MEDICATIONS AND TOURETTE'S DISORDER:

COMBINED PHARMACOTHERAPY AND DRUG INTERACTIONS

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Introduction

Tourette Syndrome (TS) or Tourette's Disorder (DSM IV) is a complex neuropsychiatric disorder characterized by a changing pattern of motor and vocal tics that begin in childhood. Many individuals with Tourette Syndrome have associated non-tic symptoms such as hyperactivity, distractibility, impulsivity, obsessions and compulsions, anxiety, depression, and anger control. These associated symptoms may occur in patterns of frequency or intensity characteristic of an additional comorbid (coexisting) disorder such as Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), or Oppositional Defiant Disorder (ODD). Whether these problems are an integral part of Tourette Disorder or are separate problems is under investigation. They may result in difficulties in school, in the work place and with social adjustment. Frequently these associated problems or comorbid disorders are a source of more distress or impairment to the individual with TS than the tics. Not all patients with tics meet the formal diagnostic criteria for Tourette Syndrome but the tics may still have significant intensity to warrant treatment.

Medication Treatment: General Indications

Medication treatment can be beneficial in both reducing the tics and the behavioral and emotional problems in the individual with Tourette's Disorder or other tic disorders. When symptoms are mild, treatment may include only support, education and monitoring. For symptoms that produce significant distress or impairment, medication treatment may be indicated. Currently there are a variety of medications available for the treatment of tics and the non-tic symptoms. There is no single medication, which is helpful to all individuals with tics or Tourette Syndrome. Tics are often mild and will frequently at least partially remit in many individuals, particularly as they go through adolescence. Often it is the behavioral and emotional features that cause the most difficulty for the child.

Tic symptoms that cause interference in the child's functioning or cause significant distress are targets for medication treatment with the goal of reducing tic severity and frequency. For individuals with mild to moderate tics, specific medications effective for tic reduction include clonidine (Catapres) or guanfacine (Tenex). For individuals with moderate to severe tics, the newer atypical neuroleptics such as risperidone (Risperdal) or older traditional neuroleptics such as haloperidol (Haldol) may be indicated. The decision to use medication should take into account a variety of factors in addition to tic severity such as the child's age, medical history and past history of response to medication. Typically one medication can be used over period of several months or longer until the tics have abated.

For many individuals, the primary symptoms requiring treatment may be behavioral or emotional, such as hyperactivity, impulsivity or obsessions and compulsions. Medications that target the non-tic symptoms such as antiobsessionals (selective serotonin reuptake inhibitors or

SSRIs) or medications for Attention Deficit Hyperactivity Disorder such as methylphenidate (Ritalin), dextroamphetamine (Dexedrine, Addreall), or atomoxetine (Strattera) may be indicated. These medications may or may not have direct effects on the tics, in addition to the effects on the behavioral or emotional symptoms.

Monotherapy or Targeted Combined Pharmacotherapy

If the major symptoms include both tics and behavioral or emotional difficulties, medication may be effective to address both sets of symptoms. The first option is called monotherapy when just one medication is used to address two or more problems; this strategy is recommended if possible as a first choice since it is easiest to use and may have the best compliance. The physician may start with one agent that can address both the tics and the non-tic symptoms such as clonidine for tics and ADHD or clonazepam (Klonopin) for tics and moderate to severe anxiety.

If monotherapy is not possible or has not been effective individuals may require the use of two (or more) medications simultaneously to control both tics and behavioral or emotional symptoms. This approach is called targeted combined pharmacotherapy, referring to the careful, judicious use of more than one medication simultaneously. Although this is a more complicated approach, it has several advantages including 1) using lower doses of each medication, reducing the likelihood of side effects associated with higher doses of single agents and 2) potential augmentation or synergism (booster effects) of combination therapy. Given the increasing recognition of the prevalence and clinical significance of the comorbid problems in individuals with TS, this approach is becoming more frequent in its use.

The combined use of haloperidol (Haldol) and fluoxetine (Prozac) would be an example of a combination used to control both tics and obsessive-compulsive behaviors. Another example is the combination of clonidine (Catapres) and dextroamphetamine (Dexedrine) to reduce both tics and symptoms of Attention Deficit Hyperactivity Disorder.

Less frequently, more than two medications can be used in the treatment of tics and the comorbid problems. This is a more complicated approach since the likelihood of interactions between the medications increases as the number of medications used together increases.

Medication Interactions: Prescribed Agents

Potential interactions between two or more medications prescribed simultaneously need to be taken into account when the decision is made to use targeted combined pharmacotherapy. These interactions include those between the prescribed medications and those that may occur when non-prescribed (“over the counter”) medications are used. All medications are metabolized or broken down by a system of enzymes in the liver and distributed to the brain where they have their active effects. This process if also necessary to prepare the drug for elimination from the body. There is a considerable amount of information about these enzymes, known as the cytochrome oxidase P450 system. Medications such as the selective serotonin reuptake inhibitors (SSRIs) can alter activity in this liver enzyme system, resulting in reduced metabolism and reduced clearance of medication. This may result in increased blood levels of medication and/or increased side effects.

There is a large variation between individuals in their response to drugs. The response may depend on genetic and environmental factors. There may be considerable variation in the response of a single person to different members of the same drug class.

Medication Interactions: Non-Prescribed Agents ("Over the Counter")

Many children with Tourette's Syndrome and other tic disorders may receive over the counter medications to reduce symptoms of upper respiratory illness such as nasal decongestants and cough suppressants. Others may take acetaminophen (Tylenol) for muscle paints or for fever, or nonsteroidal anti-inflammatory agents (NSAIDS) such as Ibuprofen (Motrin, Advil) for headaches or muscle pain. Antibiotics are frequently prescribed for children for ear infections or strep throats. While these medications are generally safe for pediatric usage, some may have significant interactions with medications prescribed for children with TS.

Specific Medications

The medications commonly used to treat symptoms of Tourette Syndrome are reviewed in the tables at the end of this brochure. They are listed by their general purpose, typical starting doses, common maximum dosages and common side effects. Children generally require lower dosages of the same medications used for adults. The neuroleptic medications (e.g. Haldol [haloperidol] and Orap (Pimozide) may have uncommon side effects such as restlessness, muscle stiffness or slowness or a rare side effect known as tardive dyskinesia (TD). Symptoms of TD may begin with twitching movements of the face and mouth, which may not disappear when the medication is discontinued.

Some medications prescribed for TS have primary indications other than the treatment of Tourette Syndrome. Catapres (clonidine), and a close relative guafacine (Tenex), have been used to control high blood pressure. Clonazepam (Klonopin) is used in the treatment of seizures as well as for the control of tics.

Whether generic medications are as effective as brand name medication needs to be studied. Some reports have suggested that bioavailability (availability of the medication and its breakdown products after oral dosing is reduced slightly for generic neuroleptics such as haloperidol when compared to the brand Haldol. Some individuals switching to generic from brand name products have reported experiencing no problems, but some have noted that the generics proved less beneficial than the brand name products. It is important that individuals review this issue with their physicians when a medication program is being started.

The more commonly used medications for ADHD are the stimulants such as Ritalin (methylphenidate), and Dexedrine (dextroamphetamine) and Adderall (mixed amphetamines). These medications may cause an increase in tics in some TS patients. Other reports have been unable to find an effect on tic frequency. Experience has shown, however, that these medications can be safely taken by some individuals with TS. For those individuals with significant ADHD symptoms, a cautious trial of stimulant medication may be helpful. A new medication for ADHD is Strattera (atomoxetine), which is reported not to increase tics.

There is no single TS "drug of choice". A careful matching of the medication to the specific needs of the individual is critical. There are no medical tests, which can predict which medication will work best. More than one medication, even within the same family of drugs

may need to be tried before the best treatment program is found. Unfortunately, there are some individuals who may not respond to any of the available medications, or may experience intolerable side effects. These individuals may be candidates for other types of treatment.

Additional medications for TS are also available although they are used less commonly. Research programs are working actively to discover new and better treatment programs. Until that time, the currently available medications can be of help to many individuals with Tourette disorder and other tic disorders.

Medications Used in the Treatment of Tics

Name		Dosage		Common Side Effects
Generic	Brand	Starting	Usual	
haloperidol	Haldol	0.25-0.5mg	1-5mg	Fatigue, weight gain, muscle rigidity, motor tardive dyskinesia, school phobias, photosensitivity, depression, cognitive dulling
pimozide	Orap	0.5-1mg	1-10mg	Same as haloperidol, EKG changes (QTc interval)
fluphenazine	Prolixin	0.25-1.0mg	0.5-6mg	Same as haloperidol
clonidine	Catapres	0.025-0.05mg	0.1mg	Fatigue, sleepiness, dry mouth, irritability, dizziness, headache, insomnia, hypo-ension, EKG changes
guanfacine	Tenex	0.25-0.5mg	0.5-3.0mg	Fatigue, irritability, hypo-tension, sleep disturbance
clonidine patch	Catapres	TTSI patch	TTSI-TTS3 patch	Same as clonidine tablets localized skin rash
clonazepam	Klonopin	0.025-0.5mg	0.5-3.0mg	Fatigue, irritability, dizziness, disinhibition

Medications Used in the Treatment of TS plus ADHD

Stimulant Medications:

Name		Dosage		Common Side Effects
Genetic	Brand	Starting	Usual	
*methylphenidate	Ritalin	2.5-10mg	10-60mg	Headache, stomach ache, appetite loss, insomnia, irritability, increased tics
*dextroamphetamine and amphetamine salts	Adderall	2.5-5.0mg	5-20mg	Same as for methylphenidate
*dextroamphentamine	Dexedrine	2.5-5mg	5-30mg	Same as for methylphenidate
atomoxetine	Strattera	0.5mg/kg/day	1.2mg/kg/day	Same as for methylphenidate

*There are delayed (extended release) acting formulations available for these drugs permitting once daily administration.

Medications Used in the Treatment of Anxiety With or Without OCD*

Name		Dosage		Possible Side Effects*
Generic	Brand	Starting	Usual	
fluoxetine	Prozac	2.5-2-mg	5-80mg	Restlessness, insomnia, gastrointestinal upset, sexual dysfunction
paroxetine	Paxil	5-10mg	10-60mg	Same as fluoxetine
clomipramine	Anafranil	25mg	50-200mg	Dry mouth, blurred vision, constipation, fatigue, EKG changes, weight gain
sertraline	Zoloft	12.5-25mg	75-300mg	Fatigue, insomnia, restlessness, weight gain, sexual dysfunction

fluvoxamine	Luvox	25mg	50-300mg	Same as fluoxetine
citalopram	Celexa	10mg	10-40mg	Dry mouth, nausea, somnolence, sexual dysfunction, insomnia

***Warning Information**

Health care providers should carefully monitor patients receiving antidepressants for possible worsening of depression or suicidality, especially at the beginning of therapy or when the dose either increases or decreases. Although FDA has not concluded that these drugs cause worsening depression or suicidality, health care providers should be aware that worsening of symptoms could be due to the underlying disease or might be a result of drug therapy.

Heath care providers should carefully evaluate patients in whom depression persistently worsens, or emergent suicidality is severe, abrupt in onset, or was not part of the presenting symptoms, to determine what intervention, including discontinuing or modifying the current drug therapy, is indicated.

Anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although FDA has not concluded that these symptoms are a precursor to either worsening of depression or the emergence of suicidal impulses, there is concern that patients who experience one or more of these symptoms may be at increased risk for worsening depression or suicidality. Therefore, therapy should be evaluated, and medications may need to be discontinued, when symptoms are severe, abrupt in onset, or were not part of the patients presenting symptoms. If a decision is made to discontinue treatment, certain of these medications should be tapered rather than stopped abruptly (see labeling for individual drug products for details) .

Because antidepressants are believed to have the potential for inducing manic episodes in patients with bipolar disorder, there is a concern about using antidepressants alone in this population. Therefore, patients should be adequately screened to determine if they are at risk for bipolar disorder before initiating antidepressant treatment so that they can be appropriately monitored during treatment. Such screening should include a detailed

Use of Drugs in the Pediatric Population

Some of the drug information that families may receive when the use of medication for tic disorder is discussed may indicate that a drug is not "approved" for children in the pediatric age group (usually under age 18 years). This information comes from what is called the "pediatric label" or "package insert". This is information jointly agreed to by both the company and the Food and Drug Administration (FDA) to support the use of the drug as indicated. It is not unusual once a drug is on the market for it to be used in either a pediatric population or for an indication that is not in the label. An example of this is the drug clonidine, which is labeled for use in the treatment of high blood pressure in adults. However it has found widespread use for other disorders including tic disorders and ADHD. The Committee on Drugs in the American Academy of Pediatrics is very aware of this issue and has published a useful statement entitled "The Uses of Drugs Not Described in the Package Insert" in the July 2002 issue of Pediatrics (pp. 181-183). This statement points out that any labeling of a drug is not intended to preclude a physician from using his or her best judgment in the use of this medication. Because of rapidly advancing knowledge in pediatric therapeutics there can be widespread acceptance of the use of a drug not labeled for children before the label may be changed. There has been a very active effort in expanding the labeled drugs for the pediatric population in the last ten years so that children, their families and practitioners will have the benefit of the most up to date indications. When a certain drug is suggested for the treatment of a tic disorder or a co-morbid disorder. There is almost always significant published research to support such a recommendation. The child's physician would be in the best position to discuss this with the family.