behavior. The one patient who did not respond to Zoloft subsequently responded to Prozac, illustrating that some individuals may respond idiosyncratically to any psychiatric treatment, and that persistence often pays off. If one drug doesn't work, another might.*]

Update 2009: Sertraline is available as a generic, and may be the most effective SSRI in the treatment of fragile X. The response rate to this drug seems to be the highest of the class, and it does not seem to be any more activating than the average for the SSRI class. Sertraline does seem to cause more GI upset than average, and this can be a problem in people with fragile X; loose stools are already an issue in fragile X (probably caused by excessive mGluR5 activity) and this medication can aggravate the problem, occasionally to the point of bowel incontinence. However, some tolerance or accommodation to this side effect usually develops over time, so it is rarely a long-term problem. In general use in the population at large, sertraline cause many problems with sexual dysfunction (both decreased libido and anorgasmia.) This could actually be seen as an advantage in the treatment of some individuals with fragile X, though the clinical presentation is more likely to include hyposexuality.

paroxetine (Paxil)

effectiveness	safety	cost	convenience
☺☺☺☺	👉👉👉	\$\$	☯☯☯☯

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; generic available

cons: can cause excessive activation, even mania in extreme cases; frequent nausea at initiation; causes dry mouth frequently; can cause some sedation; bitter tablet, no liquid available, no pediatric dosages available

use: 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. Paroxetine is an older member of this class, introduced to the US market a year after sertraline, and it has been in use even longer in other countries. Compared to other drugs in this class, paroxetine is often more sedating, and has a higher incidence of dry mouth and constipation, though most people taking it find this tolerable and usually transient.

The only significant medical concern when using paroxetine 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.

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, O-C 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. If this response does not occur, a higher dose should be considered; however, time is more important than dose in using these medications, and often simply waiting will give the best result. If one SSRI is not well tolerated, or does not work, it is sensible to try another. Response to these medications (and many others) is highly individual and idiosyncratic--a poor response to one member of this class does not mean that all the others should be avoided.

common side effects

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

diarrhea or constipation: usually transient, may use any over-the-counter (OTC) remedy

tremor: benign and transient--will improve 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

sedation: give at bed time

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 without tapering--no medically significant withdrawal syndrome can occur, though Paxil can cause some uncomfortable (but benign) side effects during withdrawal. 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 in the course of antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

dosage

children: start with 5 mg (1/4 tablet) each evening with food; this pill is rather bitter, but can be hidden in candy or applesauce or peanut butter to mask the taste; increase as tolerated for optimal effect in 3-4 week intervals to 5-20 mg per day; young children will rarely require more than 10 mg/day, some teens can metabolize 40 mg/day and tolerate this dose well.

adults: start with 10 mg per day (1/2 tab) with food for the first 3-4 weeks ; if needed, increase to 20-40 mg/day for optimal effect; most people respond to 20 mg/day if given enough time.

Update 2009: Various Paxil formulations, including generic paroxetine, have steadily lost market share over the past few years. This drug has always had more side effects than other SSRI's, though many people have no difficulty tolerating it. It was also at the center of the recent pediatric suicide controversy surrounding SSRIs, and the actions of the drugs manufacturer in this episode were less-than-stellar. As I have noted previously, suicidal ideation does not appear to be a major treatment consideration for the vast majority of fragile X patients. Dosing also appears to be a bit less predictable than for other SSRIs, so with all the other choices available these days, it's not surprising that fewer doctors are prescribing paroxetine. Nevertheless, it is a safe and effective medication which is now available in generic form.

fluvoxamine (Luvox)

effectiveness	safety	cost	convenience
😊😊😊😊	👉👉👉	\$\$	😬😬😬😬

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

use: 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. Fluvoxamine one of the newer members of this class, and is currently being marketed for the treatment of OCD. Compared to other drugs in this class, fluvoxamine is often more sedating, though most people taking it find this tolerable and usually transient.

The only significant medical concern when using fluvoxamine 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.

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, O-C 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. If this response does not occur, a higher dose should be considered; however, time is more important than dose in using these medications, and often simply waiting will give the best result. If one SSRI is not well tolerated, or does not work, it is sensible to try another. Response to these medications (and many others) is highly individual and idiosyncratic--a poor response to one member of this class does not mean that all the others should be avoided.

common side effects

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

diarrhea: transient, try any over-the-counter (OTC) remedy

sedation: this medication is usually taken at bedtime for this reason; residual daytime sedation is usually transient and will resolve over 3-7 days

tremor: benign and transient--will improve 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 medically 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 in the course of antidepressant treatment indicates an innate predisposition to Bipolar Disorder, although this notion is somewhat controversial.

dosage

children: start with 12.5 mg each night; increase as tolerated for optimal effect in 3-4 week intervals to 25-100 mg per day; young children may not require more than 50 mg/day, some teens can metabolize 200 mg/day or more and tolerate this dose well.

adults: start with 25 mg per day with food for the first 3-4 weeks ; if needed, increase to 50-300 mg/day for optimal effect; most people respond to 100 mg/day if given enough time.

reference:

Freeman CP, Trimble MR, Deakin JF, Stokes TM, Ashford JJ

Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison.

Royal Edinburgh Hospital, Scotland.
J Clin Psychiatry 1994 Jul;55(7):301-5

ABSTRACT:

BACKGROUND: To examine the efficacy of fluvoxamine and clomipramine in obsessive compulsive disorder and to compare their tolerabilities. **METHOD:** In this multicenter, randomized, double-blind trial, fluvoxamine (100-250 mg/day) was compared with clomipramine (100-250 mg/day) for 10 weeks in the treatment of 66 psychiatric outpatients, aged 18 to 65 years, with a diagnosis of obsessive compulsive disorder. The main efficacy variable was the Yale-Brown Obsessive Compulsive Scale; secondary variables were the National Institute of Mental Health Global Obsessive Compulsive Scale and the Clinical Global Impressions-Improvement scale. **RESULTS:** Seventeen patients withdrew prematurely, 6 in the fluvoxamine group and 11 in the clomipramine group. In the intent-to-treat population (34 fluvoxamine patients and 30 clomipramine patients), there were no significant differences with respect to the mean reduction in total Yale-Brown Obsessive Compulsive Scale score (last observation carried forward) at any time-point;

a mean reduction of 8.6 (33%) was seen in the fluvoxamine group and 7.8 (31%) in the clomipramine group. Similar results were obtained in virtually all secondary variables. The only exception was the obsession-free interval for the Yale-Brown Obsessive Compulsive Scale, which was significantly longer in the fluvoxamine group, especially in a population of patients with disease of > 12 months' duration ($F = 5.298$, $df = 1$, $p = .026$). Adverse events were mostly tolerable; 9 patients (5 receiving fluvoxamine, 4 receiving clomipramine) withdrew due to adverse events related to treatment. CONCLUSION: Fluvoxamine and clomipramine were equally effective in the treatment of obsessive compulsive disorder. Both agents were well tolerated; fluvoxamine produced fewer anticholinergic side effects and caused less sexual dysfunction than clomipramine, but more reports of headache and insomnia.

Wagner W, Zaborny BA, Gray TE

Fluvoxamine. A review of its safety profile in world-wide studies.
Int Clin Psychopharmacol 1994 Winter;9(4):223-7

ABSTRACT:

Fluvoxamine, a selective serotonin reuptake inhibitor, was studied extensively in 34,587 predominantly depressed patients in 66 studies conducted world-wide. These studies were largely uncontrolled trials representing the use of fluvoxamine by psychiatric and general practice physicians in everyday conditions. The safety data were analyzed according to standardized medical review and data management policies. Approximately 70% of the fluvoxamine population were female and 44% were aged 31-51 years. The modal total daily dose was 100 mg. Safety findings revealed a pharmacological adverse event profile similar to that seen with other serotonin reuptake inhibitors. Nausea was found to be the only common symptom, with an incidence rate of 16%. Approximately 2% of the fluvoxamine population reported at least one serious adverse event (per FDA criteria). Overall suicidality rates of fluvoxamine were found to be low (0.7%). No cases of zimelidine syndrome, bleeding syndrome or Guillain-Barre syndrome were identified. Overall, fluvoxamine was found to be safe and well tolerated suggesting a favorable alternative in the treatment of depression.

A Double-blind, Placebo-Controlled Study of Fluvoxamine in Adults With Autistic Disorder

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Arch Gen Psychiatry. 1996;53:1001-1008

Background

Autistic disorder is characterized by a fundamental disturbance in social interaction, impairments in communication, and a markedly restricted repertoire of activities and interests. Abnormalities in the serotonin neurotransmitter system have been identified in some persons with autism. No consistently effective and safe drugs have been developed for treating the symptoms of autism.

Methods

Thirty adults with autistic disorder completed a 12-week double-blind, placebo-controlled trial of the potent and selective serotonin uptake inhibitor fluvoxamine maleate. Behavioral ratings were obtained at baseline and after 4, 8, and 12 weeks of treatment.

Results

Eight (53%) of 15 patients in the fluvoxamine-treated group were categorized as responders compared with none of 15 in the placebo group ($P = .001$). Fluvoxamine was superior to placebo in reducing repetitive thoughts and

behavior ($P < .001$), maladaptive behavior ($P < .001$), and aggression ($P < .03$), and in improving some aspects of social relatedness ($P < .04$), especially language usage ($P < .008$). Treatment response was not correlated with age, level of autistic behavior, or full-scale IQ. Other than mild sedation and nausea in a few patients, fluvoxamine was well tolerated. No dyskinesias, adverse cardiovascular events, or seizures occurred.

Conclusions

Fluvoxamine is more effective than placebo in the short-term treatment of the symptoms of autistic disorder in adults. Controlled studies of fluvoxamine and other potent and selective serotonin uptake inhibitors seem warranted in children and adolescents with autism.

Update 2009: Luvox has gone generic, but another company has also come out with Luvox CR, a controlled-release formulation of the drug. This makes some sense, since fluvoxamine has one of the shortest half-lives of all SSRIs, so it should help to spread out absorption a bit and increase duration of action somewhat. However, it is not a time-release formulation, so the effect is small; the greatest potential benefit is a likely reduction in acute side effects with larger doses (and larger doses clearly work best for many of the anxiety symptoms associated with fragile X.) Fluvoxamine really never caught on in the US, though it has been more widely prescribed in Europe, but it is a highly effective medication which has a long track record of excellent safety (longest of any SSRI, actually.) Luvox remains an excellent choice for the treatment of the psychiatric manifestations of developmental disorders, especially in children, where its decreased propensity to cause activation is highly desirable.

venlafaxine (Effexor)

effectiveness	safety	cost	convenience
😊😊😊	👉👉👉	\$\$	🙄🙄

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 available

use: venlafaxine is an antidepressant medication which inhibits re-uptake of serotonin and norepinephrine, while causing few other effects; in this regard it can be considered a "clean" version of clomipramine. The original medication is short acting, and must be given 2 or 3 times a day--a major inconvenience; however, this also means that it reaches full therapeutic concentrations almost immediately, and may be effective sooner than others. More recently, an extended-release version (Effexor XR) has been marketed which can be given once or twice a day, and may have fewer side effects for the average person because of more gradual drug absorption. Venlafaxine has been shown to be very effective in a wide variety of mood and anxiety disorders, including OCD and depression which has not responded to tricyclic antidepressants (TCAs) or SSRIs; however, there is relatively little experience thus far in treating children.

Since venlafaxine has a similar spectrum of activity to clomipramine, a medication which has been used fairly widely in the developmentally disabled population, yet is significantly less toxic, venlafaxine can be used to treat Fragile X. Treatment with this medication can be expected to result in a decrease in irritability or mood lability; O-C symptoms and perseverative behavior should be markedly diminished; social and panic anxiety can be expected to decrease dramatically; while there is little experience in treatment of self-injurious behavior or aggression with this agent, it is likely that it will prove quite effective, given its potent serotonergic properties. The only medically significant adverse effect associated with venlafaxine administration is a dose-related increase in blood pressure, which is ordinarily benign and asymptomatic; this is not likely to pose a problem for the average healthy child.

common side effects

nausea: take with food; Pepto-Bismol recommended; transient--will resolve in 5-7 days

sedation: temporary dosage reduction may help; usually transient

tremor: transient and benign--beta blocker can help, but rarely needed

dry mouth: also transient (unlike TCAs), sugar-free gum or hard candy can help if this is persistent

uncommon side effects

activation/restlessness: temporary dosage reduction may help; usually transient; clonidine or beta blocker can be given to treat this, but is rarely necessary

insomnia: take last dose at least 4-5 hours before bedtime

dosage

adults: start with 1/2 of a 37.5 mg tablet twice a day with food; increase as tolerated to 37.5 mg two or three times a day; maximum dose of 450 mg per day is rarely needed

Update 2009: Effexor has been available in an extended release formulation for some time now (Effexor XR), and the standard immediate-release preparation has been discontinued. This typically results in fewer immediate side effects from a dose, along with greater convenience from fewer daily doses (the manufacturer advertises this as a once-a-day formulation, but it is often given twice a day if higher doses are required---still a big improvement over the original immediate-release Effexor.) However, an extended-release formulation does not make a short-acting drug like Effexor into a long-half-life compound; while the venlafaxine in Effexor XR is release gradually over a period of time, it is still metabolized and eliminated rapidly after absorption.

This brings us to a major shortcoming of venlafaxine: it has a nasty “discontinuation syndrome.” While this medication doesn’t cause physiologic dependence, tolerance, or true withdrawal (like Xanax might, for example), it can cause some unpleasant symptoms if it is discontinued suddenly.

As this is now going off-patent, Pristiq (desvenlafaxine) is being introduced as a new drug entity. For all intents and purposes, it should be entirely equivalent to the old Effexor.

trazodone (Desyrel)

effectiveness	safety	cost	convenience
😊😊	👉👉👉	\$	👁️👁️

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

use: trazodone is a novel antidepressant which is little used in general practice for its primary indication because it is simply too sedating: most people cannot tolerate a full, therapeutic dose, especially if one considers that it is also short acting and must be taken during the day to obtain a genuine antidepressant dose. However, these drawbacks are an advantage when sedation is required. Trazodone can provide safe but powerful sedation which lasts for about 8 hours, and carries no risk of abuse, dependence, or toxicity in overdose. Most of the trazodone currently prescribed in the US is used as a sleep aid for people taking SSRIs concurrently, and there is no reason why this should not be considered for Fragile X individuals. Whereas the most commonly used sedatives in adults, the benzodiazepines, are likely to cause confusion or behavioral disinhibition (loss of control) in Fragile X individuals, trazodone does not carry this risk. The most commonly used sedative in children, diphenhydramine (Benadryl), has potent anticholinergic properties which can impair memory; it can also lower the seizure threshold, and is not an especially good choice for use in Fragile X children. Although trazodone is not widely used in the general pediatric population, it is often used in developmentally disabled patients of all ages with some success, particularly as an alternative to antipsychotic medications for the management of aggression and agitation, and for treatment of insomnia. In this regard it is probably underutilized in treating Fragile X children with particularly severe agitation and aggression.

Trazodone shares its mechanism of action with nefazodone, blocking 5HT₂ receptors while inhibiting re-uptake of serotonin (and, to a lesser extent, norepinephrine); side effects of sedation and orthostatic hypotension are thought due to interaction with histamine and alpha adrenergic receptors, respectively, making these far-from-clean drugs, but nonetheless free of anticholinergic side effects.

common side effects

residual daytime sedation: dosage reduction may be helpful; taking medication one hour before bedtime (rather than right at bedtime) may allow sedative effects to wear off sooner; some adaptation will usually occur after a few days

orthostatic hypotension (like that dizziness that comes from standing up too quickly): dosage reduction may help; smaller divided doses recommended if daytime use is prescribed

uncommon side effects

priapism (persistent penile erection): discontinue medication immediately; seek prompt medical attention if symptoms do not subside quickly (rare, but serious side effect)

nausea: take with food

headache: any OTC remedy is fine

dosage

children: 25 mg at bedtime (1/2 smallest tablet) for insomnia, may increase to 100 mg as tolerated; for treatment of aggression or agitation during the day, start with 25 mg three times a day, may increase as tolerated up to 50 mg three times a day in young children, 100 mg three times a day in older (larger) children and adolescents.

adults: start with 50 mg at bedtime for treatment of insomnia, will likely need to be increased to 100-150 mg, can go as high as 300 mg dose for relief of insomnia (if this does not work, consider the possibility of mania causing insomnia); for treatment of aggression and/or agitation, start with 50 mg three times a day, can be increased up to 150-200 mg three times a day as tolerated.

Update 2009: Trazodone is one of the safest and most widely prescribed drugs in general psychiatric practice, yet its use in fragile X is still relatively rare. One reason for this state of affairs is that pediatricians have essentially no experience with trazodone, so younger patients will rarely be treated with trazodone. Another reason is the common misunderstanding of the risk of priapism with this medication. Many years ago, the risk of priapism (persistent erection) was greatly overestimated, restricting the use of trazodone. Obviously, there is no risk for females, but even in males, this is an exceedingly rare side effect (this author has prescribed this medication to many hundreds of patients and never seen a single case of priapism, nor heard of one in any colleagues.)

Trazodone has several properties which make it especially useful for the treatment of fragile X: it enhances serotonin transmission (to treat anxiety, irritability, and aggression) while blocking 5HT₂, a serotonin receptor which appears to be linked to hyperactive Gq signaling pathways in fragile X. Like mGluR5, 5HT₂ is a neurotransmitter receptor which we would like to block in just about anyone with fragile X; 5HT₂ antagonism is a major mechanism of action of all atypical antipsychotics. With trazodone, one can obtain some of the efficacy of Abilify or Risperdal without the risks or expense of an antipsychotic. Trazodone also potently antagonizes alpha 1 norepinephrine receptors. Along with mGluR5 and 5HT₂, alpha 1 receptors are linked to Gq signaling pathways. Excessive and unregulated activity in these Gq pathways may be the major cause of brain dysfunction in fragile X. While excessive activity in 5HT₂ pathways may be responsible for problems with mood and anxiety seen in fragile X, excessive activity of alpha 1 pathways may cause hyperarousal and sleep disturbance. Thus, the alpha 1 antagonism caused by trazodone may be especially helpful with the treatment of insomnia and hyperactivity/hyperarousal.

nefazodone (Serzone)

effectiveness	safety	cost	convenience
☺☺☺	👉👉👉	\$\$	☹☹

indications: irritability, anxiety, aggression, obsessive-compulsive symptoms

pros: relatively little risk of activation, mildly sedating; generic available

cons: multiple dosing necessary; no liquid, chewable, or pediatric-size dose available; rare reports of liver toxicity

use: nefazodone is essentially a new, improved version of trazodone, to which it is closely related chemically; it is significantly better tolerated than trazodone because it causes less sedation and orthostatic hypotension. The mechanism of action of nefazodone is basically identical to that of trazodone: it inhibits re-uptake of serotonin and norepinephrine, while blocking a subclass of serotonin receptor (5HT₂, the "bad" serotonin receptor). These differences mean that nefazodone is not as useful for sedation--for treatment of insomnia or acute treatment of agitation. However, nefazodone is more useful as an antidepressant, and as a treatment for anxiety disorders because therapeutic doses are far more easily tolerated.

Nefazodone offers a major advantage as a treatment for many of the typical symptoms of Fragile X: it is much less likely to cause the kind of excessive activation which is so often a problem in the treatment of children with other antidepressants. Its 5HT₂ antagonist properties also likely yield enhanced antiaggressive effects compared to SSRIs, while its noradrenergic properties probably confer greater effectiveness in treating attention deficit. One minor disadvantage of this medication is that it must be given twice a day due to its short half-life. However, this can be an ideal choice for patients who have particular problems sleeping, since most of the total daily dose can be given at bedtime for a gently sedating effect.

common side effects

sedation: usually mild and transient; temporary dosage reduction often helpful

orthostatic hypotension: benign; can be minimized by initially dividing dose further, i.e. 25 mg four times a day rather than 50 mg twice a day

nausea: take with food; Pepto-Bismol is safe to use

uncommon side effects

priapism: not actually reported with this drug, but a theoretical concern since it is closely related to trazodone; discontinue medication immediately

headache: any OTC (over the counter) remedy is fine

dosage

children: start with 50 mg at bed time and increase as tolerated in 50 mg increments, using divided doses; usual effective dose is 100-200 mg/day; 300 mg/day is usually well tolerated in older kids

adults and teens: start with 50 mg two to three times a day, increasing as tolerated over the first week to 200-300 mg per day; maximum recommended dose is 500-600 mg per day

Update 2009: Nefazodone has gone through a number of ups and downs since its introduction. Initially, it gained great popularity as an alternative to SSRIs, but its market share was gradually diluted with later entries into the antidepressant field, like Celexa and Remeron. As its patent was nearing its end, reports surfaced of rare episodes of hepatotoxicity (liver damage) in some patients. These severe adverse effects were quite rare, and the FDA did not consider the risk sufficient to justify withdrawal from the market, but it did issue a “black box” warning, which spelled commercial death for Serzone. The original manufacturer stopped selling Serzone, but generic nefazodone is still available.

Nefazodone is actually a very safe drug, despite the dire warnings. The risk of hepatotoxicity is estimated at about 1 in 250,000 per year of treatment (so, if you were on it for 10 years, you’d have a 1 in 25,000 risk of liver damage.) This is quite a bit less than similar risks from valproate or other common drugs, most of which don’t even carry this kind of warning. Nevertheless, this has scared virtually all pediatricians and child psychiatrists away from this medication, and nefazodone has been used relatively little in pediatric populations. In the end, the popularity of the SSRIs swamped nefazodone.

This is a shame, in many ways. Nefazodone is significantly less likely than most other antidepressants to induce mania in people with Bipolar Disorder, and it is also much less likely to cause excessive activation in pediatric patients. It has a mild calming and sedating effect, which greatly aids sleep. It has few GI side effects, and is generally easy to take.

For fragile X patients (of any age), nefazodone has many advantages. Like the SSRIs, it blocks reuptake of serotonin, which gives it antidepressant, anxiolytic, and antiobsessional effects. It also blocks reuptake of norepinephrine, which further boosts mood and can help with attention. It blocks 5HT₂ receptors, helping to stabilize mood and decrease aggression, and even conferring some antipsychotic effects. Finally, its antagonism of alpha 1 norepinephrine receptors may be especially helpful in facilitating sleep and decreasing hyperactivity in fragile X. While it’s far from a “clean drug” with just one mechanism of action, its multiple effects overlap very nicely with the symptoms seen in fragile X and other autism spectrum disorders. For these reasons, nefazodone is one of the most potentially useful drugs for the treatment of fragile X, even if it is one of the most under-utilized in actual practice.

bupropion (Wellbutrin)

effectiveness	safety	cost	convenience
😊😊	👉	\$\$	☯️

indications: attention deficit, hyperactivity, irritability/depression *in Fragile X girls*

pros: generally few side effects, very mildly activating, non-sedating; may be an especially effective treatment for adults with ADHD, although research on this subject is ongoing; generic available

cons: while generally non-toxic, this medication is associated with a relatively high risk of seizures, so its use cannot be recommended in males with Fragile X, or anyone with a pre-existing seizure disorder; it must be given three times a day (twice a day with time release preparation); not effective in treatment of anxiety disorders---may actually aggravate anxiety

use: bupropion is a novel antidepressant with an unknown mechanism of action; it is thought to increase dopaminergic transmission, especially in frontal areas of the brain, and so has been promoted for the treatment of ADHD, as well as depression. More recent thinking proposes a primarily noradrenergic mechanism of action, similar to desipramine. It has not been established that this medication is significantly more effective than some other antidepressants in the treatment of ADHD, but this perception is becoming more widespread among psychiatrists. Recent head-to-head comparison with methylphenidate has shown the two drugs to be of equal efficacy in treating uncomplicated ADHD. It has been established that this medication is significantly less effective than most other available antidepressants in the treatment of anxiety disorders, so it should not generally be considered as a first choice for conditions involving significant anxiety symptoms. As noted above, it is generally well tolerated, but is associated with a much higher than average risk of seizures, making it an inappropriate choice for most Fragile X boys, who already have a very high rate of seizure disorders. In the treatment of Fragile X, bupropion is probably most useful for full-mutation girls with significant hyperactivity and symptoms of Major Depression. Bupropion must be taken in multiple doses because it is short-acting, and also to reduce the risk of seizures (which is proportional to peak levels in the bloodstream). A sustained release preparation (Wellbutrin SR) is now available, and is preferred by most doctors because it has fewer reported side effects and probably a lower risk of seizures.

common side effects

nausea: take on a full stomach; usually transient

tremor: benign; can be treated with beta blocker or dosage reduction

agitation/restlessness/insomnia: temporary dosage reduction may be helpful; take at meal times--not before bed time

headache: any OTC remedy is OK to use

uncommon side effects

constipation: any OTC remedy is fine; usually transient

seizures: immediate discontinuation is necessary; risk can be reduced by taking Wellbutrin SR

dosage

adolescents and adults: start with 75 mg twice a day, increasing as tolerated to 75 mg three times a day; maximum dose of 450 mg per day must be given in at least three or four divided doses and should never be exceeded

Update 2009: Bupropion is still a widely prescribed antidepressant, though recently it has been used a bit less; this is understandable, given all the choices available in newer antidepressants. It has also become more widely appreciated that bupropion does not treat anxiety disorders, an issue which was greatly muddled by the drug manufacturer's early marketing (which emphasized that anxiety associated with Major Depression could improve during the course of treatment with bupropion.) Indeed, it is now the general consensus that bupropion will worsen most anxiety, and all true Anxiety Disorders, in a dose-dependent fashion---much like the stimulants. Thus, the current niche for bupropion is as an activating antidepressant for people with depression, but without significant anxiety. It may be more helpful with attention than many other antidepressants, and can be used as a substitute for a stimulant, or in combination with other antidepressants (esp SSRIs.) Since most people with fragile X (male and female) have a major anxiety component to their clinical presentation, this medication should probably not be widely used in the treatment of typical fragile X. However, it may find a niche in females with fragile X, without seizures, whose presentation is primarily inattentive.

clomipramine (Anafranil)

effectiveness	safety	cost	convenience
😊😊😊	👉	\$\$\$\$	🙄🙄

indications: attention deficit, hyperactivity, enuresis (bedwetting), anxiety, irritability, aggression, O-C behavior

pros: effective for many symptoms of Fragile X, long acting, numerous trials reported in neuropsychiatric populations, indicated for children (over 10)

cons: toxic in overdose, many side effects, can increase risk of seizures, no chewable or liquid

use: clomipramine was the first agent available in the US with clinically significant effects on the serotonin system, and it remains one of the most effective treatments for Obsessive-Compulsive Disorder. Chemically, it is a tricyclic antidepressant (TCA), but it has a much broader spectrum of activity than other medications in this class. It also has a relatively high incidence of side effects, even compared to other TCAs. Of particular concern to Fragile X individuals is the possibility that clomipramine can lower the seizure threshold significantly; for this reason, it is recommended that all patients be given this medication in divided doses, and this is especially important in Fragile X. The anticholinergic side effects of this medication can cause confusion and memory loss, even in developmentally normal people, but those with developmental disorders like Fragile X may be at increased risk.

Fortunately, clomipramine has already been used a fair amount in neuropsychiatric (including developmentally disabled) populations, and generally appears to be surprisingly well tolerated. Now that less toxic alternatives are available (SSRIs, venlafaxine, nefazodone) this is not usually considered a first choice, but it is a rational treatment for many of the most problematic symptoms of Fragile X. Therapy must be started at a low dose and titrated upward for best effect; because this medication can cause cardiac conduction anomalies, a baseline EKG is often obtained, along with at least one more during treatment. Also, because blood levels of this medication can vary greatly from one individual to another, therapeutic drug monitoring (measuring blood levels) has become the standard of care--especially for children--and is highly recommended. If any problems arise during treatment, serum level of the medication should be checked immediately.

common side effects

dry mouth: may be persistent; sugar-free gum or hard candy can help

sedation: usually transient, though sometimes persistent; smaller daytime doses will minimize this

nausea: start with divided doses, taken with food if possible; usually transient

orthostatic hypotension: less of a problem in children; temporary dosage reduction helpful

constipation: any OTC remedy is fine; stool softeners and fiber laxatives usually help

blurry vision: temporary dosage reduction or shifting more of dose to bed time will help; usually transient

uncommon side effects

mania/psychosis/extreme agitation: discontinue immediately

seizures: discontinue immediately

palpitations/irregular heartbeat: probably benign, but call your physician; this type of medication normally causes a small increase in pulse rate, but should not cause arrhythmias

urinary retention: catheterization may be required; call your physician--can be treated with other medications such as bethanacol

dosage:

children: begin with 12.5 mg at night (1/2 capsule dissolved in juice), increasing daily dose by 12.5 mg every 3-4 days. During this initial phase the total daily dose should be divided into two or three separate doses; increase as tolerated to 50-100 mg. Can be increased further if there is no response after 4-6 weeks to 3 mg/kg/day or a maximum of 200 mg/day.

adults:

start with 25 mg at night; increase in 25 mg increments at 3-4 day intervals to 50 mg three times a day; if no effect after 4-6 weeks, can be increased up to 250 mg/day; blood levels are recommended.

reference:

Gordon CT, State RC, Nelson JE, Hamburger SD, Rapoport JL

A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder.

Child Psychiatry Branch, National Institute of Mental Health, Bethesda, Md.
Arch Gen Psychiatry 1993 Jun;50(6):441-7

ABSTRACT:

OBJECTIVE: To determine whether clomipramine hydrochloride, a serotonin reuptake blocker with unique anti-obsessional properties, is differentially effective for obsessive-compulsive and stereotyped motor behaviors in autistic disorder compared with placebo and with the noradrenergic tricyclic antidepressant agent, desipramine hydrochloride. **DESIGN:** Following a 2-week, single-blind placebo washout phase, 12 autistic subjects completed a 10-week, double-blind, crossover comparison of clomipramine and placebo, and 12 different subjects completed a similar comparison of clomipramine and desipramine. **SETTING:** Outpatient clinic. **PATIENTS:** A referral sample of 30 male and female autistic patients were enrolled, and 24 completed the study.

MEASURES: Key outcome measures were the Autism Relevant Subscale of the Children's Psychiatric Rating Scale, the Modified Comprehensive Psychopathological Rating Scale-Obsessive-Compulsive Disorder Subscale, and the Clinical Global Impressions Scale.

RESULTS: Clomipramine was superior to both placebo and desipramine on ratings of autistic symptoms (including stereotypies), anger, and compulsive, ritualized behaviors ($P < .05$), with no differences between desipramine and placebo. Clomipramine was equal to desipramine and both tricyclic agents were superior to placebo for amelioration of hyperactivity.

CONCLUSION: Biological links between compulsions and stereotyped, repetitive behaviors in autistic disorder should be explored.

imipramine (Tofranil)

effectiveness	safety	cost	convenience
😊😊	👉	\$	👁️👁️

indications: attention deficit, hyperactivity, enuresis (bedwetting), anxiety, irritability

pros: long acting, numerous trials reported in neuropsychiatric populations, indicated for children

cons: toxic in overdose, many side effects, can increase risk of seizures

use: imipramine was the first tricyclic antidepressant available in the US, released in the late 1950's, and it remains an effective treatment for depression and some anxiety disorders, as well as ADHD. Chemically, it is related to all other tricyclic antidepressants (TCAs), and it has a typical side effect profile for medications in this class. The anticholinergic side effects of this medication can cause confusion and memory loss, even in developmentally normal people, but those with developmental disorders like Fragile X may be at increased risk.

Fortunately, this medication has already been used a fair amount in neuropsychiatric (including developmentally disabled) populations, and generally appears to be well tolerated in young people. Now that less toxic alternatives are available (SSRIs and venlafaxine) this is not usually considered a first choice, but it is a rational treatment for many of the symptoms of Fragile X. Therapy must be started at a low dose and titrated upward for best effect; because this medication can cause cardiac conduction anomalies, a baseline EKG is often obtained, along with at least one more during treatment. Also, because blood levels of this medication can vary greatly from one individual to another, therapeutic drug monitoring (measuring blood levels) has become the standard of care--especially for children--and is highly recommended. If any problems arise during treatment, serum level of the medication should be checked immediately.

common side effects

dry mouth: may be persistent; sugar-free gum or hard candy can help

sedation: usually transient, though sometimes persistent; smaller daytime doses will minimize this; after initial titration, entire dose can be given at bed time

orthostatic hypotension: less of a problem in children; temporary dosage reduction helpful

constipation: any OTC remedy is fine; stool softeners and fiber laxatives usually help

blurry vision: temporary dosage reduction or shifting more of dose to bed time will help; usually transient

uncommon side effects

mania/psychosis/extreme agitation: discontinue immediately

seizures: discontinue immediately

palpitations/irregular heartbeat: probably benign, but call your physician; this type of medication normally causes a small increase in pulse rate, but should not cause arrhythmias

urinary retention: catheterization may be required; call your physician--can be treated with other medications such as bethanacol

dosage:

children: begin with 10 mg at night , increasing daily dose by 10 mg every 3-4 days. During this initial phase the total daily dose should be divided into two or three separate doses; increase as tolerated to 50-100 mg. Can be increased further (if there is no response after 4-6 weeks) to 3 mg/kg/day or a maximum of 150 mg/day.

adults: start with 25 mg at night; increase in 25 mg increments at 3-4 day intervals to 50 mg three times a day; if no effect after 4-6 weeks, can be increased up to 300 mg/day; blood levels are recommended.

reference:

Hilton DK, Martin CA, Heffron WM, Hall BD, Johnson GL

Imipramine treatment of ADHD in a Fragile X child.

Department of Psychiatry, University of Kentucky College of Medicine,
University of Kentucky, Lexington 40536-0080.

J Am Acad Child Adolesc Psychiatry 1991 Sep;30(5):831-4

Article Number: UI92041462

ABSTRACT:

Fragile X syndrome, an X-linked genetic disorder, is the third most common cause of mental retardation. The following is a case of a 6-year-old boy with Fragile X syndrome and its characteristic cognitive and behavioral symptomatology, including attention deficit hyperactivity disorder. In addition, this child experienced initial insomnia and nocturnal enuresis, problems not previously reported with Fragile X. Previous pharmacological treatment of the syndrome's behavioral difficulties and attention deficit has included stimulants, folic acid, and neuroleptics. This is the first report of the successful use of imipramine. Imipramine also improved the boy's insomnia and enuresis, whereas methylphenidate caused an overall worsening of his condition.

Update 2009: Both imipramine and clomipramine have faded from routine use in child psychiatry, primarily because of safety concerns. While neither drug is especially toxic when used properly, therapeutic drug monitoring (blood level measurement) is considered necessary in most cases, unless very low doses are being used. Some cardiotoxicity can be seen with either drug, especially at higher levels, and in overdose. The anticholinergic side effects, which have made these drugs unpopular in the general population, can actually be useful in treating some symptoms of fragile X. However, there are so many other choices available now that few pediatricians are willing to prescribe these drugs, and child psychiatrists will likely try many other things first.

desipramine (Norpramin)

effectiveness	safety	cost	convenience
😊😊	👉	\$	🙄🙄

indications: attention deficit, hyperactivity, enuresis (bedwetting), anxiety, irritability

pros: long acting, numerous trials reported in children

cons: toxic in overdose, many side effects, can increase risk of seizures, may be somewhat more cardiotoxic than other drugs in this class

use: desipramine is the active metabolite of imipramine, first tricyclic antidepressant, and it is an effective treatment for depression and some anxiety disorders, as well as ADHD. Chemically, it is related to all other tricyclic antidepressants (TCAs), and it has a typical side effect profile for medications in this class, though with somewhat less sedation than other TCAs. The anticholinergic side effects of this medication can cause confusion and memory loss, even in developmentally normal people, but those with developmental disorders like Fragile X may be at increased risk.

Fortunately, this medication has already been used a fair amount in neuropsychiatric (including developmentally disabled) populations, and generally appears to be well tolerated in young people. Now that less toxic alternatives are available (SSRIs and venlafaxine) this is not usually considered a first choice, but it is a rational treatment for many of the symptoms of Fragile X. Therapy must be started at a low dose and titrated upward for best effect; because this medication can cause cardiac conduction anomalies, a baseline EKG is often obtained, along with at least one more during treatment. Also, because blood levels of this medication can vary greatly from one individual to another, therapeutic drug monitoring (measuring blood levels) has become the standard of care--especially for children--and is highly recommended. If any problems arise during treatment, serum level of the medication should be checked immediately.

common side effects

dry mouth: may be persistent; sugar-free gum or hard candy can help

sedation: usually transient, though sometimes persistent; smaller daytime doses will minimize this; after initial titration, entire dose can be given at bed time

orthostatic hypotension: less of a problem in children; temporary dosage reduction helpful

constipation: any OTC remedy is fine; stool softeners and fiber laxatives usually help

blurry vision: temporary dosage reduction or shifting more of dose to bed time will help; usually transient

insomnia: can disrupt sleep in some cases; if so, give during the day

uncommon side effects

mania/psychosis/extreme agitation: discontinue immediately

seizures: discontinue immediately

palpitations/irregular heartbeat: probably benign, but call your physician; this type of medication normally causes a small increase in pulse rate, but should not cause arrhythmias

urinary retention: catheterization may be required; call your physician--can be treated with other medications such as bethanacol

dosage:

children: begin with 10 mg at night , increasing daily dose by 10 mg every 3-4 days. During this initial phase the total daily dose should be divided into two or three separate doses; increase as tolerated to 50-100 mg. Can be increased further (if there is no response after 4-6 weeks) to 3 mg/kg/day or a maximum of 150 mg/day.

adults: start with 25 mg at night; increase in 25 mg increments at 3-4 day intervals to 50 mg three times a day; if no effect after 4-6 weeks, can be increased up to 300 mg/day; blood levels are recommended.

Update 2009: As is the case with imipramine and clomipramine, desipramine has faded from routine use in child psychiatry, primarily because of safety concerns. While it is not especially toxic when used properly, therapeutic drug monitoring (blood level measurement) is considered necessary in most cases, unless very low doses are being used. Some cardiotoxicity can be seen with desipramine, especially at higher levels, and in overdose---in fact, some studies suggest that it is the most cardiotoxic of all the tricyclics, and some doctors recommend routine EKGs in all patients treated with this drug. The anticholinergic side effects, which have made these drugs unpopular in the general population, can actually be useful in treating some symptoms of fragile X. However, there are so many other choices available now that few pediatricians are willing to prescribe these drugs, and child psychiatrists will likely try many other things first.

nortriptyline (Pamelor)

effectiveness	safety	cost	convenience
😊😊	👉	\$	👁️👁️

indications: attention deficit, hyperactivity, enuresis (bedwetting), anxiety, irritability

pros: long acting, somewhat better tolerated than other TCAs

cons: toxic in overdose, many side effects, can increase risk of seizures

use: nortriptyline is the active metabolite of amitriptyline, one of the first tricyclic antidepressants; however, nortriptyline is significantly less toxic and has fewer side effects than its parent compound, and so has been used far more commonly over the past 10-15 years. It is an effective treatment for depression and some anxiety disorders, as well as ADHD. Chemically, it is related to all other tricyclic antidepressants (TCAs), and it has a typical side effect profile for medications in this class. The anticholinergic side effects of this medication can cause confusion and memory loss, even in developmentally normal people, but those with developmental disorders like Fragile X may be at increased risk.

Fortunately, this medication has already been used a fair amount in neuropsychiatric (including developmentally disabled) populations, and generally appears to be well tolerated in young people. Now that less toxic alternatives are available (SSRIs and venlafaxine) this is not usually considered a first choice, but it is a rational treatment for many of the symptoms of Fragile X. Therapy must be started at a low dose and titrated upward for best effect; because this medication can cause cardiac conduction anomalies, a baseline EKG is often obtained, along with at least one more during treatment. Also, because blood levels of this medication can vary greatly from one individual to another, therapeutic drug monitoring (measuring blood levels) has become the standard of care--especially for children--and is highly recommended. If any problems arise during treatment, serum level of the medication should be checked immediately.

common side effects

dry mouth: may be persistent; sugar-free gum or hard candy can help

sedation: usually transient, though sometimes persistent; smaller daytime doses will minimize this; after initial titration, entire dose can be given at bed time

orthostatic hypotension: less of a problem in children; temporary dosage reduction helpful

constipation: any OTC remedy is fine; stool softeners and fiber laxatives usually help

blurry vision: temporary dosage reduction or shifting more of dose to bed time will help; usually transient

insomnia: can disrupt sleep in some cases; if so, give during the day

uncommon side effects

mania/psychosis/extreme agitation: discontinue immediately

seizures: discontinue immediately

palpitations/irregular heartbeat: probably benign, but call your physician; this type of medication normally causes a small increase in pulse rate, but should not cause arrhythmias

urinary retention: catheterization may be required; call your physician--can be treated with other medications such as bethanacol

dosage:

children: begin with 10 mg at night , increasing daily dose by 10 mg every 4 days. During this initial phase the total daily dose should be divided into two or three separate doses; increase as tolerated to 50 mg. Can be increased further (if there is no response after 4-6 weeks) to a maximum of 100 mg/day.

adults: start with 25 mg at night; increase in 25 mg increments at 4 day intervals to 50 mg twice a day; if no effect after 4-6 weeks, can be increased up to 150 mg/day; blood levels are recommended, especially since nortriptyline seems to have a "therapeutic window"--too much or too little can be ineffective.

Update 2009: As is the case with imipramine, desipramine, and clomipramine, nortriptyline has faded from routine use in child psychiatry, primarily because of safety concerns. While it is not especially toxic when used properly, therapeutic drug monitoring (blood level measurement) is considered necessary in most cases, unless very low doses are being used. Some cardiotoxicity can be seen with nortriptyline, especially at higher levels, and in overdose---although some studies suggest that it is the least cardiotoxic of all the tricyclics. The anticholinergic side effects, which have made these drugs unpopular in the general population, can actually be useful in treating some symptoms of fragile X. However, there are so many other choices available now that few pediatricians are willing to prescribe these drugs, and child psychiatrists will likely try many other things first.

buspirone (BuSpar)

effectiveness	safety	cost	convenience
😊😊	👐👐👐👐	\$\$	🙄🙄

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

use: buspirone is a novel compound marketed for the treatment of generalized anxiety disorder in the general population; it has also been shown to be a weak antidepressant and antiobsessional agent; however, it has been demonstrated ineffective in treating Panic Disorder in the general population, and it should be presumed ineffective in treating panic anxiety in Fragile X individuals. In developmentally disabled populations, buspirone is most valuable as a treatment for aggression. In this regard it is often dramatically effective, sometimes completely eliminating otherwise intractable aggressive behavior within two or three days. However, this seems to be very much a hit or miss proposition: about half the time it has no discernable effect on the target behavior; the other half of the time it usually works quickly and at surprisingly low doses. In fact, low doses are often reported to work better. It is a common mistake among inexperienced clinicians to increase the dose of this medication too rapidly to heroic levels, when there is likely to be a "therapeutic window", resulting in a better effect at low to moderate dosages.

Buspirone is technically a 5-HT_{1A} agonist, which means that it stimulates a subclass of serotonin receptors in both presynaptic and postsynaptic sites. It is thought that the postsynaptic 5-HT_{1A} agonism results in the antiaggressive effects by mimicking natural serotonin, but that agonism at the presynaptic receptor inhibits release of serotonin. It is likely that, in most cases, this push-me/pull-you effect results in the therapeutic window--that low doses cause primarily the postsynaptic serotonin agonism (and the therapeutic, antiaggressive effect), and that higher doses cause more and more presynaptic inhibition, cancelling out the therapeutic effect.

Buspirone has many advantages, especially its lack of significant toxicity and benign side effect profile. Unlike the antidepressants, it cannot provoke mania or cause significant activation; it is not toxic, even in massive overdose; and it does not interact significantly with most other medications. However, it does not work as often or for as many core symptoms of Fragile X as some other agents (SSRIs, for example); it does not usually help with irritability or mood instability; it only has weak antiobsessional effects, and is not likely to significantly curtail perseverative behaviors. It should be taken three times a day, and is available only as a poorly-soluble tablet, which is also quite expensive--so this is one of the least convenient medications to administer to a difficult child, and may not be feasible for some Fragile X children.

common side effects

dizziness/lightheadedness: usually transient and always benign; take with food to smoothe absorption

nausea: transient and benign; take with food; may be treated with Pepto-Bismol

uncommon side effects

insomnia: take last dose 3-4 hours before bed time

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 with meals; can be increased to 10 mg three times a day, if needed, but this should rarely be necessary and is unlikely to be more effective

teens and adults: start with 5 mg twice a day (with breakfast and dinner) for at least a week; increase if needed to 5 mg three times a day with meals; can be increased in one to two week intervals to 60 mg per day; some patients have reportedly been treated safely and without adverse effects with more than 120 mg per day, but this should not ordinarily be necessary and is unlikely to offer greater efficacy (not to mention the fact that 120 mg of BuSpar costs about \$8-10)

reference:

Ricketts RW, Goza AB, Ellis CR, Singh YN, Chambers S, Singh NN, Cooke JC 3rd

Clinical effects of buspirone on intractable self-injury in adults with mental retardation.

Southwest Institute for Developmental Disabilities at Abilene, Texas.

J Am Acad Child Adolesc Psychiatry 1994 Feb;33(2):270-6

ABSTRACT:

OBJECTIVE: The efficacy of buspirone in controlling self-injurious behavior was examined in five individuals with mental retardation. Buspirone was used alone in two individuals and as an adjunct to thioridazine in the other three. **METHOD:** Standard behavioral observation methods were used to collect data on the number of self-injurious responses of the individuals during baseline and several doses of buspirone in an open trial. **RESULTS:** When compared with baseline levels, all five individuals showed some response to

buspirone, with reductions in self-injury ranging from 13% to 72%, depending on the dose. The most effective dose of buspirone was 30 mg/day for three individuals and 52.5 mg/day for the other two. These individuals were maintained for 6 to 33 weeks on their most effective dose. Coexistent symptoms of anxiety did not predict a favorable response to buspirone therapy. CONCLUSIONS: Buspirone showed a mixed but generally favorable response in controlling intractable self-injury in this and four previous studies reporting similar cases. However, the drug should not be endorsed as a proved treatment for self-injury until similar results have been obtained from well-controlled studies of its efficacy.

J Clin Psychiatry. 1998 Feb;59(2):56-9.

Buspirone in the management of anxiety and irritability in children with pervasive developmental disorders: results of an open-label study.

Buitelaar JK, van der Gaag RJ, van der Hoeven J.

Rudolf Magnus Institute for Neurosciences, Utrecht, The Netherlands.

BACKGROUND: We evaluated the efficacy and safety of buspirone in the management of anxiety and irritability in children with pervasive developmental disorders (PDD). METHOD: Twenty-two subjects, 6 to 17 years old, with DSM-III-R diagnosed PDD-NOS (N = 20) or autistic disorder (N = 2), were included. They were treated with buspirone in dosages ranging from 15 to 45 mg/day in an open-label trial lasting 6 to 8 weeks. Responders continued buspirone treatment and were followed up for up to 12 months. RESULTS: Nine subjects had a marked therapeutic response and 7 subjects a moderate response on the Clinical Global Impressions (CGI) scale after 6 to 8 weeks of treatment. Side effects were minimal, except for 1 patient who developed abnormal involuntary movements. CONCLUSION: These results suggest that buspirone may be useful for treating symptoms of anxiety and irritability in children with PDD.

Update 2009: Buspirone is enjoying a resurgence, after being dismissed for many years as a useless drug. In part, this may be related to concerns about treatment-emergent suicidal ideation in children treated with SSRIs (something which has not been reported with buspirone.) While buspirone is certainly not the most potent serotonin-enhancing drug, this may be an advantage in some situations. In particular, the relatively mild effect of buspirone (caution: easily confused with bupropion!!!) is much more easily tolerated. This means that children (or adults, for that matter) who experience excessive activation when treated with SSRIs can still get some of the same therapeutic effects from buspirone, but in an easy-to-tolerate package. There are many patients with developmental disorders who cannot tolerate any SSRI or other new antidepressant,

but can tolerate buspirone. It should be noted that buspirone is now an inexpensive generic (though all generic drug prices have been increasing precipitously of late!), and longstanding clinical experience has shown that this medication can be dosed twice a day with little or no decrease in efficacy. Thus, two negatives in the original ratings for this drug have improved significantly. Buspirone is also used increasingly as an augmentation strategy for other medications; it is especially useful in enhancing the antiobsessional effects of SSRIs, and can be a useful addition when the maximum tolerated dose of the original drug is yielding only partial effects.

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 is of benefit to many individuals with Fragile X who suffer from troublesome hyperarousal or "overstimulation", which may result in hyperactivity, anxiety, mood lability, or even aggression. These agents are broadly divided into two classes: those which act primarily in the brain to decrease "sympathetic outflow", and thereby the release of adrenalin in the general circulation (alpha₂ agonists); and those which act primarily in the periphery to block the receptors for adrenalin (beta blockers).

Clonidine is the prototype of the alpha₂ agonists, and is one of the most commonly prescribed medications for children with Fragile X. There are other medications in this class which might be potentially useful for treatment of hyperactivity and hyperarousal, but so far only one other, guanfacine has actually been used on any widespread basis. While there is far more experience using clonidine in children, guanfacine is being used more and more by child psychiatrists for ADHD in the general population and hyperactivity in the developmentally disabled population because it is generally less sedating and somewhat longer acting.

Propranolol is the prototype of the beta blockers, but dozens more have been introduced over the last two decades. Atenolol, pindolol, and nadolol have all been used in child and adult psychiatry, but the differences between them are rather minimal. Beta blockers have not been reported to be especially effective in adult psychiatry, and several studies have actually demonstrated a lack of efficacy compared to placebo in treating various anxiety disorders; thus, most adult psychiatrists consider them ineffective as psychotropics, with only two specific exceptions. Beta blockers do seem to help some people cope with performance anxiety (such as stage fright or public speaking phobia) by minimizing the "jitters" and "butterflies in the stomach" caused by circulating adrenaline. However, these medications have little or no effect on the brain, and most forms of anxiety involve central mechanisms, not just circulating adrenaline; therefore, the major part of anxiety is unaffected in most cases (including Fragile X). The second exception is that pindolol has been reported to block presynaptic 5-HT_{1A} receptors which normally provide feedback inhibition of serotonin release. This would otherwise be considered a side effect, but it may be clinically useful as a way of speeding up the response to serotonergic antidepressants. It is unclear at this stage whether other beta blockers share this property, but pindolol might be recommended as a way to enhance the effect of an SSRI.

Child psychiatrists have a somewhat different view of beta blockers, and tend to prescribe them more frequently. Several small studies have suggested that these medications may be helpful in treating some forms of anxiety in childhood, but no comparative studies have been done. Based on personal experience and thorough review of the literature, this author cannot recommend beta blockers as a first-line treatment of anxiety disorders in any patient, especially one with Fragile X-- these medications, by themselves, simply are not very effective and not as benign as many people consider them to be (especially at the heroic doses sometimes used).

The case for beta blockers is somewhat stronger in the treatment of aggression, where many studies have reflected positively on these agents. However, their effect appears rather weak compared to other medications now available, such as anticonvulsants, SSRIs, and buspirone. Therefore, propranolol is reviewed here for its potential use as a treatment of aggressive behavior in

Fragile X; other beta blockers are too numerous to review individually, but can be considered essentially equivalent.

clonidine (oral formulation; Catapres)

effectiveness	safety	cost	convenience
😊😊😊	👐👐	\$	☯️☯️

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

use: 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" area which regulates autonomic nervous system arousal, and when activated cause feedback inhibition of this system. This is the same mechanism by which clonidine lowers blood pressure (the use for which it is marketed), but in Fragile X individuals this results in a general calming effect and a decreased sensitivity to hyperarousal or "overstimulation". Toning down this fight or flight mechanism not only decreases the "sympathetic outflow" from the brain to the rest of the body, it has psychotropic effects as well. Since activation of the locus ceruleus is often thought responsible for the phenomenon of panic attacks, it is no surprise that inhibiting it can result in subjective relief of anxiety (although, oddly enough, clonidine is not an effective treatment for Panic Disorder in the general population).

The use of clonidine for behavioral treatment of Fragile X can be expected to result in a significant decrease in hyperactivity/hyperkinesis and hyperarousal. This should be considered the primary target symptom, and when effectively treated will usually result in improved attention and concentration. Aggression is often greatly decreased, especially if an individual displays this target symptom primarily as a result of overstimulation or hyperarousal. Anxiety, as noted above, can be specifically targeted for treatment with clonidine, but this usually responds best when a given individual is also significantly hyperaroused (as in the case of some Fragile X children who have extreme difficulty with eye contact, which provokes such intense social anxiety that it can interfere with school performance).

The major practical problem in using clonidine is the initial sedation most people experience; this peaks about one hour after an oral dose and can be accompanied by dizziness, confusion,

irritability, and loss of coordination. Tolerance develops rapidly to these side effects, so the key is to start with very low doses and increase gradually. An elegant (and expensive) way around these side effects is to use the clonidine patch (Catapres TTS), which releases medication continuously for absorption through the skin, avoiding peak drug levels altogether, and greatly reducing side effects.

Clonidine can be combined with many of the other medications used to treat Fragile X. It counteracts most of the adverse physical and psychiatric effects of the stimulants, while adding to the therapeutic effect. Clonidine tends to treat hyperactivity and hyperarousal best, while the stimulants have the greatest direct effect in enhancing attention and concentration. It is not only the treatment of choice for motor and vocal tics which can sometimes develop on stimulants, it can counteract any increase in anxiety or aggression seen with the use of these medications. Clonidine is frequently used as a treatment for insomnia in hyperactive children, particularly when stimulants exacerbate this problem; a bed time dose of oral clonidine will usually result in pleasant, benign sedation without significant "hangover" at the right dose. However, insomnia itself is usually not a target symptom in its own right, but a sign of another problem like mania or extreme hyperarousal, or a side effect of medication.

Clonidine may be combined with antidepressants, especially the SSRIs, for good overall effect. These medications complement one another well, since antidepressants typically enhance attention and concentration but do not affect hyperarousal much at all (and in some cases may even cause excessive activation). And, while clonidine can tone down the physical symptoms of anxiety, the antidepressants have much greater effects on the irritability and panic that are so commonly seen in Fragile X. Interestingly, this combination of clonidine and an antidepressant is frequently used in the general population to treat Post Traumatic Stress Disorder, one of the major anxiety disorders, which involves a similar disturbance of mood and physiologic arousal.

common side effects

sedation: temporary dosage reduction will usually help; take 2/3 of total daily dose at bed time; patch form of drug will minimize 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, though this need not be done too frequently, since this medication cannot cause orthostatic hypotension

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 0.1 mg tablet at bed time, 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 0.3 mg per day

teens and adults: start with 1/2 of a 0.1 mg tablet twice a day, increasing to 0.1 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 0.6 mg per day

clonidine patch (Catapres Transdermal Therapeutic System)

effectiveness	safety	cost	convenience
😊😊😊	👐👐	\$\$\$	😞😞😞😞

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

use: 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. 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" area which regulates autonomic nervous system arousal, and when activated cause feedback inhibition of this system. This is the same mechanism by which clonidine lowers blood pressure (the use for which it is marketed), but in Fragile X individuals this results in a general calming effect and a decreased sensitivity to hyperarousal or "overstimulation". Toning down this fight or flight mechanism not only decreases the "sympathetic outflow" from the brain to the rest of the body, it has psychotropic effects as well. Since activation of the locus ceruleus is often thought responsible for the phenomenon of panic attacks, it is no surprise that inhibiting it can result in subjective relief of anxiety (although, oddly enough, clonidine is not an effective treatment for Panic Disorder in the general population).

The use of clonidine for behavioral treatment of Fragile X can be expected to result in a significant decrease in hyperactivity/hyperkinesia and hyperarousal. This should be considered the primary target symptom, and when effectively treated will usually result in improved attention and concentration. Aggression is often greatly decreased, especially if an individual displays this target symptom primarily as a result of overstimulation or hyperarousal. Anxiety, as noted above, can be specifically targeted for treatment with clonidine, but this usually responds best when a given individual is also significantly hyperaroused (as in the case of some Fragile X children who have extreme difficulty with eye contact, which provokes such intense social anxiety that it can interfere with school performance). The major practical problem in using clonidine is the initial sedation most people experience; this side effect is dramatically reduced by using the transdermal patch, although it can still occur. Once again, the key is to start with very low doses and increase gradually.

Clonidine can be combined with many of the other medications used to treat Fragile X. It counteracts most of the adverse physical and psychiatric effects of the stimulants, while adding to the therapeutic effect. Clonidine tends to treat hyperactivity and hyperarousal best, (while the stimulants have the greatest direct effect in enhancing attention and concentration). It is not only the treatment of choice for motor and vocal tics which can sometimes develop on stimulants, it can counteract any increase in anxiety or aggression seen with the use of these medications. Clonidine is frequently used as a treatment for insomnia in hyperactive children, particularly when stimulants exacerbate this problem. However, insomnia itself is usually not a target symptom in its own right, but a sign of another problem like mania or extreme hyperarousal, or a side effect of medication.

Clonidine may be combined with antidepressants, especially the SSRIs, for good overall effect. These medications complement one another well, since antidepressants typically enhance attention and concentration but do not affect hyperarousal much at all (and in some cases may even cause excessive activation). And, while clonidine can tone down the physical symptoms of anxiety, the antidepressants have much greater effects on the irritability and panic that are so commonly seen in Fragile X. Interestingly, this combination of clonidine and an antidepressant is frequently used in the general population to treat Post Traumatic Stress Disorder, one of the major anxiety disorders, which involves a similar disturbance of mood along with physiologic arousal.

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, though this need not be done too frequently, since this medication cannot cause orthostatic hypotension

skin rash: happens in about 15-20% of all people treated and may require discontinuation; check with your doctor; some rashes are in reaction to adhesive overlay, not patch itself; a topical steroid spray can be used to counteract this side effect

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 bed time, 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

1. **When to change:** even though these patches are designed to last for 7 days in the treatment of hypertension, they rarely seem to last that long for hyperactive children; expect to change patches every 3-5 days, depending on the individual; you will probably be able to tell when it is wearing out

by the child's behavior; new patches should be applied at night, since this changeover usually causes a bit of sedation.

2. Where to place: always place the patch between the shoulder blades of young children, so they cannot reach the patch to remove it; many children have pulled off the patch and chewed it, resulting in serious overdose (the patch actually contains 25 days' dose of clonidine). Tegaderm (see below) is much harder to peel off, and can solve this problem as well. Always place new patches in a new spot to minimize allergic reactions and allow the skin to breathe.

3. How to keep it on: the patches come with adhesive overlays which can stick the patch back on if it has fallen off; this will work even if the patch washes off in the tub or a swimming pool--so don't throw away a patch just because it falls off or gets wet (at \$7 apiece, you'll want to get the most out of each); if a child sweats excessively or spends a great deal of time swimming, try Tegaderm, an adhesive but breathable plastic film available at drugstores without a prescription.

4. Minimizing rebound: some children are so sensitive to sedation on medication and rebound off it that they get very sleepy when each new patch is applied, then very hyperactive as an old one is coming to the end of its useful life; patch administration smoothes out the blood levels of the medication considerably, but there are still fluctuations. One way to smoothe the level of the medication even more is to use two smaller patches in staggered fashion, so that there is always one newer patch and one older patch. For example, if a child requires about 0.2 mg of clonidine per day to achieve good control of hyperactivity, rather than using a TTS-2 patch and changing it every 3-5 days, one could use a TTS-1 patch (which has exactly half the clonidine of a TTS-2) for the first 4 days, then add a second patch on day 4, leaving the first one in place; on day 8, change the first patch for a new one, leaving the second patch in place. This staggered arrangement will give the smoothest possible level, but is a bit more elaborate, and requires that you write the date of placement on each patch so you can tell which one needs changing.

5. Avoiding overdose: one patch actually contains 25 times the daily dose of clonidine in its "reservoir"; even after it has been on for a week, a TTS-1 patch has nearly 2 mg of active drug left in it--plenty to cause overdose if it is consumed. It is, therefore, important that no child is allowed to chew or swallow any patch, whether new or used. The patch is designed to adhere during a bath or shower, but will often come off in a swimming pool during prolonged water play. It is probably wise to remove the patch and save it in a dry, secure place if your child will be in the water for an extended time, so that no other child finds it floating in the water and is tempted to chew it. Also, check daily to be sure your child is still wearing his patch; if it is been chewed or swallowed, seek medical attention immediately (initial symptoms of overdose will most likely be sedation, confusion, and dizziness). Overdoses of clonidine can be serious, but will cause no permanent harm if attended to promptly.

reference:

Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD

A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism.

Department of Pharmacy Practice, College of Pharmacy, University of Arizona, Tucson.

ABSTRACT:

BACKGROUND: Autistic individuals often exhibit hyperarousal behaviors (e.g., stereotyped body movements, self-stimulation, hypervigilance, and hyperactivity). Clonidine, an alpha 2-adrenergic receptor agonist, has been shown to be effective in reducing impulsivity, inattention, and hyperactivity associated with attention deficit disorder with hyperactivity. This study investigated the efficacy and safety of transdermal clonidine in reducing hyperarousal behaviors associated with autism. **METHOD:** A double-blind, placebo-crossover study with transdermal clonidine was performed in nine autistic males (aged 5 to 33 years). Subjects received either clonidine (approximately 0.005 mg/kg/day) or placebo by a weekly transdermal patch. Each trial lasted 4 weeks with a 2-week washout period between treatment phases. Subjects were evaluated every 2 weeks by clinician raters and weekly by parents. **RESULTS:** The clonidine treatment showed a significant difference from placebo treatment on three subscales of the Ritvo-Freeman Real Life Rating Scale (i.e., social relationship to people, affectual responses, and sensory responses). The Clinical Global Impressions scale indicated that clonidine produced a significant improvement on severity of illness, global improvement, and efficacy index for therapeutic effect of the drug. A patient global rating scale showed clonidine treatment resulted in significant improvement in comparison with placebo. Adverse effects included sedation and fatigue during the first 2 weeks of clonidine treatment. **CONCLUSION:** Results from this preliminary study show that clonidine was effective in reducing several hyperarousal behaviors and improved social relationships in some autistic subjects. Further studies are needed in a larger autistic population to determine the dose-response relationship of clonidine.

guanfacine (Tenex)

effectiveness	safety	cost	convenience
😊😊😊	👉👈	\$\$\$	🙄🙄

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

use: since clonidine is one of the most frequently used treatments for the behavioral disturbances seen in Fragile X, it was practically inevitable that guanfacine, a very closely related member of the same drug class, would eventually come into more widespread use as an alternative. 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" area which regulates autonomic nervous system arousal, and when activated cause feedback inhibition of this system. This is the same mechanism by which guanfacine lowers blood pressure (the use for which it is marketed), but in Fragile X individuals this results in a general calming effect and a decreased sensitivity to hyperarousal or "overstimulation". Toning down this fight or flight mechanism not only decreases the "sympathetic outflow" from the brain to the rest of the body, it has psychotropic effects as well. Since activation of the locus ceruleus is often thought responsible for the phenomenon of panic attacks, it is no surprise that inhibiting it can result in subjective relief of anxiety (although, oddly enough, guanfacine is not an effective treatment for Panic Disorder in the general population).

The use of guanfacine for behavioral treatment of Fragile X can be expected to result in a significant decrease in hyperactivity/hyperkinesis and hyperarousal. This should be considered the primary target symptom, and when effectively treated will usually result in improved attention and concentration. Aggression is often greatly decreased, especially if an individual displays this target symptom primarily as a result of overstimulation or hyperarousal. Anxiety, as noted above, can be specifically targeted for treatment with guanfacine, but this usually responds best when a given individual is also significantly hyperaroused (as in the case of some Fragile X children who have extreme difficulty with eye contact, which provokes such intense social anxiety that it can interfere with school performance). The major practical problem in using guanfacine is the initial sedation most people experience, though this is somewhat less than with clonidine; this peaks about one hour after an oral dose and can be accompanied by dizziness, confusion, irritability, and loss of coordination. Tolerance develops rapidly to these side effects, so the key is to start with very low doses and increase gradually.

Guanfacine can be combined with many of the other medications used to treat Fragile X. It counteracts most of the adverse physical and psychiatric effects of the stimulants, while adding to the therapeutic effect. Guanfacine tends to treat hyperactivity and hyperarousal best, while the

stimulants have the greatest direct effect in enhancing attention and concentration. It can counteract any increase in anxiety, aggression, or insomnia seen with the use of stimulants.

Guanfacine may be combined with antidepressants, especially the SSRIs, for good overall effect. These medications complement one another well, since antidepressants typically enhance attention and concentration but do not affect hyperarousal much at all (and in some cases may even cause excessive activation). And, while guanfacine can tone down the physical symptoms of anxiety, the antidepressants have much greater effects on the irritability and panic that are so commonly seen in Fragile X.

common side effects

sedation: temporary dosage reduction will usually help; take 2/3 of total daily dose at bed time

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 need not be done too frequently, since this medication cannot cause orthostatic hypotension

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 bed time, 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

reference:

An open trial of guanfacine in the treatment of attention-deficit hyperactivity disorder.

Hunt RD, Arnsten AF, Asbell MD
Division of Child Psychiatry, Vanderbilt University School of Medicine,
Nashville, TN.

J Am Acad Child Adolesc Psychiatry 1995 Jan;34(1):50-4




ABSTRACT:

OBJECTIVE: Medications such as clonidine have been shown to facilitate calming, to enhance frustration tolerance, and to reduce aggression in hyperactive children. The use of guanfacine (Tenex), an alpha 2 noradrenergic agonist similar to clonidine, was studied as an alternative because of its longer excretion half-life, decreased sedative side effects, and more selective binding profile. **METHOD:** Thirteen psychiatric outpatients diagnosed with ADHD were rated at baseline and while taking guanfacine to determine its efficacy as a treatment for ADHD. Comparisons of Conners

parent ratings within subject were used to measure behavioral changes in the subjects. RESULTS: During guanfacine treatment, patients' mean scores improved significantly overall (1.27 off, 0.85 on, $t = 2.55$, $p < .015$) and in Conners Hyperactivity (1.63 off, 0.94 on, $t = 3.69$, $p < .01$), Inattention (1.92 off, 1.21 on, $t = 3.32$, $p < .01$), and Immaturity (1.81 off, 0.92 on, $t = 3.77$, $p < .01$) factors. CONCLUSIONS: This preliminary study indicates that guanfacine is a beneficial and useful treatment of ADHD, reducing hyperactive behaviors and enabling greater attentional ability with minimal side effects. We are currently collecting data in a double-blind study measuring guanfacine's efficacy with and in comparison to methylphenidate.

Update 2009: Tenex has gone generic, which has removed industry support from clinical research with this drug; if you've followed the history of drug development, you know that this means most of the biggest proponents of Tenex (guanfacine) have lost interest in it entirely. Nevertheless, it's still a useful alternative to clonidine, a little longer acting and less potent.

propranolol (Inderal)

effectiveness	safety	cost	convenience
		\$	

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

use: propranolol is a useful medication in many ways; however, it is often prescribed for anxiety disorders, and its effectiveness in this regard is unclear. Propranolol is sometimes effective in the treatment of aggression and self-injurious behavior, though rarely as monotherapy (that is, without other drugs), and usually at very high doses. While it does have some sympatholytic properties, and can block peripheral effects of adrenaline, it is not an especially effective treatment of hyperactivity or hyperarousal, and is clearly inferior to clonidine and other alpha agonists in Fragile X children. With so many alternative agents available currently, it is unclear whether propranolol and other beta blockers have any front-line role in treatment of Fragile X behavioral problems. Propranolol finds its main psychiatric use nowadays as a treatment for many side effects of other medications; it is the treatment of choice for many types of tremor and restlessness caused by stimulants, lithium, SSRIs, and antipsychotics. In this use, beta blockers are given at low doses, have very few side effects, and are quite safe for children, even for long term administration. Use at high doses involves more risk and more side effects, and this is the type of treatment described below.

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

similar medications (can be considered equivalent)

nadolol (Corgard) pindolol (Visken)

atenolol (Tenormin)

Mood Stabilizers

This class of medications varies widely from a biochemical perspective; these medications work in very different ways. However, they all have one thing in common: they tend to stabilize moods and decrease affective lability. Most of the clinical experience in the use of these agents has occurred in the treatment of Bipolar Disorder (Manic-Depressive Illness), the best known psychiatric condition involving affective lability, but they have also been used extensively in the developmentally disabled population for many years, with generally good results. 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.

Lithium was the first medication discovered with significant mood stabilizing properties, and has been the mainstay of treatment for Bipolar Disorder for more than 20 years. It requires careful monitoring, including blood levels and thyroid and renal function testing at regular intervals, since it can be quite toxic at doses only slightly higher than the therapeutic range. While it can be lifesaving for many Bipolar patients, results in most developmental disorders are often underwhelming. It generally seems to work best for those individuals with less frequent, classic manic and depressive episodes. In most cases of "rapid cycling" mood swings, where affect is extremely unstable, lithium is ineffective. This may explain why individuals with developmental disorders such as Fragile X, who typically have very unstable moods, do not appear to benefit from lithium therapy. It is also quite rare to find physicians other than psychiatrists who are willing to prescribe lithium, given the involved nature of its use; so, many Fragile X individuals treated by neurologists or pediatricians are unlikely to even be considered for lithium treatment in the first place.

Carbamazepine, marketed as an anticonvulsant (and a particularly effective one, too), has been used a great deal over the past 10 years in psychiatry as a treatment for Bipolar Disorder. It seems to be more effective than lithium in cases of rapid cycling mood disorders of all kinds; it can be combined with lithium for even greater effect, and many of the side effects of the two cancel each other out. When it was introduced, carbamazepine was thought to have a relatively high incidence of agranulocytosis and aplastic anemia, often fatal suppression of white and red blood cell production, respectively. For that reason, weekly monitoring of drug levels and blood counts was recommended, causing quite a few people significant expense and inconvenience. However, follow-up studies have shown that these events are actually quite rare (about 1 in 100,000), so blood tests are now required much less frequently. Not only has carbamazepine been shown to be an effective mood stabilizer, it has been demonstrated to decrease the frequency of behavioral dyscontrol in many different patient populations, and it widely used as a treatment for aggression and impulsivity in the developmentally disabled.

Valproic acid is also a commonly prescribed anticonvulsant with a chemical structure and mechanism of action completely different from carbamazepine. It has more recently come into favor among psychiatrists as a treatment for mood disorders, and a number of studies supporting its therapeutic efficacy have already been published, with many more under way. It has also been used safely in children for many years, though the range of experience in different patient populations, especially the developmentally disabled, is more limited than with carbamazepine. It can rarely (approx. 1 in 50,000) cause fatal liver toxicity, so monitoring of serum drug levels and liver function tests must be done at about the same frequency as monitoring of carbamazepine.

Clonazepam is a benzodiazepine marketed as an anticonvulsant, but rarely used for that purpose. It, too, has been used in Bipolar Disorder to stabilize moods (especially to treat mania), though its therapeutic effect is generally considered relatively weak compared to lithium and the anticonvulsants. Most of the clonazepam prescribed in the US is for treatment of anxiety, especially Panic Disorder. For the general population, this is an excellent treatment--long acting and very potent in suppressing panic attacks and anticipatory anxiety. However, this medication causes some degree of mental slowing and motor incoordination in most people who take it. This is not usually a problem for the average person at therapeutic doses, and typically goes unnoticed. For Fragile X individuals it often causes more cognitive and motor impairment at therapeutic doses; it can also cause "behavioral disinhibition", or a worsening of behavioral problems--just the opposite of the desired effect--making this a risky treatment from a behavioral standpoint. Fortunately, clonazepam is nontoxic, so a trial involves no medical risk.

Risperidone is a new and revolutionary medication in many ways. It is considered an "atypical antipsychotic", but it bears little resemblance to the old "conventional antipsychotics". It has fewer side effects and is far safer than medications like thioridazine (see review); it has been rigorously demonstrated to treat many symptoms poorly responsive to conventional antipsychotics. In addition, it is reported to have significant mood stabilizing properties, and is being used in increasing frequency to treat behavioral disturbances associated with developmental disorders. It appears promising as a treatment for agitation and aggression without overwhelming sedation in a wide variety of disorders. However, it has not been around for long, so experience is quite limited--though all the experience thus far is good. A major disadvantage of risperidone at this time is that it is extremely expensive--anywhere from \$2-10 per day, depending on the dose, although most insurance plans will cover it because of its superior safety and efficacy.

In most cases, the anticonvulsants, carbamazepine and valproic acid, will be the first choices as mood stabilizers for Fragile X individuals. Some of the time, a given individual will require an anticonvulsant anyway for treatment of a seizure disorder, and if this is the case it is important to realize that not all anticonvulsants have these same mood stabilizing properties. In particular, phenytoin (Dilantin) and phenobarbital (Luminal) are devoid of mood stabilizing effects, and phenobarbital may even exacerbate affective lability and should be avoided. It would be conservative and sensible to use an anticonvulsant with mood stabilizing effects in any Fragile X child who requires treatment for a seizure disorder. Clonazepam is probably only useful at low doses for Fragile X individuals with extreme anxiety and good cognitive functioning, including many girls with Fragile X. Risperidone may be especially effective in Fragile X individuals with severe agitation and aggressive behavior which is otherwise difficult to control.

reference:

Glue P

Rapid cycling affective disorders in the mentally retarded

Sunnyside Hospital, Christchurch, New Zealand.

Biol Psychiatry 1989 Jul;26(3):250-6

ABSTRACT:

This article describes a group of 10 hospitalized, mentally retarded patients with rapid cycling affective disorders, including details of demography, pattern of illness, and response to an open trial of treatment

with lithium and/or carbamazepine. Family histories of these patients revealed high rates of mental illness, including affective disorder and mental retardation. Men had an earlier onset of affective illness and rapid cycling than did women. Half of the patients showed partial or complete improvement on lithium alone or in combination with carbamazepine; those who responded to the combined treatment had more episodes of affective illness per year than those who did not. Rates of response to treatment and some clinical characteristics of these patients were similar to those of non-mentally retarded rapid cycling patients.

lithium (Eskalith, Lithobid, Lithonate)

effectiveness	safety	cost	convenience
😊😊😊😊	👉	\$	🙄🙄

indications: mania, aggression, irritability

pros: relatively few side effects, effective mood stabilizer without significant sedation, very inexpensive, liquid available

cons: potentially toxic; careful monitoring required, including frequent blood levels

use: lithium was the first mood stabilizer to enter widespread use, and it is considered the first-line treatment of choice for Bipolar Disorder (Manic-Depressive Illness). There is much clinical experience with lithium in many different patient populations, with well documented efficacy in many other conditions. Lithium is unique among the medications listed here, since it is not actually a drug, but a mineral which is mined rather than manufactured; its mood stabilizing properties were discovered quite accidentally, but have proven a godsend to millions of people around the world. The mechanism of action of lithium remains obscure, though it is thought to affect the serotonin system, but in a way which is distinct from all other known medications.

This is an appropriate treatment for children with mania, and is usually well tolerated; it has been used for many years as a major treatment for aggression; however, experience in treating children with developmental disorders has often been disappointing. Lithium seems to be less effective in stabilizing moods when changes are very frequent (so-called "rapid cycling"), and more effective in classic manic-depressive patients with sustained highs followed by prolonged lows. Most Fragile X individuals fall into the former category, and are not usually thought of as good lithium candidates, although a discrete and sustained manic episode can certainly occur in a person with Fragile X. Lithium also does not seem to be as potent an anti-aggressive treatment as the newer antidepressants and some anticonvulsants, though some individuals experience dramatic relief from it. Lithium can be combined with many other medications to augment their effects: lithium augmentation of antidepressants is a commonly used and powerful treatment of depression and anxiety disorders; lithium can be combined with other mood stabilizers like carbamazepine and valproic acid for greater effect in hard-to-treat cases.

The greatest disadvantage of lithium is its low therapeutic index: blood levels only a little higher than therapeutic can be toxic. For this reason, careful monitoring is required, and the dose must be fine-tuned to achieve a blood level within the rather narrow therapeutic range. This frequent blood-drawing can be difficult for a tactilely-defensive Fragile X child; fortunately, once a therapeutic dose is found, levels can be checked much less frequently as long as the dose remains unchanged. There is little chance of any significant psychiatric side effects occurring with lithium treatment, though some patients do complain of feeling lethargic or apathetic. The most common, major medical side effect of lithium administration is hypothyroidism: lithium hinders the normal function of the thyroid gland at usual doses, and this can be serious enough to require thyroid hormone supplementation. Thyroid functions are normally checked regularly along with lithium

levels. Lithium has been reported to cause damage to the kidneys in rare instances, and so renal functions are also checked regularly, though this is very unlikely in younger patients.

Recent research suggests an interesting new Fragile X indication for lithium; lithium has been shown to inhibit the same intracellular signalling pathway which functions excessively in Fragile X. When lithium was given to *drosophila* (fruit flies) which had the fly version of the Fragile X gene knocked out, it completely rescued the cognitive deficits which these flies exhibit. Lithium is now being studied in the Fragile X knockout mouse, with very promising early results. This may lead to Fragile X clinical trials of lithium in the near future---stay tuned for results.

drug interaction warning: NSAIDs (anti-inflammatory drugs like Motrin, Advil, ibuprofen, Naprosyn, Aleve, and others) should not be taken for prolonged periods while taking lithium; they can cause rapid increases in serum lithium levels. A single dose is no problem

common side effects

nausea/diarrhea: take with food to minimize this; usually transient

tremor: usually mild and only at peak levels; entire dose can be taken at night to minimize this; can be treated with a beta blocker (i.e. propranolol)

frequent urination: since lithium is a salt, it is excreted entirely through the kidneys; as this occurs, water is pulled along, resulting in increased urine volume; be sure to drink plenty of fluids each day to avoid dehydration; if urination is extreme, call your doctor

uncommon side effects

sedation: entire dose can be taken at bed time; if sedation or fatigue is extreme, thyroid functions should be checked ASAP

edema (swelling of soft tissues): small amount is probably benign; otherwise call your doctor

clumsiness/incoordination: can be signs of neurotoxicity, lithium level may be too high

dosage

in all cases medication should be started at a relatively low dose and titrated upward to achieve a therapeutic serum lithium level; lithium carbonate is available in 150 and 300 mg capsules and tablets, 450 mg controlled-release tablet; lithium citrate is a liquid version which can be mixed into juices (and is reasonably palatable)

Update 2009: The lithium story keeps getting better all the time. Lithium has now been shown in a number of animal models to rescue the basic synaptic defects in fragile X and to restore cognitive function. Most impressively, human clinical trials have shown similar benefits.

Neuropharmacology. 2009 Feb;56(2):463-72

Elevated glycogen synthase kinase-3 activity in Fragile X mice: Key metabolic regulator with evidence for treatment potential.

Min WW, Yuskaitis CJ, Yan Q, Sikorski C, Chen S, Jope RS, Bauchwitz RP.

St. Luke's-Roosevelt Institute for Health Sciences, Columbia University, 432 W. 58th St., Rm. 411, New York, NY 10019, USA.

Significant advances have been made in understanding the underlying defects of and developing potential treatments for Fragile X syndrome (FXS), the most common heritable mental retardation. It has been shown that neuronal metabotropic glutamate receptor 5 (mGluR5)-mediated signaling is affected in FX animal models, with consequent alterations in activity-dependent protein translation and synaptic spine functionality. We demonstrate here that a central metabolic regulatory enzyme, glycogen synthase kinase-3 (GSK3) is present in a form indicating elevated activity in several regions of the FX mouse brain. Furthermore, we show that selective GSK3 inhibitors, as well as lithium, are able to revert mutant phenotypes of the FX mouse. Lithium, in particular, remained effective with chronic administration, although its effects were reversible even when given from birth. The combination of an mGluR5 antagonist and GSK3 inhibitors was not additive. Instead, it was discovered that mGluR5 signaling and GSK3 activation in the FX mouse are coordinately elevated, with inhibition of mGluR5 leading to inhibition of GSK3. These findings raise the possibility that GSK3 is a fundamental and central component of FXS pathology, with a substantial treatment potential.

Neuron. 2005 Mar 3;45(5):753-64.

Pharmacological rescue of synaptic plasticity, courtship behavior, and mushroom body defects in a Drosophila model of fragile X syndrome.

McBride SM, Choi CH, Wang Y, Liebelt D, Braunstein E, Ferreiro D, Sehgal A, Siwicki KK, Dockendorff TC, Nguyen HT, McDonald TV, Jongens TA.

Section of Molecular Cardiology, Department of Medicine, Medical Scientist Training Program, Albert Einstein College of Medicine, Bronx, NY 10461, USA. smcbride@aecom.yu.edu

Fragile X syndrome is a leading heritable cause of mental retardation that results from the loss of FMR1 gene function. A Drosophila model for Fragile X syndrome, based on the loss of *dfmr1* activity, exhibits phenotypes that bear similarity to Fragile X-related symptoms. Herein, we demonstrate that treatment with metabotropic glutamate receptor (mGluR) antagonists or lithium can rescue courtship and mushroom body defects observed in these flies. Furthermore, we demonstrate that *dfmr1* mutants display cognitive deficits in experience-dependent modification of courtship behavior, and treatment with mGluR antagonists or lithium restores these memory defects. These findings implicate enhanced mGluR signaling as the underlying cause of the cognitive, as well as some of the behavioral and neuronal, phenotypes observed in the Drosophila Fragile X model. They also raise the possibility that compounds having similar effects on metabotropic glutamate receptors may ameliorate cognitive and behavioral defects observed in Fragile X patients.

J Dev Behav Pediatr. 2008 Aug;29(4):293-302.

Open-label treatment trial of lithium to target the underlying defect in fragile X syndrome.

Berry-Kravis E, Sumis A, Hervey C, Nelson M, Porges SW, Weng N, Weiler IJ, Greenough WT.

Department of Pediatrics, Rush University Medical Center, University of Illinois at Chicago, IL 60612, USA. elizabeth_M_berry-kravis@rush.edu

OBJECTIVE: In fragile X syndrome (FXS), it is hypothesized that absence of the fragile X mental retardation protein (FMRP) disrupts regulation of group 1 metabotropic glutamate receptor (mGluR and mGluR5)-dependent translation in dendrites. Lithium reduces mGluR-activated translation and reverses phenotypes in the *dfxr* mutant fly and *fmr1* knockout mouse. This pilot add-on trial was conducted to evaluate safety and efficacy of lithium in humans with FXS. **METHODS:** Fifteen individuals with FXS, ages 6-23, received lithium titrated to levels of 0.8-1.2 mEq/L. The primary outcome measure, the Aberrant

Behavior Checklist --Community Edition (ABC-C) Irritability Subscale, secondary outcome measures (other ABC-C subscales, clinical global improvement scale (CGI), visual analog scale for behavior (VAS), Vineland Adaptive Behavior Scale (VABS)), exploratory cognitive and psychophysiological measures and an extracellular signal-regulated kinase (ERK) activation assay were administered at baseline and 2 months of treatment. Side effects were quantified with a standardized checklist and lithium level, complete blood count (CBC), thyroid stimulating hormone (TSH), and chemistry screen were done at baseline, 2 weeks, 4 weeks and 2 months. RESULTS: The only significant treatment-related side effects were polyuria/polydipsia (n = 7) and elevated TSH (n = 4). Although the ABC-C Irritability Subscale showed only a trend toward improvement, there was significant improvement in the Total ABC-C score (p = 0.005), VAS (p = 0.003), CGI (p = 0.002), VABS Maladaptive Behavior Subscale (p = 0.007), and RBANS List Learning (p = 0.03) and an enhanced ERK activation rate (p = 0.007). Several exploratory tasks proved too difficult for lower-functioning FXS subjects. CONCLUSIONS: Results from this study are consistent with results in mouse and fly models of FXS, and suggest that lithium is well-tolerated and provides functional benefits in FXS, possibly by modifying the underlying neural defect. A placebo-controlled trial of lithium in FXS is warranted.

The evidence to date indicates that lithium is likely to be as effective in treating the core deficits of fragile X as the long-awaited mGluR5 antagonists. It has been reasonably well tolerated in clinical trials, and it's an inexpensive, widely available medication with a long track record. So why isn't everyone with fragile X on lithium? There are several good reasons, and many more not-so-good reasons.

Most importantly, lithium has a general reputation as a fairly toxic medication; this is partially deserved. Lithium can be toxic if the levels are not maintained within a rather narrow range, though the kind of acute lithium toxicity that results from excessive levels is typically easy to spot and rapidly reversible---it does not usually cause any long term harm, just some unpleasant symptoms. Of course, the only way to stay within this narrow range is to actually measure lithium levels in blood samples. Obtaining these blood samples from individuals with fragile X can be quite an ordeal, and this represents another major obstacle to the acceptance of lithium therapy.

Lithium can also impair thyroid function, and even cause acute hypothyroidism requiring immediate medical attention. However, this is usually an insidious, slowly-developing problem which can be caught early by regular thyroid testing. For this reason, regular testing of thyroid function is a necessary part of medical monitoring for anyone taking lithium. The most sensitive indicator of thyroid function is measurement of Thyroid Stimulating Hormone (TSH) in the blood, but a TSH level can simply be added to regular lithium levels.

carbamazepine (Tegretol)

effectiveness	safety	cost	convenience
☺☺☺	👉👈	\$\$	☹

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 of drug after 1-2 months), multiple daily doses necessary (2-3 times a day), therapeutic drug monitoring required (blood levels)

use: carbamazepine is one of the most commonly prescribed anticonvulsants in the U.S.; many Fragile X individuals take this medication for seizure disorders. It is also used quite extensively in psychiatry to treat mood disorders and aggression. Carbamazepine's mood stabilizing properties were discovered serendipitously after it was marketed as an anticonvulsant, but it has subsequently been demonstrated effective in a number of psychiatric conditions, including Bipolar Disorder (Manic-Depressive Illness), Schizoaffective Disorder, drug withdrawal syndromes, some personality disorders, and many different forms of aggression in virtually all patient populations. Its precise mechanism of action is still unknown, but carbamazepine is thought to work by stabilizing the electrical activity of the limbic system, a network of brain structures which appear to control emotions. Carbamazepine is not known to affect specific neurotransmitter systems, so its mechanism of action is distinctly different from most other psychotropic medications, such as SSRIs, and may offer some therapeutic advantages for difficult-to-treat cases. This drug has been used extensively in the treatment of behavioral problems in developmentally disabled populations, initially on the assumption that most of these folks had abnormal brain electrical activity (i.e. on EEG), and that the drug might somehow correct this abnormal activity. It is probably the most commonly used treatment of aggression in this setting, and can be very effective in some cases. However, it has since been shown in a number of different patient populations that an abnormal EEG does not predict mood stabilizing response to carbamazepine; people with normal EEG and no history of neurological problems can derive great benefit from this medication as a treatment for mood disorders.

The most important fact to keep in mind when carbamazepine is employed is that this medication can take a very long time to exert its optimal effect; some patients will improve and stabilize gradually for 6 months or more after reaching therapeutic levels of the drug. Another important consideration is the dose prescribed and the level maintained: the "therapeutic range" quoted by most labs is for the anticonvulsant effect of carbamazepine; using it as a mood stabilizer, a few patients will do well at lower levels, and many will experience no improvement at all until the upper limit of the range is exceeded. Also, this medication causes a phenomenon called autoinduction of liver enzymes: it induces its own metabolism, so people who have taken it for several months metabolize faster than those just starting to take it. This does not continue indefinitely, but it does mean that Tegretol levels will go down over the first few months if the dose remains the same. Initially, this makes frequent dosage adjustment necessary if a therapeutic level is to be maintained. This same increase in drug metabolism can cause concurrently administered

medications also to be metabolized more quickly, and this should be considered by the prescribing physician.

When carbamazepine was first introduced, there were several cases of fatal agranulocytosis--a lethal suppression of white blood cell production. Following this catastrophe, rigorous guidelines for monitoring blood counts were issued, at one point recommending weekly testing. It has since been found that this is quite unnecessary, and that this adverse reaction is very rare (about 1 or 2 per 100,000); it can be spotted early with less frequent monitoring and virtually always reverses promptly with discontinuation of the drug, with no long term damage resulting. Nowadays, a complete blood count (CBC) is usually obtained whenever a Tegretol level is ordered, about every 2-4 weeks during the initial dose adjustment phase of treatment, then no more than quarterly.

common side effects

sedation: usually transient; 2/3 of daily dose can be taken at night to minimize this

clumsiness/incoordination: usually transient (while dose is increasing); temporary dose reduction will help until adaptation occurs

rash: allergic skin rashes are relatively common with this medication; discontinuation may be necessary--consult your physician

uncommon side effects

nausea: usually transient--take with food

dizziness: virtually always transient; smaller divided doses will help

excessive bruising: a sign of bone marrow suppression--stop immediately and call your doctor

dosage

children: usually start with 100 mg twice a day, either as a chewable tablet or suspension; titrate up to therapeutic range (4-12 micrograms per milliliter) in 100 mg increments at 1-2 week intervals

adults: start with 100 mg three times a day, increasing in 100 mg increments at 1 week intervals to achieve therapeutic level; dose may be increased beyond this range if drug appears well tolerated and condition has not improved after 4-6 weeks of treatment

Update 2009: Carbamazepine, now available in several generic formulations, is a good anticonvulsant that has been shown to possess mood-stabilizing and antidepressant qualities. It has proven occasionally helpful in psychiatric treatment of fragile X, though its psychotropic effects are relatively weak; fortunately, it causes little weight gain and little cognitive impairment. It has fallen from favor among psychiatrists, primarily because of the need for therapeutic drug monitoring (ie blood levels) and the availability of Trileptal, which is certainly easier and probably safer to use.

valproic acid/valproate (Depakene/Depakote)

effectiveness	safety	cost	convenience
☺☺☺	🧤🧤	\$\$	☹️

indications: mania, aggression, irritability

pros: approved for use in children, safe for long-term administration, available as "sprinkles" capsules, which are easily mixed with soft foods

cons: difficult to dose properly; multiple daily doses necessary (2-3 times a day), therapeutic drug monitoring required (blood levels); can cause dysphoria, fatigue, or lethargy

use: like carbamazepine, valproic acid is one of the most commonly prescribed anticonvulsants in the US; many Fragile X individuals take this medication for seizure disorders, but it is also used quite extensively in psychiatry to treat mood disorders and aggression. Its mood stabilizing properties were discovered serendipitously after it was marketed as an anticonvulsant, but it has subsequently been demonstrated effective in some psychiatric conditions, including Bipolar Disorder (Manic-Depressive Illness), Schizoaffective Disorder, some personality disorders, and aggression in developmentally disabled patient populations. Its precise mechanism of action is still unknown, but valproic acid is thought to work by enhancing transmission of GABA (gamma-amino butyric acid), one of the primary inhibitory neurotransmitters in the brain. The psychiatric use of valproic acid is somewhat newer than that of carbamazepine, but otherwise these medications are used in much the same way. They are chemically unrelated, however, and have distinctly different side effects; this medication also has rare but potentially lethal medical complications: it can cause severe hepatotoxicity (liver damage) in about 1 in 50,000 patients, and so its use requires careful monitoring also. In general, valproic acid is more effective in treating or preventing mania than for treating or preventing depression, so it is probably not the best choice for a Fragile X individual who is primarily anxious or irritable without significant manic symptoms. While some clinicians consider this medication an effective anti-aggressive medication, there is neither as much clinical experience nor as much research backing for this indication as there is for carbamazepine or lithium.

common side effects

nausea/vomiting: can be taken with food to minimize; usually transient

sedation: usually transient--if this becomes a problem, 2/3 of daily dose can be taken at night

fatigue/lethargy: distinct from sedation, since it is not dose-related; may require discontinuation, but temporary dose reduction may help

dysphoria: dosage reduction may help; could require discontinuation, since it defeats the purpose of using this medication as a mood stabilizer

uncommon side effects

excessive bruising: can be an early indication of toxicity; consult your physician immediately

edema (swelling): also can be an early sign of toxicity; consult your physician immediately

tremor: usually benign and transient

headache: usually benign and transient; *given the possibility of hepatotoxicity with this medication and recent reports of liver damage associated with frequent use of acetaminophen (Tylenol), it is probably wise to use ibuprofen or aspirin for symptomatic treatment of headaches while taking this medication.*

dosage

children: start with 125 mg twice a day (Depakote sprinkles mixed with applesauce or other favorite food); increase as tolerated to achieve therapeutic blood level (50-100 micrograms per milliliter)

adults: start with 250 mg twice a day; increase as tolerated to therapeutic level; *some people will experience moderate mood stabilizing effects at levels significantly below the therapeutic range for anticonvulsant effects*

Update 2009: Psychiatrists' love affair with Depakote is well into its second decade, and this medication is prescribed for a wide array of off-label uses. The active ingredient, valproic acid, has attracted the attention of basic scientists and clinical researchers in the fragile X field because of its known ability to alter histone acetylation and reactivate some genes. However, this effect is non-specific and the drug levels required are probably toxic; in vitro results have not been promising:

Pharmacogenet Genomics. 2008 Aug;18(8):738-41.

Modest reactivation of the mutant FMR1 gene by valproic acid is accompanied by histone modifications but not DNA demethylation.

Tabolacci E, De Pascalis I, Accadia M, Terracciano A, Moscato U, Chiurazzi P, Neri G.

Medical Genetics, Catholic University, Rome, Italy.

Fragile X syndrome (FXS), the leading cause of inherited mental retardation, is due to expansion and methylation of a CGG sequence in the FMR1 gene, which result in its silencing. We previously demonstrated a reactivation of FMR1 in FXS cells treated with the DNA demethylating drug 5-azadeoxycytidine, and, to a lesser extent, with the histone deacetylating drug butyrate. To identify other reactivating drugs, we now treated three FXS lymphoblastoid cell lines with valproic acid (VPA), a well-known antiepileptic drug, causing histone deacetylase inhibition and, possibly, DNA demethylation. After VPA treatment, FMR1-mRNA levels were low and FMRP protein was undetectable. The gene remained methylated, whereas histones were acetylated and a modest variation of histone methylation was observed. These results confirm the histone hyperacetylating effect of VPA but do not support its putative DNA demethylation activity. The primary role of DNA demethylation in the reactivation of the FMR1 gene was confirmed.

Nevertheless, the drug was tested in a small fragile X clinical trial, the results of which have been presented at fragile X meeting, but not yet published. The results from this trial showed a small behavioral benefit, as one might expect from the known psychotropic/mood stabilizing properties of valproate, but no evidence of gene reactivation in fragile X patients. No FMRP production was noted in response to valproate treatment, so it is unlikely that valproate can be viewed as a specific treatment for fragile X.

clonazepam (Klonopin)

effectiveness	safety	cost	convenience
😊😊	👉👉	\$\$\$	🕒🕒

indications: anxiety, mania, obsessive-compulsive behavior

pros: non-toxic, fast acting

cons: causes cognitive impairment, may cause behavioral disinhibition; no pediatric formulations available, expensive

use: clonazepam is a benzodiazepine (chemically related to Valium) which is marketed as an anticonvulsant, but which is used primarily as an anxiolytic and sedative in the US. It is the most potent anti-panic agent currently available and is widely prescribed as a treatment for Panic Disorder. Clonazepam has also been shown effective in the treatment of other anxiety disorders, including OCD and social phobia; it can be quite effective (at very high doses) as a treatment for acute mania, leading some psychiatrists to speculate that this compound may have mood stabilizing properties not shared by other benzodiazepines--a point which is by no means well established. As an anticonvulsant, clonazepam raises the seizure threshold, making seizure activity less likely; however, all benzodiazepines (including this one) cause dose-related cognitive impairment, including decreased fine and gross motor coordination, decreased attention and concentration, and decreased memory. It is no surprise, then, that these medications can cause behavioral problems in developmentally disabled individuals, so-called "paradoxical excitement" or "behavioral disinhibition". In other words, sedative medications of this type are unlikely to calm Fragile X children, and may have the opposite effect; for this reason, they are not generally recommended as first line treatments for anxiety in fully affected individuals, although clonazepam may have a role in treating higher-functioning Fragile X females with significant, discrete anxiety disorders. There are many other drugs in this class, and they are very widely prescribed (many believe overprescribed); this manual has limited space, and these drugs are mostly quite similar, so it is recommended that other benzodiazepines be considered essentially equivalent to clonazepam. Your doctor can explain any pertinent differences if another benzodiazepine is prescribed.

common side effects

sedation: transient, but dosage reduction is advisable; tolerance develops over the course of 1-2 weeks (which is one reason this class of medications can cause problems when used as a sleep aid)

ataxia (poor balance and difficulty walking): similar to the effect of excessive alcohol; some tolerance develops, but dosage reduction is indicated

rebound anxiety: although clonazepam has a very long half-life in the body, if the medication is not taken regularly, rebound anxiety and even agitation are quite common; it is important to take the medication regularly; ordinarily, two or three missed doses in a row are necessary to provoke rebound

uncommon side effects

weight gain: may necessitate discontinuation, since it is not always dose related

stupor: obviously, the result of excessive dose; proper dosage can be difficult to estimate in advance, since metabolism varies widely; hold all sedating medications until mental status returns to normal

dosage

children (6-12): start with one half of a 0.5 mg tablet (0.25 mg) at bed time, increase gradually as tolerated to optimal effect; usually, twice a day dosing is adequate, but some individuals may find three or four times a day more effective

teens and adults: start with 0.5 mg twice a day, increasing as tolerated to optimal effect; as noted above, twice a day is usually fine, though some do better with more frequent, smaller doses

Update 2009: Psychiatrists continue to prescribe clonazepam widely for the treatment of anxiety disorders, and as an adjunctive treatment in many other conditions. However, it is less commonly used today in the treatment of developmental disorders, especially since the atypical antipsychotics have become more popular.

risperidone (Risperdal)

effectiveness	safety	cost	convenience
☺☺☺	👉👉👉	\$\$\$\$	☯☯☯

indications: mania, aggression, SIB, irritability, psychosis

pros: very effective, easy to take (once-a-day,) relatively non-toxic, few side effects

cons: extremely expensive, no pediatric formulations available (but liquid is available; instant-dissolving tablet now available)

use: risperidone is a newer antipsychotic medication which represents a major advance in the treatment of schizophrenia and other psychoses; however, its safety and efficacy in a wide range of psychiatric disorders is now being increasingly appreciated. For example, risperidone is being prescribed to large numbers of people with Alzheimer's Disease to treat the agitation and delusional symptoms which are so often a part of that illness. Not only does risperidone appear to treat these symptoms, it often results in improved cognitive functioning as well. This was the first of the class of "atypical antipsychotics" which have largely replaced the older, conventional antipsychotics like Haldol, Thorazine, and Mellaril. Newer agents, like Risperdal, are much safer, having much less propensity to cause the horrific involuntary motor side effects that conventional antipsychotics all can cause. They also do more than the older medications: in schizophrenia, this means that social withdrawal and emotional blunting can respond to treatment. In Alzheimer's Disease and other dementias, aggression and paranoia, which typically responded poorly to older medications, can be treated with fewer sided effects. In Fragile X and other developmental disorders, more severe forms of aggression, self-injurious behavior, mania, and other psychotic states can be treated effectively and with little risk. This is not to imply that risperidone is a miracle drug: it does not work for everyone, and the effect is not at all specific to Fragile X; nevertheless, it is a significant step forward, and other sophisticated new medications like it have since been marketed. In Fragile X, risperidone should probably be reserved for treatment of more severe behavioral disturbances which pose a significant threat to the afflicted individual or others. Treatment with this medication can be expected to result in significant mood stabilization, a decrease in aggression or SIB, and elimination of psychotic symptoms (if present--the author believes true psychosis to be relatively rare in Fragile X individuals). 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.

Compared to olanzapine, risperidone is generally considered to have greater intrinsic antidepressant effect; it may not be as useful as olanzapine in treating mania, and may have somewhat less mood-stabilizing effect. It is an ideal choice where an antipsychotic is required, yet a significant amount of dysphoria or irritability is also present.

common side effects

sedation: usually transient; all of medication can be taken at bed time, although the manufacturer recommends evenly divided morning and night doses; this side effect is much less prominent if dose is started low and titrated upward gradually

muscle stiffness (dystonia): dosage reduction is indicated; hold dose until side effect subsides

orthostatic hypotension (dizziness upon standing): taking at night will greatly reduce this problem; dosage reduction may also be helpful

uncommon side effects

restlessness (akathisia): dosage reduction or bed-time administration can help; can be treated with propranolol if necessary

nausea: take with food; even a small snack can help

dosage

children: start with the smallest dose, 0.25-0.5 mg at bed time; increase in 1-2 week intervals by 0.5 mg to optimal effect; with limited clinical experience in children, dose range is still unclear; young children usually do not need more than 2 mg/day

teens and adults: start with 0.5 mg twice a day; if needed, increase gradually at 1-2 week intervals up to 2 mg twice a day; doses higher than this are unlikely to be more effective, but will almost certainly have more side effects; entire dose can be given at bed time

Update 2009: As noted in the introduction to this new edition, risperidone has been formally approved by the FDA for the treatment of irritability associated with autism, resulting in much greater use in the general treatment of developmental disorders. Risperidone is also now available as a generic drug, the first of the “atypicals” to go generic. The expiration of the patent has prompted the maker of Risperdal to reformulate and repackage the drug in several ways, seeking to protect its market share (thus Invega and Risperdal Consta) but there is no basic difference between generic risperidone and these new formulations. Since the use of all atypical antipsychotics is increasing in psychiatric treatment generally, and in the developmental disorders field particularly, this is a good point to remind everyone that these medications are not entirely benign, and a number of general “class risks” are always lurking in the shadows. These adverse effects are well known to psychiatrists, but other physicians who may prescribe these drugs may not be as familiar with the risks.

Here is the officially approved class warning for all atypical antipsychotics; many of these risks apply as well to the older, “typical” antipsychotics, and may even be a greater risk with the older drugs. Ordinarily, this statement is added to the drug info for each medication, with the specific brand name pasted in, but the warning is the same for all drugs in this class, though the relative risks of each adverse effect may differ somewhat.

IMPORTANT SAFETY INFORMATION FOR (ALL ANTIPSYCHOTICS)

Elderly Patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ANTIPSYCHOTICS are not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS) is a rare and potentially fatal side effect reported with **ALL ANTIPSYCHOTICS**. Call your doctor immediately if the person being treated develops symptoms such as high fever; stiff muscles; shaking; confusion; sweating; changes in pulse, heart

rate, or blood pressure; or muscle pain and weakness. Treatment should be stopped if the person being treated has NMS.

One risk of **ANY ANTIPSYCHOTIC** is that it may change your heart rhythm. This effect is potentially serious, and you should talk to your doctor about any current or past heart problems. Some medications interact with **ANTIPSYCHOTICS**. Please inform your healthcare professional of any medications or supplements that you are taking.

Tardive Dyskinesia (TD) is a serious, sometimes permanent side effect reported with **ALL ANTIPSYCHOTICS**. TD includes uncontrollable movements of the face, tongue, and other parts of the body. The risk of developing TD and the chance that it will become permanent is thought to increase with the length of therapy and the overall dose taken by the patient. This condition can develop after a brief period of therapy at low doses, although this is much less common. There is no known treatment for TD, but it may go away partially or completely if therapy is stopped.

High blood sugar and diabetes have been reported with **ALL ATYPICAL ANTIPSYCHOTICS**. If the person being treated has diabetes or risk factors such as being overweight or a family history of diabetes, blood sugar testing should be performed at the beginning and throughout treatment with **ALL ATYPICAL ANTIPSYCHOTICS**. Complications of diabetes can be serious and even life threatening. If signs of high blood sugar or diabetes develop, such as being thirsty all the time, going to the bathroom a lot, or feeling weak or hungry, contact your doctor.

ANTIPSYCHOTICS can raise the blood levels of a hormone known as prolactin, causing a condition known as hyperprolactinemia. Blood levels of prolactin remain elevated with continued use. Some side effects seen with these medications include the absence of a menstrual period; breasts producing milk; the development of breasts by males; and the inability to achieve an erection. The connection between prolactin levels and side effects is unknown.

ALL ANTIPSYCHOTICS should be used cautiously in people with a seizure disorder, who have had seizures in the past, or who have conditions that increase their risk for seizures.

Extrapyramidal Symptoms (EPS) are usually persistent movement disorders or muscle disturbances, such as restlessness, tremors, and muscle stiffness. If you observe any of these symptoms, talk to your healthcare professional.

ALL ANTIPSYCHOTICS may make you more sensitive to heat. You may have trouble cooling off, or be more likely to become dehydrated, so take care when exercising or when doing things that make you warm.

The most common side effects that occurred with **ALL ANTIPSYCHOTICS** were restlessness and extrapyramidal disorder (for example, involuntary movements, tremors and muscle stiffness).

olanzapine (Zyprexa)

effectiveness	safety	cost	convenience
😊😊😊	👉👈	\$\$\$\$	🙄🙄🙄

indications: mania, aggression, SIB, irritability, psychosis

pros: very effective, easy to take, relatively non-toxic, few side effects

cons: extremely expensive, no pediatric formulations available (rapid-dissolving tablet is available); significant weight gain is common

use: olanzapine is a relatively new antipsychotic medication which, like risperidone, represents a major advance in the treatment of schizophrenia and other psychoses; however, its safety and efficacy in a wide range of psychiatric disorders is now being increasingly appreciated. As with risperidone, it is being prescribed to large numbers of people with Alzheimer's Disease to treat the agitation and delusional symptoms which are so often a part of that illness. Not only does olanzapine appear to treat these symptoms, it often results in improved cognitive functioning as well. This new class of "atypical antipsychotics" is replacing the older, conventional antipsychotics like Haldol, Thorazine, and Mellaril. Newer agents, like Zyprexa, are much safer, having much less propensity to cause the horrific involuntary motor side effects that conventional antipsychotics all can cause. They also do more than the older medications: in schizophrenia, this means that social withdrawal and emotional blunting can respond to treatment. In Alzheimer's Disease and other dementias, aggression and paranoia, which typically responded poorly to older medications, can be treated with fewer sided effects. In Fragile X and other developmental disorders, more severe forms of aggression, self-injurious behavior, mania, and other psychotic states can be treated effectively and with little risk. This is not to imply that olanzapine is a miracle drug: it does not work for everyone, and the effect is not at all specific to Fragile X; nevertheless, it is a significant step forward, and other sophisticated new medications like it are on the way. In Fragile X, olanzapine should probably be reserved for treatment of more severe behavioral disturbances which pose a significant threat to the afflicted individual or others. Treatment with this medication can be expected to result in significant mood stabilization, a decrease in aggression or SIB, and elimination of psychotic symptoms (if present--the author believes true psychosis to be relatively rare in Fragile X individuals). 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.

Compared to risperidone, olanzapine has somewhat less intrinsic antidepressant activity, but appears to be a good mood-stabilizer and anti-manic agent. It is a good choice when an anti-psychotic is required and a bipolar pattern of mood disorder is present. However, experience over the past few years has shown conclusively that olanzapine causes more weight gain than other medications in this class, and this effect is especially prominent in children. Drug-induced diabetes is not uncommon, and massive weight gain is a frequent reason for switching to an alternative atypical antipsychotic. Olanzapine clearly causes a marked increase in appetite, especially in children; this may be treatable by co-administration of H2-blockers such as Axid or Zantac, but this practice is not yet widespread.

side effects:

sedation: usually transient; all of medication can be taken at bed time; this side effect is much less prominent if dose is started low and titrated upward gradually

muscle stiffness (dystonia): dosage reduction is indicated; hold dose until side effect subsides

orthostatic hypotension (dizziness upon standing): taking at night will greatly reduce this problem; dosage reduction may also be helpful

weight gain: may require discontinuation/alternative drug; can be attenuated with H2-blockers such as Axid (nizatidine) or Zantac (ranitidine) et al.

uncommon side effects

restlessness (akathisia): dosage reduction or bed-time administration can help; can be treated with propranolol if necessary

nausea: take with food; even a small snack can help

dosage

children: start with the smallest dose, one half of a 2.5 mg tablet (1.25 mg) at bed time; increase in 1-2 week intervals by 1.25 mg to optimal effect; with limited clinical experience in children, dose range is still unclear

teens and adults: start with 2.5 mg at night; if needed, increase gradually at 1-2 week intervals up to 15 mg a day; doses higher than this are unlikely to be more effective, but will almost certainly have more side effects.

Update 2009: As noted above, olanzapine causes more weight gain than the other drugs in the atypical antipsychotic class. Indeed, more recent experience has shown that, especially in younger patients, olanzapine causes more weight gain than any other known medication. This effect appears to be inversely age dependent: younger patients gain more, older patients generally gain less, and elderly patients rarely gain any weight at all. This weight gain is often accompanied by “metabolic syndrome”, a catch-all term encompassing diabetes, hypertension, altered lipid profile, increased cholesterol, and other cardiac risk factors. 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.

quetiapine (Seroquel)

effectiveness	safety	cost	convenience
😊😊😊	👉👉👉	\$\$\$\$	👁️👁️👁️

indications: mania, aggression, SIB, irritability, psychosis

pros: very effective, easy to take, relatively non-toxic, few side effects

cons: extremely expensive, no pediatric formulations available, multiple daily doses required

use: quetiapine is one of the newer “atypical” antipsychotic medications which represent a major advance in the treatment of schizophrenia and other psychoses; however, its safety and efficacy in a wide range of psychiatric disorders is now being increasingly appreciated. For example, quetiapine is being prescribed to large numbers of people with Alzheimer's Disease to treat the agitation and delusional symptoms which are so often a part of that illness. Not only does quetiapine appear to treat these symptoms, it often results in improved cognitive functioning as well. This is part of a new class of "atypical antipsychotics" which is replacing the older, conventional antipsychotics like Haldol, Thorazine, and Mellaril. Newer agents, like quetiapine, are much safer, having much less propensity to cause the horrific involuntary motor side effects that conventional antipsychotics all can cause. They also do more than the older medications: in schizophrenia, this means that social withdrawal and emotional blunting can respond to treatment. In Alzheimer's Disease and other dementias, aggression and paranoia, which typically responded poorly to older medications, can be treated with few sided effects. In Fragile X and other developmental disorders, more severe forms of aggression, self-injurious behavior, mania, and other psychotic states can be treated effectively and with little risk. This is not to imply that quetiapine is a miracle drug: it does not work for everyone, and the effect is not at all specific to Fragile X; nevertheless, it is a significant step forward, and other sophisticated new medications like it are on the way. In Fragile X, quetiapine should probably be reserved for treatment of more severe behavioral disturbances which pose a significant threat to the afflicted individual or others. Treatment with this medication can be expected to result in significant mood stabilization, a decrease in aggression or SIB, and elimination of psychotic symptoms (if present--the author believes true psychosis to be relatively rare in Fragile X individuals). 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.

Compared to risperidone, and especially olanzapine, quetiapine causes less weight gain, and is highly unlikely to cause muscle stiffness; it may cause somewhat more sedation during initiation.

common side effects

sedation: usually transient; most of medication can be taken at bed time, although the manufacturer recommends evenly divided morning and night doses; this side effect is much less prominent if dose is started low and titrated upward gradually

muscle stiffness (dystonia): dosage reduction is indicated; hold dose until side effect subsides

orthostatic hypotension (dizziness upon standing): taking at night will greatly reduce this problem; dosage reduction may also be helpful

uncommon side effects

restlessness (akathisia): dosage reduction or bed-time administration can help; can be treated with propranolol if necessary

nausea: take with food; even a small snack can help

dosage

children: start with the smallest dose, 25 mg at bed time; increase in 1-2 week intervals by 25 mg to optimal effect; typical dose is 100-300 mg per day in divided doses

teens and adults: start with 25 mg twice a day; increase gradually at 1-2 week intervals up to 300 mg twice a day; doses higher than this are unlikely to be more effective, but will almost certainly have more side effects

Update 2009: Quetiapine is actually the most frequently prescribed antipsychotic medication in the US, as of this writing. However, about half of all Seroquel prescriptions are written as an adjunctive sleep aid. In effect, Seroquel has found a niche as a rather expensive sleeping pill. This use cannot be recommended as a general practice, since this exposes the user to the serious adverse effects of antipsychotics, such as TD and NMS (see update in Risperdal review), even though the dose of the drug is subtherapeutic and it is not acting as an antipsychotic. Seroquel is probably the most sedating of the newer antipsychotics; this is often a problem, preventing adequate dosing (especially since it must be given 2 or 3 times per day.) In some cases, this can be an advantage---especially if a fragile X individual is quite hyperactive and/or hyperaroused. Seroquel is a potent antagonist at alpha 1 and histamine receptors, which probably explains its sedative effects. Some recent studies suggest that quetiapine is not as effective as most other available antipsychotics in the treatment of schizophrenia, even when the full, recommended doses are used (and in real life, it is difficult to use the full dose, because of sedation.) Whether this applies to the treatment of fragile X and other autism spectrum disorders is unknown, but it is clearly most useful for the patient who requires some degree of sedation.

aripiprazole (Abilify)

effectiveness	safety	cost	convenience
😊😊😊😊	👉👉👉	\$\$\$\$	👁️👁️👁️

indications: mania, aggression, SIB, irritability, psychosis

pros: very effective, easy to take, relatively non-toxic, few side effects

cons: extremely expensive, no pediatric formulations available

use: aripiprazole is the newest of the “atypical” antipsychotic medications, which represent a major advance in the treatment of schizophrenia, Bipolar Disorder, and other psychoses; however, its safety and efficacy in a wide range of psychiatric disorders is now being increasingly appreciated. For example, aripiprazole is being prescribed to people with Alzheimer's Disease to treat the agitation and delusional symptoms which are so often a part of that illness. Not only does aripiprazole appear to treat these symptoms, it often results in improved cognitive functioning as well. This is part of a new class of "atypical antipsychotics" which has replaced the older, conventional antipsychotics like Haldol, Thorazine, and Mellaril. Newer agents, like aripiprazole, are much safer, having much less propensity to cause the horrific involuntary motor side effects that conventional antipsychotics all can cause. They also do more than the older medications: in schizophrenia, this means that social withdrawal and emotional blunting can respond to treatment. In Alzheimer's Disease and other dementias, aggression and paranoia, which typically responded poorly to older medications, can be treated with few sided effects. In Fragile X and other developmental disorders, more severe forms of aggression, self-injurious behavior, mania, and other psychotic states can be treated effectively and with little risk. This is not to imply that aripiprazole is a miracle drug: it does not work for everyone, and the effect is not at all specific to Fragile X; nevertheless, it is a significant step forward, and may be the most effective single agent currently available. In Fragile X, aripiprazole should probably be reserved for treatment of more severe behavioral disturbances which pose a significant threat to the afflicted individual or others. Treatment with this medication can be expected to result in significant mood stabilization, a decrease in aggression or SIB, and elimination of psychotic symptoms (if present--the author believes true psychosis to be relatively rare in Fragile X individuals). 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.

Compared to risperidone, and especially olanzapine, aripiprazole causes less weight gain (may even cause weight loss), and is highly unlikely to cause muscle stiffness; it has a very long half-life, so levels of the drug accumulate in the system for about 2 weeks--and take a similar time to flush out upon discontinuation. This means that when switching from other atypical antipsychotics to Abilify, some gap in efficacy may be seen while aripiprazole levels build up; this can be avoided by starting a small dose of Abilify before entirely discontinuing the previous medication (a so-called “cross-over”).

Aripiprazole is unique among the antipsychotics in that it does not block dopamine receptors--it is a “partial agonist” at the D2 receptor; this means that in areas of the brain where dopamine levels are low (thought to be a mechanism of attention deficit), it enhances transmission. In areas of excessive dopamine transmission (long thought to be the basis of psychosis) it will decrease dopamine

transmission. This modulatory effect can simultaneously treat agitation and psychosis, while also helping with attention and cognitive performance. Given that many individuals with Fragile X and other developmental disorders are treated with both antipsychotics and stimulant medications (Ritalin and Risperdal are common prescribed together, though this is not recommended because of inherent antagonism), Abilify would seem to be an ideal treatment for this population. Clinical experience with Abilify in Fragile X has been excellent, with efficacy clearly superior to other available antipsychotics and mood stabilizers; side effects have generally been milder than other agents as well. With little risk of weight gain, lower incidence of movement disorders, and little sedation, this medication may be the treatment of choice for serious behavioral and psychiatric problems in Fragile X.

common side effects

sedation: usually transient; medication should be taken at bed time to minimize side effects; this side effect is much less prominent if dose is started low and titrated upward gradually

orthostatic hypotension (dizziness upon standing): taking at night will greatly reduce this problem; dosage reduction may also be helpful

uncommon side effects

restlessness (akathisia): dosage reduction or bed-time administration can help; can be treated with propranolol if necessary

muscle stiffness (dystonia): dosage reduction is indicated; hold dose until side effect subsides

nausea: take with food; even a small snack can help

dosage

children: start with the smallest dose, 2.5 mg at bed time; increase in 1-2 week intervals by 2.5 mg to optimal effect; typical dose is 5-10 mg per day

teens and adults: start with 5 mg at bed time; increase gradually at 1-2 week intervals up to 20 mg per day; doses higher than this are unlikely to be more effective, but will almost certainly have more side effects

Update 2009: At this point, Abilify must be considered the first choice of the atypical antipsychotics for the treatment of developmental disorders, and for virtually any condition requiring an antipsychotic in pediatric patients. It has a huge side effects advantage, in that it rarely causes weight gain in children; it is also more effective in most cases of fragile X, since it enhances mood and attention more than other drugs in its class, by virtue of its unique effects on dopamine transmission. The only drawback is that some kids find it a bit activating, so if sedation is absolutely required, Seroquel or Risperdal might be better choices.

thioridazine (Mellaril)

effectiveness	safety	cost	convenience
😊😊	👉	\$	👁️👁️

indications: mania, aggression, psychosis

pros: inexpensive, rapid tranquilizing effect, suspension available

cons: highly sedating; powerful anticholinergic side effects can cause confusion and memory loss; can cause a number of movement disorders, including some that are irreversible

use: thioridazine is an antipsychotic medication of the "conventional" type which has been available for many years, and is quite similar in most ways to the many other agents available (under trade names such as Thorazine, Haldol, Loxitane, Serentil, Navane, Prolixin, Trilafon, Stelazine, and others). While these medications differ somewhat in their side effect profiles, they all do basically the same thing: block dopamine receptors. This is the basis of their antipsychotic effect; they are also commonly referred to as neuroleptics or major tranquilizers. The greatest problem with these medications as a class is that they block dopamine receptors indiscriminately throughout the brain; since dopamine is an important neurotransmitter with many different functions, this can cause a wide array of serious side effects. This is the type of medication most people are thinking of when they worry that psychotropic medication will make them "feel like a zombie". For no good reason, thioridazine is the drug in this class most often chosen by child psychiatrists and pediatric neurologists, and so it is reviewed here as the prototype of the class. The following comments, however, apply to neuroleptics in general. These medications can provide rapid relief of mania or severe aggression, and they are the standard treatment for psychotic symptoms such as hallucinations and delusions. As previously noted, this author considers true psychosis to be relatively rare in the course of Fragile X; indeed, aggressive behavior is far and away the most common reason for these medications to be prescribed in the developmentally disabled population, including Fragile X. There are now many alternative treatments for aggression, and these should be considered before resorting to an antipsychotic, given the serious adverse effects associated with medications like thioridazine.

The most terrifying adverse effect of neuroleptic treatment is the development of tardive dyskinesia. This is an irreversible movement disorder consisting of involuntary, rhythmic movement of various muscle groups (usually starting in the mouth and face, then progressing to the arms, legs, or trunk) which persist long after the medication is discontinued. There is no effective treatment for this condition. It seems to correlate with cumulative exposure to antipsychotic medications; in other words, it is most likely when an individual has been treated with high doses for many years. Unfortunately, this happens quite often to people with developmental disabilities, since they often are started on these medications early in life, then continued indefinitely. Since these medications are not particularly effective as specific treatments for symptoms of Fragile X, autism, or any other developmental disorder, high doses are often required to eliminate target symptoms like aggression. Thus, today we see hundreds of thousands of older individuals with developmental disorders with permanent tardive dyskinesia--and there has been a dramatic backlash within the psychiatric profession against the indiscriminate use of these medications. The government has also issued numerous guidelines and regulations prohibiting the institutional use of neuroleptics in non-psychotic individuals unless they pose an immediate danger to themselves or others. However, most Fragile X

individuals are not institutionalized, and are not covered by these regulations. Many physicians still see these medications as an appropriate first-line treatment for all sorts of behavioral disturbances accompanying developmental disorders; they are not, and parents should be suspicious of any physician recommending this type of drug for an initial trial in a Fragile X patient.

Tardive dyskinesia may sound awful enough, but these medications cause other serious movement disorders which are, fortunately, usually reversible. *Dystonia* is an involuntary contraction of a muscle group which can be quite disabling, but is also readily treated with adjunctive medications. It is usually thought that muscular young men are most susceptible to this side effect. *Akathisia* is a form of motor restlessness which is drug induced, but sometimes difficult to distinguish from hyperactivity or anxiety. It can sometimes be treated with adjunctive medications, but is often a more refractory side effect than dystonia, and usually requires dose reduction. *Parkinsonian tremor* is a common but usually subtle side effect which is amenable to treatment and not often disabling.

More subtle side effects of antipsychotic drugs include anergia (general sluggishness), impaired concentration and memory, and gradual, long-term weight gain.

It is important to know that antipsychotic medications should not be prescribed in combination with stimulants, because these medications tend to cancel each other out--making treatment pointless. In the section on psychostimulants, the mechanism of action was described as primarily enhancement of dopamine transmission in the frontal lobes (plus some indiscriminate increase in dopamine transmission in other areas which can cause or aggravate psychosis). Antipsychotics, on the other hand, block dopamine transmission throughout the brain, perhaps explaining why they decrease attention and concentration, and clinically appear to prevent stimulants from having any net effect. Nevertheless, children with difficult behavioral problems are prescribed this illogical combination with alarming frequency.

The following recommendations are offered for anyone prescribed this type of medication:

1. get a second opinion, preferably from a qualified psychopharmacologist
2. consider a trial of risperidone or olanzapine---newer, safer, and more effective medications
3. be sure that you are well informed of the significant risks involved in this type of treatment
4. always try to use the minimum effective dose
5. always try to use these medications for a limited time, attempting discontinuation after 3-6 months

common side effects

sedation: entire dose can be taken at bed time

dry mouth: sugarless gum or hard candy will help

constipation: stool softeners are preferred treatment

blurry vision: bed time administration will minimize this

uncommon side effects

dystonia: Cogentin(benzotropine) or Benadryl(diphenhydramine) are often used to alleviate this involuntary muscle contraction

akathisia: propranolol is the treatment of choice

seizure: all medications of this class significantly lower the seizure threshold; if seizures occur, discontinue the medication immediately

Many other side effects (too numerous to list here) are possible with these medications; if in doubt, stop the medication; abrupt discontinuation of antipsychotic medication is not hazardous.

dosage: varies too widely for even basic guidelines; best discussed with a qualified physician

Update 2009: No one uses this drug any more, and that is appropriate. Not recommended for any reason.

naltrexone (ReVia, Trexan)

effectiveness	safety	cost	convenience
😊😊	👉👉	\$\$\$\$	🙄🙄🙄

indications: SIB (self-injurious behavior)

pros: few side effects, can result in rapid decrease in SIB--in some cases; once a day or every-other-day dosing

cons: extremely expensive; no pediatric formulation; rare cases of toxicity

use: naltrexone is an opiate antagonist; that is, it blocks the effect of exogenously administered opiate drugs, such as morphine and heroine. It was originally marketed under the trade name Trexan to do just that: block the effect of street drugs so that addicts would be able to remain abstinent longer. More recently, it has been shown effective in preventing relapse of alcoholics, presumably by blocking the effects of *endogenous* opioids (naturally occurring substances thought to block pain signals, mediate reinforcement, satiety, and some pleasurable sensations). Subsequently, it was remarketed under the new name ReVia, at a higher price but otherwise unchanged.

It has long been thought that some individuals, regardless of diagnosis, who engage in self-injurious behavior manage to provoke release of these endogenous opioids (endorphins and enkephalins are the best known of this group), resulting in sensations which might be soothing, anxiolytic, euphoric, or otherwise pleasurable. In essentially all cases of SIB of this type, the individual (if verbal) describes analgesia during the self-injury, i.e. there is no sensation of pain. Dramatic self-mutilation is often seen in patients with severe personality disorders or dissociative disorders (like multiple personality disorder); this is relatively rare in Fragile X individuals, unless they have been subjected to deprived institutional settings. When these self-mutilators are given naltrexone, the injury once again hurts, rather than provoking this paradoxical "rush", or pleasurable sensation; the behavior usually subsides rapidly thereafter.

While some cases of SIB in Fragile X may fit this pattern, this is by no means the rule. In many cases, Fragile X children injure themselves during periods of great anxiety or overstimulation, and the actual injury is quite minimal. Handbiting is the classic example of this type of SIB, and is not likely to respond to naltrexone treatment. Compare this to institutionalized children who might bang their heads against a concrete wall for hours if not restrained, sometimes causing massive tissue damage. This is the type of SIB which does often respond to naltrexone treatment. The critical distinction for predicting drug response seems to be the presence of this profound analgesia, which can be effectively eliminated by the naltrexone. This may be why the literature shows such conflicting results in trials of naltrexone: some studies achieve dramatic results while some actually see a worsening of certain forms of SIB.

Naltrexone has no true psychoactive properties under most circumstances; it simply prevents an undesirable behavior. Nor does it have any notable side effects for the vast majority of people who take it. However, in rare cases naltrexone (at high doses) has caused signs of mild liver toxicity, so some physicians like to monitor liver function to catch any possible problem early. The major disadvantage is the outrageous cost of the drug: more than \$5 per tablet, despite the fact that this drug has been on the market for many years.

common side effects

nausea: take with food

uncommon side effects

blockade of opioid analgesia: occasionally an individual who has been taking regular doses of a narcotic (Percocet for headaches, for example) will experience opioid withdrawal precipitated by initiation of naltrexone; this is uncomfortable but rarely dangerous

dosage

children and adults are usually begun at 25-50 mg by mouth once a day (any time);

some individuals will obtain a better response at 100 mg/day, but higher doses are not usually recommended

reference:

Buzan RD, Dubovsky SL, Treadway JT, Thomas M

Opiate antagonists for recurrent self-injurious behavior in three mentally retarded adults.

University of Colorado Health Sciences Center in Denver, USA.

Psychiatr Serv 1995 May;46(5):511-2

ABSTRACT:

Opiate antagonists have shown promise for treating a subset of self injurious patients. The authors report on the use of naltrexone with three mentally retarded adults who had long histories of self-injurious behavior and unsuccessful behavioral and drug treatments; for all three, the self-injurious behavior was substantially decreased. The authors have found a positive response for half the self-injurious patients for whom naltrexone has been tried. Before any drug therapy is initiated, environmental reinforcers of the behavior should be sought out and modified, and any reversible medical and psychiatric disorders should be treated.

Update 2009: Naltrexone never quite lived up to its initial promise, and has largely faded from use. It has never been demonstrated that naltrexone can have any beneficial effect on the core symptoms of any autism spectrum disorder, as was initially hoped. However, this medication could still be useful in rare cases of fragile X or autism where self-injurious behavior is especially severe.

APPENDIX A:

Anxiety and Depression in Parents of Fragile X Children

As parents of children with Fragile X syndrome, we are all well aware of how stressful our jobs are; in addition, most of us understand that stress can cause a number of harmful effects. However, some common and serious medical disorders are often overlooked when we think about “stress-related conditions.” I am referring to Major Depression and Panic Disorder, two of the most common afflictions of mankind. There is a certain stigma attached to these illnesses, perhaps less true today than in the past, but definitely still present. This may be one reason why these conditions are not often addressed openly in the Fragile X community. Hopefully, this article will “destigmatize” the subject a bit, and get some beleaguered parents the help they need.

As parents of children with special needs, we are likely to be at a greater risk for developing Major Depression or Panic Disorder precisely because of this difficult role in which we find ourselves. It is important to remember that this is not the result of any weakness or personal failing; it’s not even a reflection of how well we are managing. Stress affects everyone, competent and incompetent alike. And unfortunately, more competent people often end up with more responsibility (and more stress) just because they are able.

What Is Major Depression?

This is the official term for what many people call melancholia, clinical depression, endogenous depression, or biological depression. It is not simply feeling blue for a little while. Major Depression is an incredibly common illness: recent studies estimate that nearly 25% of women in the US will develop at least one episode of Major Depression during the course of their lives; men suffer at about half that rate -- still a hefty 10-12%. Much has been made of this 2 to 1 ratio, which seems to hold true around the world; current consensus holds that this is primarily a hormonal effect, and that men are simply more susceptible to other things (substance abuse and criminality, for example). Major Depression is also a potentially fatal illness: approximately 15% of sufferers eventually commit suicide. Others survive, but cannot function, and this is one of the leading causes of absenteeism and disability. Most disturbing is the finding that Major Depression significantly impairs the ability of parents to raise their children. Several studies have shown that children raised by depressed mothers are far more likely to suffer behavioral and emotional problems, even when genetic effects are accounted for.

These are the symptoms of Major Depression:

1. depressed or irritable mood most of the day, nearly every day (persistent dysphoria)
2. diminished interest or pleasure in most activities (anhedonia)

3. significant change in appetite or weight (either up or down)
4. insomnia or oversleeping nearly every day
5. physical restlessness (agitation) or slowing (psychomotor retardation)
6. fatigue or loss of energy nearly every day
7. constant feelings of worthlessness or guilt
8. decreased concentration or indecisiveness
9. recurrent thoughts of death or suicide

The presence of at least 5 of these symptoms for at least two weeks is diagnostic of Major Depression. Unfortunately, there is no blood test to confirm the diagnosis, and although there are numerous “biochemical markers” which have been discovered throughout the years, none of these is useful as a screening tool. Some medical conditions, like diabetes and hypothyroidism, may need to be ruled out. This is one of the most important reasons for anyone concerned about depression to start by seeing their primary care physician.

What Is Panic Disorder?

Just as many people with Major Depression are told “Everyone gets depressed now and then,” people with Panic Disorder are told “Everyone has anxiety.” However, most people don’t have panic attacks. Panic Disorder is a condition in which people experience recurrent, spontaneous panic attacks. It is difficult to convey the feeling of a panic attack to someone who has never had one, but it is defined as follows:

A period of intense fear developing abruptly and reaching a peak within 10 minutes, with at least 4 of these symptoms:

1. palpitations or pounding heart
2. sweating
3. trembling
4. shortness of breath or smothering
5. choking
6. chest pain
7. nausea or abdominal distress
8. feeling dizzy or faint
9. derealization or depersonalization (feeling detached from surroundings or oneself)
10. fear of losing control or going crazy

11. fear of dying
12. numbness or tingling
13. chills or hot flushes

These attacks feel quite “physical” and most people are convinced that this is a serious medical problem. They are right, but it’s not the usual problem like a heart attack or an ulcer. Many people even go to the emergency room with panic attacks, and although these are increasingly being recognized and treated appropriately, more often patients are simply given a pat on the back and told “Everything is fine.” But everything is not fine. Typically, the attacks continue, often becoming more and more frequent. Each one is a terrifying experience, and it is only normal human nature to do anything to avoid having another one; in most cases, people assume that something provoked the attack -- being in an elevator or a large store or driving on the highway. They naturally avoid those situations, but the attacks continue (because they are actually happening more or less at random), so Panic Disorder sufferers often find their range of activities steadily shrinking, resulting in a secondary condition known as Agoraphobia (literally “fear of the marketplace”). In severe cases, people with Agoraphobia cannot leave their homes and sometimes they can’t even leave their beds.

The Role of Stress

Why mention both of these conditions together? One reason is that they occur together in many individuals; about half the people with Panic Disorder will eventually have an episode of Major Depression, and the same 2:1 female:male ratio applies to Panic Disorder. Another reason is that most cases of Panic Disorder respond to the same treatments used in depression, even if patients aren’t depressed at the time. Both conditions are thought to be stress-related, and both are thought to have significant genetic underpinnings. One way to conceptualize the interaction between an underlying genetic susceptibility and stress in the environment is through the “weak link hypothesis.” Basically, this states that enough stress will make just about anyone sick (something which has been well demonstrated by research), but that *how* you get sick is determined by what you are most vulnerable to (the weak link in the chain).

In fact, most people who become depressed or suffer from anxiety disorders have been through periods of extraordinary stress. This runs counter to the old notion of “reactive depression”, the idea that “anyone would be depressed in that situation”. We now know that this sort of stress is typical and that it does not mean that a discrete disorder should not be treated or that it will not respond to treatment. This is precisely the predicament many Fragile X parents find themselves in: they are overwhelmed by stresses which would probably affect anyone.

Part of this misconception about the nature of Major Depression and Panic Disorder arises from a fundamental misunderstanding of what stress is. The old school of thought stated that stress was primarily generated by loss, disappointment, or conflict. While these are certainly stressful, it is crucial to recognize that good things can be stressful, too. From a biological perspective, getting married is just as stressful as getting divorced and receiving a promotion is as stressful as being laid off. Change seems to be inherently stressful, whether good or bad.

Psychiatry is beginning to understand the biological basis of Major Depression and Panic Disorder, and it appears that stress hormones play a pivotal role. It seems that there is a normal mechanism in the brain for regulating moods and suppressing anxiety. This mechanism acts something like the automatic transmission in a car: under normal circumstances, our mood shifts automatically to suit the driving conditions. Many people like to think they are in control of this process, but there really is no manual override. Under prolonged stress, the transmission can get burned out and stuck in low gear. The transmission fluid in this analogy is a neurotransmitter called serotonin, and it's probably no accident that most of the medications which treat depression and anxiety disorders enhance the actions of serotonin.

Treatment

The best news of all is that Panic Disorder and Major Depression are just about the most treatable of all medical conditions. Many different treatment options exist and there is simply no way to review all of them here; however, a brief overview may be helpful.

Psychotherapy is a tried and true technique which is still an effective treatment for depression and anxiety disorders. However, there are many different types of psychotherapy, and many different types of professionals who do it; a choice can be difficult. The type of psychotherapy best established as an effective treatment for depression is cognitive therapy, a type of brief psychotherapy in which the numerous cognitive distortions and illogical thinking which accompany depression are directly confronted and overcome, often using "homework" assignments outside the therapy sessions. A similar technique, cognitive/behavioral therapy is the most effective form of psychotherapy for treating anxiety disorders; it typically blends writing assignments with actual excursions to confront avoided situations (like shopping malls or elevators). Unfortunately, only a tiny fraction of the psychotherapists currently practicing are well versed in these techniques; a referral from a friend or a support group is worth its weight in gold.

Interpersonal psychotherapy is another type of therapy which can be of benefit in treating depression (but probably not anxiety disorders); it focuses on problems in relationships as a cause of stress and depression, and seeks to improve function within relationships as a way of treating depression. Traditional psychodynamic psychotherapy may also be helpful, but this has been difficult to establish scientifically; it may also be a moot point, since few insurance companies will pay for this sort of long-term therapy, which effectively puts it beyond the means of the average person.

Whichever type of psychotherapy is chosen, it is advisable to keep a few general points in mind:

1. Set definite goals to resolve specific problems (symptoms)
2. Expect results in 8-10 sessions
3. Enlist those around you to objectively evaluate your progress; ask your spouse if there has been noticeable improvement

4. Be prepared to try another therapist if you are not making progress (don't accept rationalizations for lack of progress, i.e. "this goes way back to childhood, we'll need to work on this in more depth")
5. An effective therapist is not necessarily the one you like the best
6. Therapy is not supposed to be fun, but it shouldn't be torture either
7. Get a second opinion if things aren't going well

Medications are the other mainstay of treatment for anxiety disorders and depression; the combination of antidepressant medication and appropriate psychotherapy has been shown over and over to be the most effective treatment for these conditions. The first-line treatment for depression and most anxiety disorders these days is a class of medications collectively referred to as selective serotonin reuptake inhibitors (SSRIs). Currently available from this class in the US are Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Celexa (or Lexapro---both citalopram), and Luvox (fluvoxamine). They all have the advantages of convenient, once-a-day dosing, a broad spectrum of activity in many different disorders, and great safety (they are not toxic at any dose). Their major disadvantage is that they are expensive, but generic equivalents (at least for Prozac, Paxil, and Luvox) have recently become available. They share many of the same side effects: common nausea or heartburn, occasional jitters or insomnia, and frequent sexual dysfunction. Fortunately, most of these side effects subside quickly as the body adjusts to the presence of the drug.

Older antidepressants are still used and can still be quite effective. The tricyclic antidepressants (TCAs) most commonly prescribed are imipramine, desipramine, amitriptyline, and nortriptyline. All are available in generic form, which is quite economical. They have significantly greater side effects than SSRIs, but they are different side effects, which might be easier for a given individual to tolerate. They usually cause dry mouth, sedation, constipation, and some dizziness; in addition, these medications are very toxic in overdose, and should always be kept away from children. TCAs are just as effective as SSRIs in treating Major Depression and Panic Disorder, though they are much less effective for some other conditions such as Obsessive-Compulsive Disorder or Eating Disorders, for which SSRIs are the treatment of choice.

Two newer antidepressants, Effexor (venlafaxine) and Serzone (nefazodone), do not fit neatly into any class, but share many of the features of the other newer antidepressants. The major difference is that both require 2-3 times daily dosing, so they are somewhat less convenient. There are still other types of antidepressant medications too numerous to list. Ask your doctor for written information about the medication he prescribes for you; it is impossible to remember all the complex information relayed during an office visit.

Anti-anxiety medications (minor tranquilizers) are often used together with antidepressants for quicker relief of symptoms such as insomnia and restlessness. While some people find them useful, they are not adequate treatment for Major Depression by themselves. Some people with Panic Disorder (and without depression) find that this type of medication alone can prevent panic attacks and allow them to function normally; however, relatively high doses are required for this purpose. The antidepressants are generally considered superior in the long run, especially since they prevent the occurrence of depression (something to which people with Panic Disorder are highly susceptible).

Some general considerations when taking these medications for anxiety and depression:

1. Make sure you understand how the medication should be taken
2. Know who to call if there are problems or questions
3. Remember that antidepressants all take 2-3 weeks to start working, and that the effect is greatest after 10-12 weeks -- a long wait, but worth it
4. Most side effects occur in the first few weeks -- hang in there!
5. Call your doctor before deciding to stop these medications; stopping abruptly can cause some unpleasant effects
6. If the medication is not working after a long enough time, tell your doctor -- you may not be taking enough; the effective doses vary greatly from person to person
7. Many primary care doctors are quite comfortable prescribing these medications, but if yours isn't, see a specialist (a psychiatrist)
8. If you feel that your doctor (whichever kind) is not taking the time to explain the treatment to you, or is not available to answer questions about your medications, get a second opinion
9. The more you know, the better; read as much as you can, and ask your spouse or family to read about your treatment -- they may have many misconceptions

Reading

When fighting either depression or an anxiety disorder, knowledge is your greatest weapon. Learn as much as you can; you will need this information to combat the general ignorance in society at large concerning these illnesses. The following come highly recommended:

“Feeling Good”, “The Feeling Good Handbook”, and “Ten Days to Self-Esteem” by David Burns MD -- one of the founders of Cognitive Therapy explains how to do it yourself. These texts also have nice chapters explaining medications.

“The Anxiety Disease” by David Sheehan MD -- a classic description of Panic Disorder and its treatment which is especially good for helping family members understand what a panic sufferer is going through.

“You Mean I Don’t Have to Feel This Way?” by Colette Dowling -- written by a woman who has Panic Disorder and Major Depression; well-researched, extensively referenced, fascinating and still easy to read.

“Don’t Panic” by R. Reid Wilson PhD -- the best non-medical source for do-it-yourself techniques to control Panic Disorder, written by the leading authority on non-medical interventions for anxiety disorders. It also has a short section on medications.

Summary

Panic Disorder and Major Depression are two of the most common afflictions of the human race, yet both are terribly under-recognized and under-treated. Parents of children with Fragile X

may be at particular risk for developing these illnesses, because of the tremendous stress of raising developmentally disabled children. These conditions can be effectively treated, but misconceptions in our society and even in the health care profession can impede appropriate treatment. If you have suffered debilitating anxiety or depression, please realize that it is not your fault, and that you will almost certainly get well with proper treatment.

Glossary of Terms

adrenaline	same as epinephrine
affect	the outward, observable expression of mood
affective	pertaining to mood states
agonist	a substance which activates a naturally occurring receptor
antagonist	a substance which blocks the activation of a naturally occurring receptor
anxiogenic	producing anxiety
ataxia	Partial or complete loss of coordination of voluntary muscular coordination
autonomic	a function of the nervous system (such as regulation of respiration or heart rate) which occurs without voluntary control
contraindication	a condition which mitigates against the use of a particular treatment; a relative contraindication means that other treatment alternatives should be explored; an absolute contraindication means that a particular treatment should never be used under the circumstances described
dopamine	a major neurotransmitter; dopamine in frontal areas of the brain is thought to regulate attentional processes; in other areas, dopamine mediates motor coordination and various drive states (hunger, thirst, etc.); excessive dopaminergic transmission in yet other areas is hypothesized to be responsible for psychotic states
epinephrine	a neurotransmitter as well as a circulating amine with potent effects on a variety of autonomic functions
full mutation	in Fragile X, the form of the FMR-1 gene which is responsible for the disorder; a full mutation usually contains an expanded segment of DNA with more than 200 CGG repeats (usually 500-1000 repeats)
hyperkinesis	excessive motor activity
indication	a rational use for a particular treatment; "off-label" indications are common in psychiatry: these are uses for a medication which are commonly accepted in clinical practice, but not officially approved by the FDA
metabolite	a substance produced by the enzymatic action of the body's metabolism on a "parent compound"
mosaic	a genetic variation in which the expression of a gene or genetic defect is not uniform throughout the body; in Fragile X mosaicism, some cells have a premutation, while others have a full mutation; mosaic individuals may be less severely affected in some cases
neuron	a nerve cell; neurons all possess electrical activity which can be discharged in brief (millisecond) pulses when sufficiently excited; not all cells in the brain are neurons, some are glia, which act as insulation and scaffolding for the neurons

neurotransmitter	a substance which carries signals from one nerve cell (neuron) to others; some neurotransmitters are excitatory, and will make the receiving cell more likely to discharge its electrical activity; other neurotransmitters are inhibitory, making the receiving cell less likely to fire; still others are neuromodulatory, having subtle, long term effects on the receiving cells
noradrenaline	same as norepinephrine
norepinephrine (NE)	a neurotransmitter important in regulation of anxiety and autonomic functions
pathology	a disease state (or the medical specialty devoted to its study)
pathophysiology	the mechanism by which a disease process causes harm
physiologic	pertaining to the physical function of the body
postsynaptic	occurring on the receiving end of the synapse
premutation	in Fragile X, the FMR-1 gene can exist in several forms; the premutation is a fully functional form (asymptomatic) which is susceptible to further expansion to a full mutation in future generations
presynaptic	occurring on the side of the synapse from which neurotransmission originates
psychopharmacologist	a physician, trained in psychiatry, who specializes in the use of psychotropic medications
psychopharmacology	the use of pharmaceutical agents to treat mental disorders and behavioral disturbances
psychotherapy	the use of specialized forms of interpersonal contact to affect the outcome of psychological disorders; <i>cognitive</i> therapy examines the assumptions and illogical thought processes which might exacerbate psychic distress; <i>behavioral</i> therapy attempts to modify thoughts through structured behaviors; <i>psychodynamic</i> therapy examines unconscious conflict as a source of psychic distress
psychotropic	having an affinity for the brain; affecting mental processes
serotonin (5-HT)	an important inhibitory neurotransmitter which is thought to be the primary regulator of moods and anxiety in the human brain
sympathetic nervous system	a branch of the autonomic nervous system which regulates states of arousal and the "fight or flight" response
synapse	the gap between neurons, measuring just a few microns, across which neurotransmitters communicate
tic	an involuntary, sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization