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Treatment-refractory Tourette Syndrome

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ABSTRACT

Tourette Syndrome (TS) is a complex neurodevelopmental condition marked by tics and frequently associated with psychiatric comorbidities. While most cases are mild and improve with age, some are treatment-refractory. Here, we review strategies for the management of this population. We begin by examining the diagnosis of TS and routine management strategies. We then consider emerging treatments for refractory cases, including deep brain stimulation (DBS), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and novel pharmacological approaches such as new vesicular monoamine transporter type 2 inhibitors, cannabinoids, and anti-glutamatergic drugs.

Contents

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1. Introduction

Tourette Syndrome (TS) is a complex neurodevelopmental condition marked by tics as well as a variety of psychiatric comorbidities. When tics are severe enough to impact quality of life, patients may not respond to or tolerate treatment. Here, we review strategies for the management of treatment-refractory TS. To help in the conceptualization of these strategies, we briefly review the diagnosis of TS and routine management strategies. We then consider definitions and clinical characteristics of treatment-refractory TS and the role of psychiatric comorbidities in apparent refractoriness. Finally, we examine potential new treatments, including deep brain stimulation (DBS), electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and novel pharmacological approaches.

1.1. Epidemiology and diagnosis of Tourette Syndrome

Tourette Syndrome (TS) is frequently encountered by both psychiatrists and neurologists. Diagnostic standards for TS are established by the 5th Edition of American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) (APA, 2013). According to DSM-5 criteria, a tic is "a sudden, rapid, recurrent, non-rhythmic … movement or vocalization," and TS should be diagnosed when a patient has exhibited both multiple motor and one or more vocal tics over the course of at least one year, with onset prior to age 18. DSM-5 also requires that abnormal movements cannot be better attributed to another medical condition such as Huntington disease or the effects of a substance like cocaine. The syndrome is relatively common, with an estimated overall prevalence of 0.77%–1.1% (Cubo, 2012). The age of onset varies from 2–21, with a mean age of onset of 7 for motor tics, and a mean age of onset of 11 for phonic tics (Robertson, 2008a, 2008b).

1.2. Treatment of non-refractory Tourette Syndrome

Existing treatment guidelines for TS vary slightly, but share several features. In each case, it is recommended that patients with tics first receive psychoeducation (Cath et al., 2011; Muller-Vahl et al., 2011; Roessner et al., 2011; Verdellen et al., 2011; Shprecher et al., 2014). If there is an indication for treatment (i.e., tics are disruptive or reduce quality of life), then the preferred initial intervention is some form of behavioral therapy, which may include Comprehensive Behavioral Intervention for Tics (CBIT) (Himle et al., 2014), Habit-Reversal Therapy (HRT), or Exposure and Response Prevention (Bate et al., 2011; Dutta and Cavanna, 2013; Wile and Pringsheim, 2013).

Alpha-2 agonists, namely clonidine and guanfacine, are often considered first-line pharmacotherapy for tics (Pringsheim et al., 2012), and both clonidine (McKeith et al., 1981; Leckman et al., 1982, 1985, 1991; Goetz et al., 1987; Roos et al., 1987; Gancher et al., 1990; Gaffney et al., 2002; Hedderick et al., 2009) and guanfacine (Chappell et al., 1995; Fras, 1996; Cummings et al., 2002) have a substantial evidence base. Many providers also consider atypical (second-generation) antipsychotics to be first-line treatments, and some guidelines support this (Roessner et al., 2011). Controlled trials support the use of pimozide, haloperidol, fluphenazine, risperidone, aripiprazole, olanzapine, and quetiapine (Ross and Moldofsky, 1978; Shapiro et al., 1983, 1989; Goetz et al., 1984; Shapiro and Shapiro, 1984; Bruun and Budman, 1996; Sallee et al., 1997; Onofrj et al., 2000; Bruggeman et al., 2001; Dion et al., 2002; Gaffney et al., 2002; Mukaddes and Abali, 2003; Scahill et al., 2003; Copur et al., 2007; de Jonge et al., 2007; Copur et al., 2011; Wijemanne et al., 2014). There is less evidence to guide the choice of one antipsychotic over another, with most comparative studies suggesting similar efficacy and tolerability (Ross and Moldofsky, 1978; Shapiro and Shapiro, 1984; Shapiro et al., 1989; Sallee et al., 1997; Bruggeman et al., 2001).

Treatment of TS with tetrabenazine, a vesicular monoamine transporter type 2 (VMAT2) inhibitor that causes presynaptic dopamine depletion (Asher and Aminoff, 1981; Jankovic, 1982; Jankovic and Orman, 1988), is also supported by considerable clinical experience, though all published data is strictly open label (Jankovic et al., 1984; Jankovic and Rohaidy, 1987; Singh and Jankovic, 1988; Paleacu et al., 2004). In the US, tetrabenazine is approved only for the treatment of chorea associated with Huntington Disease (Frank, 2010), but in Europe and Canada it is approved for other hyperkinetic conditions, including TS (Chen et al., 2012).

Finally, botulinum toxin has well-established efficacy for other hyperkinetic movement disorders (Simpson et al., 2008) and has been utilized with some benefit in TS (Salloway et al., 1996; Trimble et al., 1998; Marras et al., 2001; Porta et al., 2004; Aguirregomozcorta et al., 2008; Vincent, 2008). In general, its utility is limited to simple, focal tics, where a local intervention is appropriate. It should be considered primarily when the severity of the tic makes it disabling or potentially injurious, as with a "whiplash" tic causing risk for radiculopathy or myelopathy (Kwak and Jankovic, 2000; Kwak et al., 2000).

2. Characterization of treatment-refractory Tourette Syndrome

2.1. Apparent refractoriness

As with other medical conditions, inadequate response after multiple therapeutic trials can be a frustrating experience for both the patient with TS and for his or her provider. Nevertheless, it is important to carefully assess the adequacy of those therapeutic trials and the reasons they appear to have failed before declaring a patient's condition to be treatment-refractory, since some patients with TS may appear to be treatment-refractory without actually being so. For example, a child with TS referred for "refractory" symptoms had previously had a poor response to low doses of topiramate (i.e., 50 mg per day). He was subsequently tried on neuroleptics, which produced weight gain and other side effects. Upon re-challenge with higher doses of topiramate, his tics were substantially improved (JJS, personal communication). Incorrect diagnosis is a second potential reason to mischaracterize a patient as having refractory TS, as tardive dyskinesia, myoclonus, or psychogenic movement disorders can sometimes be mistaken for tics. The reader is referred to a general review of hyperkinetic movement disorders, such as (Fahn, 2011), for guidance on distinguishing these symptoms. Third and more commonly, a patient may appear to fail an effective drug because the side-effects of the medication are intolerable. For instance, he or she may have an adequate reduction in tics while taking guanfacine, but find it excessively sedating. This may lead to complaints of poor response and a request for a medication change, or to reduced adherence to the medication, resulting in relapse. Providers must be aware of the side-effect profile of medications used for TS and employ strategies to mitigate those side-effects to preserve therapeutic response. Fourth, patients may appear to be refractory simply because they have not had access to all available therapies (including expert psychiatric care and behavioral therapy). One of the coauthors (DRS) followed an adult male patient who received DBS for refractory TS, but continued to have intermittent and severe periods of tic exacerbation.