The Treatment of Tourette's Syndrome: Multimodal, Developmental Intervention

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The increasing clinical recognition of milder phenotypic variants of Tourette's syndrome and the keener appreciation of its phenomenological continuity with other transient and chronic tic syndromes have required a greater comprehensiveness and sophistication in the assessment and management of the disorder. Treatment must be individualized based on considerations of the source and degree of functional impairment associated with tics, the current and future impairment associated with comorbid illnesses, the available internal and external sources of support and capacities for coping, and the challenges that the tics and comorbidities present at varying stages of development. Specific therapeutic interventions must target not only tic symptoms, but also comorbid illnesses and coping strategies that can profoundly influence the unique impact that tic symptoms may have on an individual's well being during childhood and adolescence, and later into adulthood.

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Tourette's syndrome (TS) consists of chronic motor and vocal tics that begin in childhood. The disorder is frequently associated with a broad range of other emotional and behavioral disturbances, and for this reason it is probably more frequently diagnosed and treated by psychiatrists than neurologists. TS is an increasingly frequent clinical diagnosis, most likely because of an increased recognition of tics by clinicians, parents, and school personnel, rather than because of an actual increase in its prevalence. With increasing clinical recognition of the disorder has come an increasing appreciation of the enormous breadth of tic symptom severity, in particular the much milder forms of TS that previously would never have come to clinical attention.

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The more frequent identification of milder phenotypic variants of TS has necessitated an increasingly wiser and more sophisticated assessment of the need and indications for particular treatment modalities. This assessment considers the total child and the child's environment, including the functional impairment produced by the tics and associated comorbid conditions, the universal and idiosyncratic challenges of particular developmental stages, the child's unique adaptive capacities, family and school supports, and the natural history of the disorder, all considered in the context of the potential risks and benefits of the available therapeutic interventions.

The diagnostic criteria for TS, if applied strictly to the general population, could quite easily diagnose an exceptionally large number of children with TS, even though the criteria have been developed explicitly to help limit the number of children who receive the diagnosis (Table 1).[1] The criterion that the tics must have been present for 1 year is meant to distinguish TS from the transient and benign tic disorders that affect between 5% and 20% of children in the general population.[2,3] Whether the tics of mild forms of TS differ in terms of their phenomenology, heritability, natural history, or pathophysiology from these other childhood tic disorders is unknown. Similarly, no evidence currently exists to suggest that having had both motor and vocal tics predicts a different natural history than does having had either form of tic alone. TS is therefore currently conceptualized as lying on a spectrum of tic diathesis[4] in which individuals who have few or no tics comprise one end of the spectrum, while those who have several transient or enduring tics comprise the bulk of the distribution. These latter individuals are the silent majority who typically do not come to clinical attention. Persons with

Table 1. Tourette's Syndrome Diagnostic Criteria*

Tic Criteria
Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently
Frequency and Duration Criteria
The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months
Age at Onset
The onset is before age 18 years
Exclusionary Criteria
The disturbance is not due to the direct physiologic effects of a substance (eg, stimulants) or a general medical condition (eg, Huntington's disease or postviral encephalitis)

*Adapted from reference 1.

frequent and forceful tics that persist through time are, at the other end of the spectrum, in the relative minority.

Largely because of the broad range of symptom severities now seen clinically, the failure to consider these many influences on the child's general well-being, perhaps more in TS than in most neuropsychiatric disorders, can yield clinical decisions that are less than helpful to the child and the child's family. If the complexities of this clinical decision making can confuse clinicians, they can confuse families even more. Educating families about the factors involved in making treatment decisions is therefore necessary for establishing an effective treatment alliance. Because of the understanding and hope that it provides, education is also the single most important treatment modality that we have in TS.

PSYCHOEDUCATION

The Significance of Tic Symptoms

Families and clinicians not infrequently presume that because a diagnosis of TS is made, medication is inevitably warranted. This assumption betrays a naiveté about what and who are being treated—it is not tics, but a child.

Tic symptoms *per se* probably poorly predict long-term occupational, social, and emotional adjustment of these children. Nor does current "objective" tic symptom severity (the frequency, intensity, and number of tic symptoms) predict the overall current level of adaptive functioning. It is not uncommon, for example, to see children with severe tic symptoms who are in every discernible respect happy, confident, well related, popular, academically successful, and comfortable with their families; it is also not uncommon, on the other hand, to see children whose tic symptoms are mild and that nevertheless contribute disproportionately to their dysphoria, lack of confidence, low self-esteem, poor peer relations, teasing, unsatisfying school performance, and family discord.

This lack of tight concordance between symptom severity and functional capacity does not mean that objective tic symptom severity is entirely irrelevant in making treatment decisions. More severe tic symptoms are more likely to interfere with intended motor or speech acts, and children with more severe tic symptoms are in a probabilistic sense more likely to be teased and to suffer in self-esteem. But these sources of interference are not assured in any particular child, and only careful, sensitive listening to the child and family can alert the clinician to the source and degree of interference, if any, the tics produce.

The Significance of Comorbid Conditions

Clinically identified TS is frequently accompanied by any of a broad range of comorbid conditions. One of these conditions, obsessive-compulsive disorder (OCD), has been shown to be a variant manifestation of the putative TS vulnerability gene.[5] This variant manifestation of the genetic predisposition to TS no doubt contributes to the greater prevalence of OCD in clinically identified TS patients than in community control samples. Some evidence suggests that some forms of attention-deficit/hyperactivity disorder (ADHD) may also be a variant expression of the TS genetic diathesis, although the rates of ADHD in families of TS patients are at most only modestly elevated above those in control families and appear primarily in family members who have TS,[6] indicating that the high rate of ADHD seen with TS in clinic samples (nearly 50%) is probably not largely explained by the variable expression of the TS gene. ADHD is found in only 8% of those who in epidemiologic samples meet diagnostic criteria for TS,[7] a prevalence approximating that of the general population.

Other disorders that commonly affect clinically identified TS patients include depression, general anxiety, separation anxiety, learning disabilities, and nonspecific disruptive behavioral problems. These disorders do not seem to affect family members of TS clinic patients more often than they affect control families unless the family member has OCD, suggesting that the disorders are not additional variant manifestations of the TS gene[8] and that tic disorders in the absence of OCD do not in themselves bode poorly for an individual's overall well-being, at least as gauged coarsely by their risk for developing a depression or anxiety disorder. The increased prevalence of these disorders in TS clinic populations (and perhaps that of ADHD as well) therefore most likely reflects a clinic ascertainment bias in which children who have multiple disorders are more likely to present to clinic than are children who have just a single illness.[9] Children who happen by chance to have both tics and disruptive behaviors, for example, may come to clinical attention primarily because of their behavioral disruption. At the time of clinic evaluation, tics are noticed, TS is diagnosed, and the behavioral disruption is erroneously attributed to TS. The treatment implication here is that the child's comorbid illnesses, not the tics, are often what require treatment.

Another possible explanation for the high rate of comorbidity in TS is that for unknown reasons some of the

comorbid conditions may affect tic symptom severity. Clinical anecdote, for example, suggests that tics increase in severity during periods of affective illness. The presence of affective illness may then predispose children with tics to more severe illness, thereby effectively lowering the threshold to clinical identification. The possibility that comorbid conditions influence tic symptom severity has important treatment implications in that the treatment of the comorbidities can have significant "trickle down" beneficial effects, either on the tics themselves or on the child's coping capacities.

Psychosocial Context: Risk and Protective Factors

The most frequent and pressing concern of parents whose children are being evaluated for tics (even if the concern is unspoken) is what long-term implications the tics have for their child's well-being. Clinicians must emphasize that the most important predictors of long-term outcome and well-being have little or nothing to do with the presence of tics. Intelligence and the quality of socialization have been shown repeatedly to be the best long-term predictors of outcome, regardless of diagnosis.[10] Bright, academically successful children who have close and enduring friendships are likely to continue to be successful interpersonally and professionally throughout their lives, regardless of their future tic symptom severity. Comorbid conditions are often either chronic or recurring,[11–13] and they can profoundly affect social, occupational, or emotional functioning. Their presence or absence will therefore often have a much greater impact on long-term outcome than will the presence of tics.

The child's response to the presence of tics will be important in predicting long-term functioning, and this response is often plainly evident early in the course of an evaluation. Although the most effective coping strategies will vary with each child, the general character and relative effectiveness of the child's coping strategies are most clearly seen in the quality of the child's self-esteem as it relates to his tic symptoms. Tic symptoms that seem to be impairing self-esteem need to be taken seriously by clinicians when planning treatment strategies, because the relatively ineffective coping strategies that are responsible for this breakdown in the resiliency of self-image are likely to persist during the chronic course of tic symptom evolution through childhood, adolescence, and adulthood.

Equally important in the assessment of coping strategies is the availability to the child of emotional support from family and teachers. Parents can help their child by treating the tics as they would any other physical stigma—as an unusual endowment that in no way affects their unconditional love for their child; they must try to help the child find some degree of equanimity with and resignation to the presence of tics, while at the same time trying to empathize unobtrusively with whatever pain the tics might cause.

Above all, tics should not be regarded as willful behaviors. Families and teachers who expect children simply to stop their tics and who react punitively when the child is unable to do so will risk severely undermining his self-esteem and increasing his anxiety, which paradoxically can actually exacerbate rather than attenuate tic symptoms. As children mature, however, they will usually become increasingly adept at the temporary partial suppression of their tics during socially appropriate times.[14] This increasing capacity for temporary volitional suppression should not be misinterpreted as meaning that tics are willfully produced. A sometimes useful analogy is the ability that we all have to suppress eyeblinking: we cannot suppress blinking indefinitely, and we eventually and inevitably must give in to the need to blink. Simply because blinking can be temporarily suppressed, however, does not mean that it is volitional.

Developmental Context

With these most important prognosticators of overall outcome placed in the proper perspective, families are better prepared to assimilate knowledge of tic symptom natural history. Families should know that only probabilistic generalizations can be made about tic symptoms and that nothing certain can be said about future symptom severity for their individual child. No blood tests and no particular aspects of clinical presentation successfully predict the long-term course of symptom severity.

Despite the limitations in prognosticating for individuals, the general prognosis for tic symptoms is relatively optimistic. By early adulthood, nearly one third of TS patients will no longer have tic symptoms. Another third will have milder tic symptoms than they had in childhood, and the remaining third of patients will continue to have relatively severe tic symptoms and functional impairment.[4] Severely debilitating TS in adulthood is a rarity and represents the furthest extent of a very broad spectrum of symptom severity. Preliminary follow-up studies suggest that the relative severity of tic symptoms in childhood is a weak but positive predictor of symptom severity in adulthood, so that relatively mild or severe tic symptoms in childhood tend to predict mild or severe symptoms, respectively, in adulthood.[15]

Despite the genuine cause for optimism concerning the long-term outcome of tic symptom severity, the path leading to the outcome is often rocky. Tics at their onset (usually in early grade school) are most often infrequent and mild. They may, in fact, be initially identified by parents as a mere habit. The tics eventually increase in frequency, forcefulness, or number until they are brought to clinical attention. Families usually have noted by then a distinct tendency for tics to fluctuate in severity, worsening predictably during times of stress. They should be informed that this waxing and waning can be expected to continue in the future. They should also know that this symptom

fluctuation is likely to be superimposed on a trajectory of tic symptom severity that gradually increases up to and during puberty, and that then gradually decreases through adolescence until it reaches a relatively stable level by early adulthood. Occasionally tics will unexpectedly decrease rather than increase during preadolescence, and hoping for this is not unreasonable; but anticipating at least a temporary, though protracted, period of exacerbation in the coming years can be a helpful defense for the child and his family in preparing for the future.

The presence of OCD bodes for a longer period of symptom persistence, usually at least into later adolescence, when tic symptoms are generally on the wane. Unlike the presence of tics, TS-related OCD also carries a higher risk for additional comorbid illnesses that include depression, anxiety disorders, and simple phobias.[8] The modal onset of OCD symptoms is 9 or 10 years of age, and children with tics should not be considered to be out of the window of risk for new onset OCD until they reach later adolescence.[16,17] The presence of obsessions and compulsions should be assessed at regular clinic visits for TS children during this time. ADHD symptoms, on the other hand, are nearly always present at the time of initial clinic visit. If absent, families can be reassured that these symptoms are not likely to arise in the future.

The child's psychosocial supports will change with the child's age and stage of emotional development. These changes further complicate the assessment of the impact of tics on the child's life. The same objective level of tic symptom severity, for instance, may cause little or no impairment in self-esteem early in elementary school, while in later grade school and in early adolescence they can have a much greater impact on self-esteem. These are the years when peers place tremendous importance on physical appearance and group membership, and tics are an easy target for peer teasing and rejection. Children with TS who are well socialized and confident are much more likely to withstand the cruelties of group membership in childhood than are children without these assets. The presence of tics in children of this age who lack confidence and a positive self-regard, on the other hand, may prompt them to see themselves as less attractive and less desirable, even in the absence of peer teasing. Unfortunately, the time when children's narcissistic investment in physical appearance is greatest also happens to be the time when tic symptom severity is at its worst.

Another important developmental consideration is the relatively unusual exacerbation of tic symptoms in mid- to late-adulthood. The rapid or sustained severe exacerbation of tic symptoms at this time warrants a complete medical, neurologic, and psychiatric evaluation. Thyroid abnormalities, new onset anxiety or affective disturbances, substance abuse, early dementing illnesses, and menopause in women seem in our clinical experience to be the most common underlying causes of late-life symptom exacerbation.

PSYCHOTHERAPIES

Supportive Psychotherapy

Educating the child and family about TS natural history and prognosis lays the foundation for all other treatment interventions. By far the most frequent intervention in TS is reassurance and support, and this begins at the time of the initial evaluation. Families are most likely to present for evaluation at a time of symptom exacerbation, and they are therefore often eager for rapid intervention. Similarly, they will call or visit during subsequent symptom exacerbations and will need advice as to what action to take.

Parents must be reminded that symptom severity fluctuates over days, weeks, and even months, and that symptom changes can therefore be evaluated reliably only on a time scale of weeks to months, preferably at least 6 to 8 weeks. If medication is either started or increased during symptom exacerbations that are of briefer duration, a decrease in severity will inevitably be misattributed to the effects of the medication, when in fact it is due to the natural waning of tic symptoms. Increasing medication during acute symptom exacerbations often leads to an upward creep of the dosage to levels that are both unnecessary and more prone to producing bothersome side effects. Encouraging the child and family to try to ride out the acute symptom storm until the symptoms either subside or remain severe long enough to suggest a genuine average worsening of symptoms is nearly always indicated. "What goes up must come down" is a useful rule of thumb. When exacerbations that produce functional interference are temporary but frequent, it may be time to consider beginning a medication that may help dampen the magnitude of the symptom exacerbations, even if this means maintaining the medication during periods of natural symptom waning as well.

Parents will usually ask whether any nonmedication interventions have proven helpful in reducing tic symptoms. Few such treatments have been developed, and unfortunately their efficacies have not received the systematic and rigorous investigation they deserve. Their usefulness is probably modest at best, and very few clinicians with the necessary training are available to institute them even if their efficacies were firmly established.

Mental Imagery

The use of mental imagery has been reported to produce rapid and sustained improvement in tic symptom severity in four children.[18] The authors speculated that this technique, which involves sustained, relaxed attention to pleasant imaginary scenes without the use of an explicit suggestion for tic reduction, is helpful because it gives the child a sense of control over what is experienced (and tic

symptoms, they propose, typically produce a sense of loss of control). Although this may be the correct explanation for the observed symptom reduction with this technique, clinical experience abundantly indicates that with relaxation alone—coming home to relax after a long day at school, for instance—tic symptoms often dramatically increase, not decrease. Clinical experience also suggests, on the other hand, that the sustained absorption of attention and concentration in interesting and enjoyable tasks—it may be playing an interesting game, for instance—typically reduces tic symptoms over the short term, for reasons that are still unknown. The use of visual imagery may exploit this ability of absorbed attention to reduce tic symptom severity. Because of its apparent safety, this often-neglected potential treatment modality warrants further controlled clinical study.

Habit Reversal

This behavioral therapy uses awareness training to prevent or interrupt tic behaviors, competing behavioral responses (such as paced, soft blinking for eyeblinking tics) to prevent specific tics, relaxation techniques to reduce concomitant stress, and reinforcement such as praise by family members to help reduce tic frequency. Open trial data in 5 subjects (children and adults) demonstrated a statistically significant 30% to 50% reduction in tic frequency compared with little or no change in 5 wait-listed control subjects.[19] These preliminary open-trial data must be interpreted cautiously in light of the known placebo response seen in TS treatment studies. Further controlled studies are needed.

Dynamic Psychotherapies

Early reports of the successful treatment of tics with psychoanalysis[20] have not been further substantiated, and clinical experience indicates that dynamic psychotherapies have little or no efficacy in reducing tic symptoms. Yet, in some instances, dynamic psychotherapies that address life stress, anxiety, and depression do seem to be helpful in reducing the severity of tics, probably as a by-product of reducing comorbid symptoms that can exacerbate tics or that can interfere with defense mechanisms that help the patient cope with the presence of tic symptoms. In general, however, dynamic psychotherapies are not indicated in the treatment of TS.

MANAGING COMORBID DISRUPTIVE BEHAVIORS

The Conundrum

"Are the disruptive, aggressive, and oppositional behaviors that can occur in TS patients actually complex tics?" This is the question over which many families, educators, and clinicians can endlessly puzzle, and the one that poses a most difficult treatment dilemma. The issue is whether the behaviors should be regarded as largely involuntary and whether they therefore should be accepted and ignored. This question is a philosophical one that hinges upon the conceptual dichotomies of voluntary and involuntary action, and normal and disease-related behavior. The question is probably unanswerable. It is therefore probably best left to philosophers rather than to parents and clinicians.

The real issue is what practical consequences the behaviors have. The paramount concern is whether the behaviors pose a risk to the safety of the child or others. If the behaviors do pose a risk, then intervention is needed. An additional concern is whether and to what degree the behaviors interfere with the child's social and emotional functioning. If the interference is substantial, intervention again is needed. Oppositionality that interferes with school or family functioning, for example, should be addressed. Some "disruptive" behaviors, on the other hand, such as the touching or tapping of objects, or rough and tumble play, for most children pose little or no risk to safety and generally do not interfere with other realms of functioning. When intervention is warranted for disruptive behaviors, the most effective treatment consists of behavioral management. Medication alone is generally of little help, although the judicious use of medications, especially for comorbid ADHD, can sometimes help the child make better use of behavioral management techniques.

Behavioral Management

This treatment modality is probably still undervalued and it most certainly is still underutilized. Although behavioral management is probably not helpful for reducing tic symptoms, it often is the only therapeutic recourse for managing the disruptive behaviors that can accompany TS. Behavioral management consists of firm and consistent limit setting, the use of "time outs" to help reduce sensory and affective stimulation during periods of acutely worsened behavioral disturbance, and the establishment of a contingency reward system to help shape prosocial behaviors over the longer term.[21] Teaching parents these techniques initially can be somewhat time consuming and labor intensive; once trained, however, parents quickly become expert in the behavioral management of their own particularly challenging child. Clinicians then are only infrequently called upon for consultation. The technique is therefore empowering of the parental authority and support that are needed to help foster an adequate sense of personal safety and self-mastery in their child.

PHARMACOTHERAPIES

Expectations for Tic Symptom Reduction

No known medications suppress tic symptoms completely. This must be made clear to both children and parents. Unrealistic expectations for what medications are able to accomplish can, when those expectations are not

met, quickly disrupt a treatment alliance and provoke a resistance to trying in the future medications that offer a legitimate hope for genuine symptom relief. In addition to preventing a disruption in the treatment alliance, a realistic appraisal of potential symptom relief is, moreover, an ethical imperative when providing informed consent for undertaking the medication trial.

Set Specific and Appropriate Target Criteria

The target criteria for the pharmacotherapy of tics are not as obvious as they may seem. Reducing objective tic symptom severity is only one possible goal, but it is probably more aptly regarded as a means to achieving other, more relevant ends, such as (1) improving self-esteem, if this has been affected adversely by the tics; (2) minimizing peer teasing; (3) reducing distractibility caused by tics; (4) reducing the demands on energy and attentional resources that are required to suppress tics in social, school, and occupational settings; and (5) reducing the interference from tics in motor or speech acts. The unique target criteria for any individual child will be established by the comprehensive assessment of impairment that the tic symptoms produce. The target criteria must be clear to all parties of the treatment alliance, so that a medication trial that reduces impairment, even if the objective improvement in the severity of tic symptoms is small, can appropriately be regarded as a success. Conversely, if impairment is not reduced by the medication, the trial should be regarded as unsuccessful, regardless of whatever reduction in objective tic symptom severity has been achieved.

Start Low and Go Slow

The tics of TS will usually have been present for months or years prior to clinic evaluation, and they almost certainly will be present for years to come. Patience on the part of children, parents, teachers, and clinicians is imperative if pharmacotherapy is to be undertaken thoughtfully and safely. Once the decision to treat with medication has been made, rushing in with agents that are potentially toxic or overly sedating can frighten the parents and child into aborting the medication trial prematurely and into refusing all further trials in the future. The rush to treatment in such an instance has done more harm than good. *Primum non nocere.*

All medications have potential side effects, and those that reduce tic symptoms are no exception. All currently available agents, in fact, are sedating, some more than others. Overly sedating children, especially during school time, is doing them no service; this is particularly true when a potential target criterion is to minimize the interference from tics in learning and attending at school. Sedation from any medication can be minimized simply by starting the medication at a low dose and permitting tolerance to the medication sedative effects to develop by increasing the dose gradually into the therapeutic range. The other possible acute side effects of most medications can be minimized using this same simple strategy.

Addressing Comorbidities

Comorbid illnesses are often the source of greatest functional impairment in TS, and they often can exacerbate tic symptom severity. Treating these conditions effectively can therefore provide proportionately the greatest benefit to TS patients. Assessing whether these comorbid conditions are present is a prerequisite to beginning pharmacotherapy for tics.

TS PHARMACOTHERAPIES

Medication therapies for TS are, frankly, woefully inadequate. The medications that are the most predictably helpful for tics pose the greatest side effect risks, especially for children. Medications that pose the least risk, on the other hand, also benefit the fewest patients. Even when medications are helpful, the degree of tic symptom reduction is rarely robust, and it is too often short-lived. Despite the inadequacies of conventional medications, the recent advent of seemingly effective medications having substantially improved safety profiles has, for the first time in more than a decade, offered genuine hope for a significant treatment advance.

Adrenergic Agonists

The first-line of pharmacotherapy for tics is currently clonidine. Clonidine is an imidazoline derivative whose central pharmacologic action was long thought to be its agonist activity at presynaptic adrenergic autoreceptors. Increased activity of presynaptic autoreceptors reduces activity in postsynaptic adrenergic neurons. Overactivity of central noradrenergic systems is believed to be responsible for the exquisite sensitivity of tics to stress.[22] This belief motivated in part the early attempts with clonidine to reduce tic symptoms by reducing activity in postsynaptic adrenergic systems, thereby attenuating the patient's stress sensitivity.[23,24] Clonidine now, however, is known also to have important direct postsynaptic effects at higher dosages, primarily in the prefrontal cortex.[25] Prefrontal circuits are thought to govern behavioral inhibition through projections to other cortical and subcortical motor centers. It is therefore possible that increasing activity in prefrontal postsynaptic circuitry with clonidine mediates tic symptom reduction.

Initial impressions of clonidine's efficacy have been substantiated in one parallel, double-blind, placebo-controlled study of 40 TS children and adults,[26] although this positive finding was not replicated in a crossover study of 34 TS children with comorbid ADHD.[27] In general, clonidine appears to be clinically helpful in 40% to

50% of patients who tolerate it, and motor tics may improve more than phonic tic symptoms.[26] The dose-limiting side effect is usually sedation, although irritability, lightheadedness, sleep disturbance, and dry mouth are also seen, especially in children. Clonidine should be started at a dose of 0.25 mg once or twice daily to allow tolerance to develop to the sedative effects. The dose can then be increased gradually (changing no more often than every 5 to 7 days) to 0.1–0.3 mg per day in three or four divided doses. Guanfacine, another adrenergic agonist that produces less sedation than clonidine, may have some efficacy in tic symptom reduction (see ADHD treatment, below), although clinical experience is too preliminary to advocate its use in the treatment of tics.

Dopamine Antagonists

Dopamine receptor blockers were historically the first class of medication discovered to improve tic symptoms.[28] The high-potency D_2 receptor blockers haloperidol and pimozide have been the agents most traditionally used and studied in TS, although any of the typical D_2 blockers, including lower potency agents, would probably be helpful for tics. These agents are the most predictably effective medications for tics, decreasing tic severity for 70% to 80% of patients who take them.[29] The side effect profiles of haloperidol, a butyrophenone, and pimozide, a diphenylbutylpiperidine, are similar and include parkinsonism, acute dystonia, akathisia, sedation, sexual dysfunction, and anticholinergic effects.[30] Both carry the risk of tardive dyskinesia with prolonged exposure, and the use of these medications requires close monitoring for the potential emergence of dyskinesia. Early comparison of the side effect and treatment response rates for these two agents suggested that pimozide may be slightly more effective and may produce fewer side effects than haloperidol,[31,32] although the only study that directly compared these two medications indicated that their side effect and treatment response rates were not significantly different.[33] Pimozide may in addition be associated with a variety of electrocardiographic changes that require monitoring, including prolongation of the QT_c interval and the attendant risk for potentially fatal arrhythmias.[33] It is unknown whether the use of these dopamine antagonists alters in any way the natural history of the disorder.

The high-potency agents should be started at a dose of 0.25–0.5 mg/day. Because of the inherent fluctuation of tic symptom severity and the need to assess severity over a time span of weeks to months, the upward dose increments generally should not be instituted more frequently than every 3 to 6 weeks. Doses higher than 3 mg in children and 5 mg in adults are unlikely to provide further improvement in tic symptom control and are increasingly likely to produce untoward side effects that can interfere with academic and occupational performance as well as blunt affect and impair cognition.

The "Atypical" Agents

Because D_2 blockers (the older, so-called "typical" agents) and the serotonin antagonists (the newer "atypical" medications) seem to be effective in treating many of the same disorders, it is plausible that the atypical agents, like the standard D_2 blockers, could be helpful in treating tics. Open trials of the atypical agent risperidone thus far indicate that doses ranging from 0.5–4.0 mg/day may be effective for TS, reducing tic symptom severity by nearly 50%.[34,35] The profile of possible side effects is similar to that for haloperidol and pimozide, although the incidence of side effects seems to be far less with risperidone. The markedly reduced risk of tardive dyskinesia makes this new class of medication particularly attractive, offering the promise of treatment responsiveness similar in degree to haloperidol and pimozide but witha side effect and safety profile that is as good as or possibly even better than clonidine. Controlled clinical trials of risperidone and open trials of newer atypical agents are now underway.

Risperidone, a benzisoxazole derivative, is a high-potency antagonist of the serotonin 5-HT_2 receptor subtype and a much weaker antagonist of the dopamine D_2 receptor. Its mechanism of action in treating tic disorders is unknown, although it may derive its efficacy in part through blockade of serotonergic projections to the ventral striatum,[36] a brain region implicated repeatedly in the pathophysiology of TS.[37–39] Its modest D_2 blocking properties are likely responsible to some degree for its efficacy, since clozapine, another serotonin 5-HT_2 receptor blocker with more potent D_1 and D_4 blocking activity, seems not to benefit tic symptoms, and may even exacerbate them.[40]

More Experimental Agents

With rare exception, other medications that may have some effectiveness in reducing tic symptoms have been studied only in uncontrolled, open trials. The benzodiazepine clonazepam in combination with neuroleptics produced a broad range of reduction in tic symptom severity for 7 TS adolescents and adults,[41] and a 50% mean reduction in 7 TS children with ADHD treated adjunctively with clonidine.[42] Endogenous benzodiazepines are important neurotransmitters in the basal ganglia, providing a reasonable theoretical rationale for a trial of this relatively safe medication either alone or in combination with more traditional tic medications when augmentation of the therapeutic response is needed. Clonazepam may be particularly likely to reduce tic symptoms in adults who have comorbid anxiety disorder.

The addition of nicotine chewing gum to haloperidol administration has been reported to be effective in 10 TS children. The nicotine gum reduced tic symptoms and improved attention in 80% of the children, although beneficial effects lasted less than an hour, and 70% stopped using the gum because of nausea or poor taste.[43] A transdermal nicotine patch has been tried with some success in

children and adults taking neuroleptics, although these are results of uncontrolled open trials,[44,45] and the potentiation effects are probably short-lived. Nicotine in the absence of neuroleptic medication produced no improvement.[43]

Several case reports have suggested that hormonal manipulation may be helpful in reducing tic or OCD symptoms.[46–49] A double-blind crossover trial of the androgen receptor blocker flutamide compared with placebo in 13 TS adults has recently demonstrated a significant improvement in motor tic severity (Peterson BS, Zhang H, Bondi C, et al. Manuscript submitted). Although the medication was well tolerated, it appeared to lose its efficacy after several months of administration, possibly because physiologic compensatory mechanisms were successful in overriding or bypassing the androgen receptor blockade. Because of this short-lived response and the potential for serious adverse side effects of prolonged use in children, antiandrogens are unlikely to earn an important place in the treatment armamentarium for TS. The importance of these medication trials consists primarily in potentially explaining some portion of the difference between sexes in TS prevalence,[50] the disorder being 4 to 10 times more common in boys than in girls.

PHARMACOTHERAPY FOR COMORBID ADHD

ADHD affects nearly 50% of children in TS clinic populations. Inattention and distractibility often impair academic performance, and impulsivity can disrupt relationships with family and friends. The risk that continuing ADHD poses in general for the future development of conduct disorder, substance abuse, anxiety, and affective disorder is well documented[13,51] and warrants close clinical attention and diligent attempts at intervention. The co-occurrence of tics and ADHD poses unique pharmacologic treatment challenges.

Stimulant Medications

Clinical anecdote has long suggested that stimulant medications, the usual first line of pharmacotherapy for ADHD, can worsen tic symptoms. Recent more systematic investigations have provided support for this contention. Retrospective studies have indicated a worsening of tics in 30% to 50% of children with ADHD and tics who take stimulants, and the development of tics in 10% of ADHD children who did not have tics previously.[52–54] One prospective crossover study administered low to mid-range dosages of methylphenidate for 2 weeks to children with ADHD and tics. A dose-related increase in motor and vocal tic severity was seen in clinician ratings, although teachers rated vocal tic severity as less.[55] This apparent contradiction between clinician and teacher ratings of severity might by explained by the possible improvement in behavioral disruption that stimulants can produce, which the teachers could then have confounded with an improvement in tic symptoms.

Despite these strong indications that stimulants pose a serious risk of tic symptom exacerbation, the presence of tics is not an absolute contraindication to the use of stimulants in the treatment of ADHD. In rare instances, stimulants can produce a dramatic improvement in school performance and ADHD symptoms without producing a discernible functional impairment due to acute tic symptom exacerbation. It should be emphasized that the long-term effects of stimulant use on the natural history of tics or OCD symptoms are unknown, and some epidemiologic data implicate stimulant exposure in the etiology of OCD.[56] The risk/benefit assessment for these children who benefit dramatically from stimulants (and who do not benefit from other ADHD medications) is therefore particularly complex. It is recommended that the prescribing of stimulants to a child who has tics be undertaken by an expert in the natural history and pharmacotherapy of tic disorders. Carefully documented informed consent, preferably even informed written consent, is important whenever prescribing stimulant medication to individuals who have a personal or family history of tics.

Tricyclics

The efficacy of tricyclic medications, most commonly desipramine, in the treatment of ADHD has been well documented.[57–59] Desipramine also appears to be useful for the treatment of ADHD that occurs concomitantly with tics. A retrospective chart review of the use of desipramine in 33 children who had both tics and ADHD indicated an improvement in both tics and ADHD symptom severity,[60] and an open trial reported a moderate or marked improvement in ADHD symptoms without tic exacerbation in 5 of 7 children who had ADHD and tics.[61] A controlled double-blind crossover trial of desipramine (25 mg q.i.d.), clonidine (0.05 mg q.i.d.), and placebo in 37 subjects showed desipramine to be superior to both clonidine and placebo for ADHD symptoms. A trend toward reduction in tic symptoms was also seen during desipramine administration.[27] The dosing of desipramine in these studies was to typical antidepressant levels.

The obvious advantage to the use of tricyclics in TS with comorbid ADHD, if their efficacy is confirmed, is that improvement in ADHD symptoms can be achieved in some children without exacerbating tic symptoms, and perhaps while even improving them (although in our experience, occasionally tic symptoms do seem to worsen in some individuals even with tricyclic medications). The main disadvantage to the use of tricyclics, and desipramine in particular, are the four case reports of sudden death in children taking desipramine.[62–64] The risk of sudden death has not yet been associated with the other antidepressants; nortriptyline has therefore largely supplanted desipramine in the treatment of ADHD in children, although its efficacy has yet to be firmly established.[65]

Adrenergic Agonists

The adrenergic agonists clonidine and guanfacine are the usual first-line agents for the treatment of ADHD in the presence of tics. Unlike stimulants, they do not exacerbate tics, and they possibly could even improve tic symptom severity. Unlike the tricyclics, they pose negligible cardiac risk. Both are α_2-agonists whose efficacies are thought to derive from their affinity for the α_{2A}-adrenergic postsynaptic receptors in prefrontal cortex, the purported substrate for the working memory components of attention and behavioral inhibition. Guanfacine has more activity at this α_{2A}-receptor subtype, which is thought to be responsible for its greater efficacy in enhancing working memory of nonhuman primates.[25] Clonidine has greater affinity for the α_{2B}-receptor subtype that is located primarily in the thalamus, which may be responsible for its greater proclivity to produce sedation. Clonidine has a short half-life (4–10 hours) and requires three to four times per day dosing, whereas guanfacine's longer half-life (10–30 hours) allows for two to three times per day dosing, a potential advantage for children in school settings.

Of the two medications, clonidine has the more proven track record. It has been shown to be effective for ADHD without tics[66] and for TS without ADHD.[26] It is therefore reasonable to assume that clonidine is likely to be helpful for ADHD that occurs comorbidly with tics, although in the only double-blind crossover study to directly test this hypothesis, clonidine was not significantly better than placebo, and desipramine was better than clonidine, in treating ADHD symptoms.[27]

Open-trial data support the use of guanfacine in the treatment of ADHD. An average of 3.2 mg/day of guanfacine in 13 ADHD children and adolescents without tics was helpful and well tolerated.[67] Ten children with TS and ADHD taking 1.5 mg/day of guanfacine showed improvement in ADHD and tic symptoms in another open trial.[68] Dosing of the medication is started at 0.5 mg/day and increased gradually up to 3 mg/day divided into two or three doses.

More Experimental Modalities

The stimulant-like structure of bupropion has prompted speculation that it might be useful in treating ADHD symptoms without appreciably worsening tics. One case series of four children has thus far suggested, however, that bupropion's stimulant-like effects may include a propensity for worsening tic symptoms.[69]

Other investigators have used L-deprenyl (selegilene), an MAO inhibitor, in an attempt to achieve stimulant-like effects on the monamine system in ADHD children without exacerbating tics. L-Deprenyl is an irreversible inhibitor of MAO-B that in doses of 15 mg/day or less does not affect MAO-A. These modest doses of L-deprenyl do not require dietary restriction. L-Deprenyl is metabolized to L-amphetamine and methamphetamine, however, and the biological activity of these compounds raises the theoretical possibility that they could worsen tic symptoms. An open trial of 29 children with ADHD and tics reported that deprenyl produced a clinically meaningful reduction in ADHD symptoms in 90% of the children without exacerbating tics.[70]

TREATMENT OF OCD COMORBIDITY

OCD affects 30% to 60% of all TS subjects. The OCD that afflicts the families of TS patients is thought to be a variable manifestation of the putative TS vulnerability gene. OCD is therefore currently believed to consist of at least two biological subtypes, OCD that is and OCD that is not related to TS. This biological subtyping may have important treatment implications in that the OCD that occurs in the context of a personal or family history of tic disorders may be less responsive to standard antiobsessional agents.[71] When standard antiobsessional agents fail or produce less than desirable treatment response, the addition to ongoing antiobsessional therapy of a low-dose tic medication (either a typical or atypical agent) seems to augment the response considerably for tic-related but not non-tic-related forms of OCD.[72]

The general treatment scheme for TS-related OCD therefore consists of the initial use of standard antiobsessional agents, such as fluoxetine 10–40 mg/day, fluvoxamine 25–200 mg/day, or clomipramine 25–200 mg/day. The younger the child, the lower will be the effective and maximum tolerated dosages. Children are typically more sensitive than are adults to the activating effects of fluoxetine and fluvoxamine in particular, and children also are more sensitive to the sedative effects of clomipramine. These side effects usually limit the dosage of medication that can be tolerated. For young children who dislike or refuse to swallow capsules, the elixir formulation of fluoxetine is usually tolerable.

These antiobsessional medications have been reported to produce tic symptom exacerbation in some children,[73] although the magnitude of this problem clinically does not seem to be large. When side effect–induced dose limitations or inherent limitations in treatment responsiveness produces unsatisfactory therapeutic gains from these medications alone, the addition of a low dose of a D_2 or 5-HT_2 blocking agent can be considered. Dosages between 0.5 and 1.5 mg of haloperidol, or 0.5 and 2 mg of risperidone, are usually sufficient to augment the treatment response.

TREATMENT OF COMORBID AFFECTIVE AND ANXIETY DISORDERS

TS symptoms can be exquisitely stress sensitive.[22] Affective illnesses (either major depression or bipolar disorder) and anxiety can be thought of as endogenous stressors

that exacerbate tic symptoms. In our clinical experience, some of the most severely affected children with TS, and those who remain more severely symptomatic into adulthood, are more likely to suffer from severe anxiety, major depressive, and bipolar disorders. The possible presence of these disorders must be carefully assessed in children who are severely symptomatic, in adults who remain symptomatic, and in previously symptomatic adults whose symptoms inexplicably worsen. Successfully treating comorbid anxiety and affective disorders with medication or psychotherapy in these instances can reduce tic symptoms considerably.

Comorbid major depressive and bipolar disorders in children are treated much like they would be in adults, with the usual caveats about starting medications at low dosages and titrating slowly. Anxiety disorders in children seem generally to be less responsive to benzodiazepines and to alternative anxiolytics such as buspirone. Antidepressants and psychotherapy seem to be more clinically helpful for children suffering from an anxiety disorder.

CONCLUSION

Therapeutic wisdom is predicated upon a deep understanding of the nature of the disease process being treated. The deep understanding of Tourette's syndrome involves the recognition of a specific genetic vulnerability that will, under the appropriate environmental circumstances, develop into a particular complex of TS-related symptoms having a characteristic evolution over the course of an individual's development. The functional consequences of these genetic, environmental, and developmental determinants will be further influenced by the individual's coping abilities and adaptive strengths. Effective clinical management will recognize the ways in which heritability, comorbidity, family and social support, and individual coping mechanisms determine the individual's specific clinical presentation at each stage of development, and the ways in which these determinants can be modified and utilized most effectively for therapeutic aims.

Drug names: bupropion (Wellbutrin), buspirone (BuSpar), clomipramine (Anafranil), clonazepam (Klonopin), clonidine (Catapres), clozapine (Clozaril), desipramine (Norpramin and others), fluoxetine (Prozac), flutamide (Eulexin), fluvoxamine (Luvox), guanfacine (Tenex and others), haloperidol (Haldol and others), methylphenidate (Ritalin), nortriptyline (Pamelor and others), pimozide (Orap), risperidone (Risperdal), selegilene (Eldepryl).

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