

MEDICAL INTERVENTION IN FRAGILE X SYNDROME

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Children and adults with fragile X syndrome often present to the physician with a variety of behavioral problems. These problems are typically seen in fragile X syndrome so they are presumed to be caused by a lack or a deficiency of normal FMR-1 protein (FMRP) production from the FMR1 gene which is dysfunctional in fragile X syndrome. FMRP is normally present in all neurons and its absence causes some changes in brain structure and function, and presumably changes in neurotransmitter systems that we can improve by the use of medication. Although there is presently no cure for fragile X syndrome, there are a variety of medications that can improve the behavior problems seen in fragile X syndrome.

Not every fragile X child will have difficulty with the behaviors discussed below, and not every child will respond to each medication. When problems occur, a medication is usually prescribed on a trial basis and often two or more trials of medication are needed before finding one that works. Sometimes more than one medication is used to treat a combination of problems and sometimes medications are used together because of a synergistic effect. Side effects are discussed below and should be monitored carefully so that they do not become more problematic than the symptom, which is being treated. A close communication and follow up visits are needed with your doctor in order to adjust the medication level and monitor the side effects.

It is important to remember that medication is not the only treatment for fragile X syndrome. The use of therapy in the motor and language areas and special education intervention are essential in the treatment program for a child with fragile X syndrome. In addition, counseling and behavior modification programs with positive reinforcement can be extremely important for children with significant behavior problems. However, medication can also be helpful to improve the behavior problems so that the other behavior interventions can work more effectively than without medication.

Some of the more common behavior problems that respond to medication include: hyperactivity, impulsive behavior, attention difficulties, mood fluctuations, aggressive outbursts, anxiety and obsessive or compulsive behavior. These problems and their treatment with medication are described below.

Attention Problems and Hyperactivity

Almost all young fragile X boys, and approximately 1/3 of girls who are affected with fragile X syndrome have significant attention problems which are usually associated with hyperactivity, although not always. Stimulant medications, including methylphenidate (Ritalin) or dextroamphetamine (Dexedrine or Adderall), are usually tried as a first-line medication and are available in both long acting and short acting forms. They are effective because they stimulate both the dopamine and the norepinephrine neurotransmitter systems and this effect improves attention, hyperactivity, inhibition and visual motor coordination. If the child is able to focus and concentrate on academic tasks, then learning should improve. The child may feel more organized and in better control of impulsive behavior such that frustration and tantrum behavior may decrease and an improved self-image may emerge. Stimulant medication is helpful in approximately 60 to 70% of fragile X patients who are school aged. It is less effective in the adolescent or the preschool child and side effects are more common. Stimulants can stimulate the cardiovascular system so that the blood pressure and heart rate can increase. The appetite is often suppressed and sometimes, sleeping problems occur. Stimulant medications may also worsen motor tics if they are a problem originally. Most side effects worsen at higher doses and

irritability or tantrum behavior may worsen when the medication wears off. In my experience, fragile X patients seem to do better with a relatively low dose of stimulants (i.e. methylphenidate 0.2-0.3 mg/kg/dose) since side effects can be a significant problem for many.

A common alternative to using stimulants for the treatment of hyperactivity, is clonidine, which is a medication also used for the treatment of high blood pressure in children and adults. This medication is better for calming down behavior, such as hyperactivity, but it doesn't work as well for improving attention and concentration compared to stimulants. It tends to improve tics and it does not decrease the appetite. Preliminary studies suggest that it may be helpful in stabilizing the mood, however, sedation is a significant side effect. Sleepiness can be excessive, particularly in the first 2 weeks of use so that a very low dose is used initially (i.e. 1/4 or 1/2 tablet, twice a day - each tablet is 0.1 mg). Clonidine also comes in a patch form, Catapres TTS, which is replaced every 5 to 7 days, allowing for continuous release. The patch tends to cause less sedation, but in approximately 20% of cases, the skin can be irritated at the site of the patch.

Clonidine can be used successfully in the preschool child who is 3 years of age or older. A very low dose should be used (i.e. 1/4 of a tablet once or twice a day) and children should be monitored for low blood pressure, dizziness or fainting. Clonidine is particularly helpful for sleeping problems, including wakefulness and difficulty in getting to sleep. When given before bedtime, the sedation side effect facilitates bedtime processing, falling to sleep and staying asleep.

Clonidine works by lowering overall norepinephrine levels both centrally and peripherally. It can be used together with methylphenidate or other stimulants. Whereas the stimulants improve attention to a greater degree in the classroom, clonidine is the most effective in the late afternoon and evening to help with calming behavior.

Alternative medications for treatment of attention problems and hyperactivity are the tricyclic antidepressant medications, such as imipramine, which is also helpful for enuresis (bedwetting) and desipramine. These medications are not the first choice of treatment because an increase in outburst behavior has been noted in a limited number of cases with fragile X syndrome. The tricyclics can also cause an increase in cardiac conduction time, particularly at higher doses, so the ECG must be monitored periodically.

Folic acid has been a controversial treatment in fragile X syndrome. It has been reported to be effective in improving hyperactivity in only a limited number of prepubertal patients and, in general, it appears to be less effective than stimulant medication. However, it can be used at a young age, particularly in the child who is too young for stimulant medication. Dr. Turk (1992) has reviewed the use of folic acid in fragile X syndrome.

Mood fluctuations and/or aggressive outbursts

Moodiness and aggressive outbursts are problems for many boys affected by fragile X syndrome. It is especially common in adolescent and young adult males. Outbursts may be characterized by aggressive verbalization or physical outbursts with hitting, kicking or biting. This can be a serious problem that may jeopardize placement in the home or in an apartment living situation. In the past antipsychotic medications, which are major tranquilizers, have often been prescribed in these situations when environmental modifications have not been helpful. However, antipsychotic medications have significant and often long-term side effects, such as tardive dyskinesia. Therefore, safer medications should be used whenever possible, unless psychotic behavior is complicating the aggression.

Often the outburst behavior is precipitated by overreaction to stimuli in an individual who has mood fluctuations or mood lability on a regular basis. Medications that stabilize mood, such as the anticonvulsants, carbamazepine (Tegretol) or valproic acid (Depakote), can be helpful in improving behavior and decreasing outbursts in individuals who do or do not have seizures or

abnormal EEGs. Alternatively fluoxetine (Prozac) a serotonin reuptake inhibitor, has been shown in a survey to be helpful in decreasing aggression or outburst behavior in approximately 70% of fragile X males. Other serotonin agents, such as sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), or citalopram (Celexa) may also be helpful, according to anecdotal reports.

More significant aggression that does not respond to the previously mentioned medications may require the use of an atypical antipsychotic. These medications have a lower risk of tardive dyskinesias compared to older antipsychotics. Atypical antipsychotics include risperidone (Risperdal) and olanzapine (Zyprexa). When used in relatively low doses they can be safe and effective for treatment of aggression, severe ADHD, and significant mood instability (Hagerman 1999). Gabapentin (Neurontin) is a new anticonvulsant that can be helpful for treatment of mood instability and, by anecdotal reports, helpful for aggression in patients with fragile X syndrome. It is often combined with other medications previously described and it does not require monitoring of serum levels (Hagerman 1999).

Females who are mildly affected by fragile X syndrome may also experience mood instability, anxiety or depression, particularly if they are mothers who are raising fragile X children with significant behavior problems. Fluoxetine or other serotonin agents may be helpful in these women, however, simultaneous counseling is also beneficial and should be utilized to monitor any side effects from the medication, such as suicidal ideation, mania, or increases in anxiety or depression.

Anxiety or obsessive/compulsive behavior

Anxiety is a common problem in fragile X syndrome and may be seen on a daily basis, particularly in new situations. Panic attacks may also occur in males and females affected by fragile X syndrome. Although benzodiazepines, such as Valium and Xanax are effective for anxiety, they are addictive, sedating, and the withdrawal process is problematic for most patients. If used only intermittently, or in low doses, they are less problematic. A newer anti-anxiety agent, buspirone (Buspar) is not addictive and not sedating, although it is less effective for treatment of panic attacks than the benzodiazepines. Fluoxetine and other serotonin agents mentioned above are also helpful in the treatment of anxiety. Imipramine and clonidine may also improve anxiety, although their primary benefit is in the treatment of hyperactivity.

Sometimes obsessive thoughts or compulsive behavior is a problem for fragile X children or adults. Perseveration in speech and behavior is very common in fragile X and it may be difficult to separate this behavior from obsessive or compulsive behavior. The serotonin agents, such as fluoxetine and sertraline, are helpful for obsessive thinking or compulsive behavior. These symptoms may be present in females, but may be a more significant problem in males and approximately 50 to 70% may respond to serotonin agents. In addition, Clomipramine, a tri-cyclic, may also be helpful, but monitoring blood levels and an ECG is important in follow-up.

This article should serve only as an introduction to the use of medications in fragile X syndrome. All of the suggestions described here should be reviewed with your doctor before they should be tried in children or adults who are impacted by fragile X syndrome. For further reading see Tranfaglia 1998, Hagerman 1996, and Hagerman 1999.

RECOMMENDED READING

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