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Pharmacological treatment of Tourette syndrome

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ABSTRACT

Tourette syndrome (TS) is a highly heritable yet heterogeneous childhood onset disorder. The cardinal movement disorder required for diagnosis is tics. As persons with tics or TS often have obsessive/compulsiveness, inattention, hyperactivity, impulsivity, anxiety, and anger outbursts, the presence of tics should prompt clinicians to look for these other conditions. While randomized controlled trials provide valid evidence of efficacy for symptoms in isolation, implications for treatment of complex patients meeting criteria for multiple diagnoses is not always clear. In this review, the authors critically review factors influencing decisions whether and how to treat medically tics as well as OCD and ADHD in the presence of tics.

1. Introduction

Tics, the cardinal symptom of Tourette syndrome (TS), are patterned involuntary, "unvoluntary" (compelled by inner urge), or habitual movements (motor tics) or sounds (phonic tics), often preceded by a premonitory sensation (Dooley, Gordon, Wood, Camfield, & Camfield, 2003; Jankovic, 2001; Kurlan, 2010; Kompoliti & Goetz, 1998). The premonitory phenomenon helps in differentiation of tics from other jerk-like movements such as myoclonus and chorea, which occur without preceding urges (Kwak, Dat Vuong, & Jankovic, 2003; Woods, Piacentini, Himle, & Chang, 2005). Tics are quite common in otherwise normally developing children (Snider, Seligman, & Ketchen, 2002) and are approximately twice as common in children receiving special education services as those who are mainstreamed (Kurlan, 1994; Kurlan, Como, & Miller, 2002; Kurlan, Whitmore, Irvine, McDermott, & Como, 1994; Palumbo, Maughan, & Kurlan, 1997).

Although generally considered childhood disorders, tics can persist into adulthood, but usually with lower frequency and reduced intensity (Bloch & Leckman, 2009; Bloch, Peterson, & Scahill, 2006; Leckman, Zhang, & Vitale, 1998; Pappert, Goetz, Louis, Blasucci, & Leurgans, 2003). Adult onset tics usually represent re-emergence of childhood onset tics, but other causes of tics besides TS, such as drugs (e.g. CNS stimulants, cocaine, neuroleptics), Huntington disease, neuroacanthocytosis, autism, and other neurological disorders should be considered as possible etiologies. Most clinical trials and studies address treatment of tics in childhood, but some, particularly studies of new medications or other treatments, include or focus on adults (Chae, Nahas, & Wassermann, 2004; Gilbert, Budman, Singer, Kurlan, & Chipkin, 2014; Jankovic, Jimenez-Shahed, & Brown, 2010; Okun, Foote, & Wu, 2013; Scahill, Leckman, Schultz, Katsovich, & Peterson, 2003; Wilhelm, Peterson, & Piacentini, 2012).

Achieving the most effective treatment of tics in TS is contingent on proper diagnosis of the movement disorder and judicious use of available interventions. In many cases, no medication is needed and simple reassurance will suffice. When medication is prescribed, the goal is to reduce the tic frequency and intensity so that the tics no longer impair the patient's function at home, school, or at work, and no longer interfere with social activities and interactions. Achieving the most effective and safest treatment of the child or adult with TS requires thorough assessment and treatment for other cognitive and emotional problems (Carter et al., 2000; Gilbert, 2006; Singer, 2005; Zinner, 2004). Effective pharmacologic treatment is aided by collaborative, realistic assessment with the individual and family of tic-related and comorbidity-related impairment.

Treatment of tics in TS has been the subject of a number of excellent review articles (Jankovic & Kurlan, 2011a; McNaught & Mink, 2011; Wu, Harris, & Gilbert, 2010). These reviews include guidelines for medication selection, dosing, and monitoring for side effects. In this paper we will focus our review on oral pharmacological treatment for tic, ADHD, and OCD symptoms in TS but also discuss more broadly the issues influencing treatment decisions. In addition to oral medications, many patients with TS manifested chiefly by focal tics, such as blinking and cervical tics, may be treated with local injections of botulinum toxin (Kwak, Hanna, & Jankovic, 2000; Marras, Andrews, Sime, & Lang, 2001). This approach is particularly effective in the treatment of repetitive head jerking (so called

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"whiplash" tics), that can cause secondary myelopathy, and other potentially disabling tics (Dobbs & Berger, 2003; Krauss & Jankovic, 1996; Lin, Wang, Wong, Wu, & Lin, 2007; Muroi et al., 2002). Some tics are so severe and even life-threatening (hence the term "malignant TS") (Cheung, Shahed, & Jankovic, 2007) that they cannot be managed medically and in such cases deep brain stimulation may be considered (Mink, Walkup, & Frey, 2006). This therapeutic intervention is beyond the scope of this review and is covered elsewhere in this volume.

2. Treatment of the non-tic symptom spectrum in TS

2.1. Who should treat TS and its comorbidities?

An important treatment issue in TS is where to seek treatment if the primary care physician and/or patient desire specialty care. Often in persons with TS, cognitive, behavioral and emotional problems cause far more impairment than tics (Bernard, Stebbins, & Siegel, 2009; Carter et al., 2000). In both community and clinic settings, the majority of children and adults with tics or TS also have troublesome non-tic problems including symptoms of Attention Deficit Hyperactivity Disorder (ADHD), Obsessive Compulsive Disorder (OCD), other forms of anxiety, substance abuse, aggression, or anger control difficulties (Comings, 1994; Freeman, 2007; Kurlan et al., 2002; Zinner, 2004). Genetic studies also clearly demonstrate high rates of these same problems in families of TS probands, including both parents ("bilineal transmission") and even in family members who do not have tics (Comings & Comings, 1990; Grados & Mathews, 2008). Children diagnosed with autistic spectrum disorders often present with tics and may meet criteria for TS (Canitano & Vivanti, 2007; Comings & Comings, 1991; Lawson-Yuen, Saldivar, Sommer, & Picker, 2008). Thus whether we consider ADHD or OCD "comorbidities" of TS or manifestations within the spectrum of a heterogeneous neurobehavioral disorder, physicians involved in the management of patients with TS must be skilled in not only treating tics but the entire spectrum of symptoms that commonly affect patients with TS.

The roles of neurologists and psychiatrists have traditionally lead to fractionated care, particularly when the mental health diagnoses receive different (less) reimbursement by health insurance companies which prioritize medical (neurological) over mental health coverage. However, there are a number of other disorders in which neurological and psychiatric symptoms commonly co-exist. In addition to TS, other examples of such overlap include the adult and childhood epilepsies (Brodie, Chadwick, & Anhut, 2002; Franks, 2003; Hesdorffer et al., 2004), multiple sclerosis (Patten, Fridhandler, Beck, & Metz, 2003; Patten & Metz, 1997), cerebrovascular diseases (O'Brien, Erkinjuntti, & Reisberg, 2003; Robinson, 2003; Taragano, Allegri, Vicario, Bagnatti, & Lyketsos, 2001), Parkinson's disease (Klaassen et al., 1995; Mindham, Marsden, & Parkes, 1976), tardive dyskinesia (Klaassen et al., 1995), and Huntington's disease (Bonelli, Wenning, & Kapfhammer, 2004). Thus in these and many other neurological conditions, neurologists should be skilled in managing the associated behavioral or psychiatric problems. Given the high prevalence of movement disorders in psychiatric patients, it is similarly reasonable for psychiatrists to feel some level of comfort with diagnosis and evaluation of movement disorders. In many cases, the best approach is for these disciplines to work collaboratively with multiple specialties to provide the most comprehensive and expert care.

With these considerations in mind, clinicians who see large numbers of TS patients should be prepared to treat non-tic symptoms of TS. A reasonable expectation might be that neurologists providing or directing fairly comprehensive care for TS would treat ADHD and OCD in many cases, but refer to psychiatrists those TS patients manifesting severe OCD, psychosis, auditory hallucinations, mania, and suicidal ideation. Similarly, psychiatrists treating TS would treat tics in many cases, but might refer to neurologists patients demonstrating particularly severe tics, suspected seizures, drug induced movement disorders, suspected secondary tic disorders, or progressive cognitive impairment.

2.2. Evidence-based treatment of ADHD in persons with TS

Most double blind, randomized, placebo-controlled clinical trials of treatments for behavioral diagnoses attempt to recruit a relatively pure sample of individuals whose impairing symptoms emanate from the primary diagnosis. Thus, subjects who suffer from other DSM-V diagnoses are typically excluded, particularly if these other diagnoses are severe enough to require current treatment. In the cases of conditions like TS, where meeting criteria for two or more DSM-V diagnoses is the rule rather than the exception, this practice favors validity at the expense of generalizability (Gilbert & Buncher, 2005). As most studies have been small, and the majority of large, rigorous clinical trials of ADHD and OCD treatment exclude TS, it is difficult to know whether estimates of effect size in clinical trials are generalizable to TS in the community. Furthermore, while the practice of evidence-based medicine is encouraged, it is important to acknowledge that most patients with TS referred to a specialty clinic would be excluded from the controlled trials that provide "the evidence".

Treatment of ADHD in TS is more complicated than treatment of ADHD without co-occurring TS, for at least two main reasons. First, in some individuals with TS, tics or other repetitive behaviors may worsen when stimulant medications are prescribed for ADHD. That is, even when inattention, hyperactivity, and impulse control problems reliably and reproducibly diminish on stimulants, tics, compulsions, or stereotypies can concurrently escalate, often in a dose-sensitive (Bloch, Panza, Landeros-Weisenberger, & Leckman, 2009) fashion. While observed by clinicians for many years, this stimulant-induced exacerbation is not a universal occurrence and indeed may be quite uncommon (Denckla, Bemporad, & MacKay, 1976; Tourette Syndrome Study Group, 2002). In such cases, a more beneficial outcome may be achieved with nonstimulants for ADHD, such as atomoxetine, or combining a stimulant with an alpha 2 adrenergic agonist or a dopamine receptor blocking agent or tetrabenazine. Indeed, when patients present with the combination of troublesome tics and ADHD we often treat the tics first and add a stimulant later. This strategy should be carefully explained to the patients and their parents, particularly those who (often incorrectly) perceive this risk of stimulants outweighing their potential benefits. A second important challenge in TS is the potential for diagnostic misclassification of both inattention and hyperactivity symptoms of ADHD. In TS with anxiety, OCD, or high functioning autism, sometimes what appears by observation or standardized DSM-V based ratings (Conners, Sitarenios, Parker, & Epstein, 1998; DuPaul, Power, Anastopoulos, & Reid, 1998; Wolraich et al., 2003) to be a *deficit in attention* is actually wholly or in part a *misdirection of attention* ("attention direction disorder"). The individual with TS, instead of paying attention to what is salient to the rest of the classroom or family, may attend to internal premonitory tic urges, poorly filtered sensations, obsessions, ruminations, or areas of special interest. In such cases, treatment with a stimulant may increase the child's internally directed focus. The result can be increased tics, increased OCD symptoms, increased autistic behavior or stereotypies, marked agitation, or what parents sometimes describe as a "zombie" phenomenon where empathy is further diminished and/or the child's spontaneity and creativity are stultified. Clinical experience suggests that many such children

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