

Pediatric Psychopharmacology:

Psychopharmacology of Tic Disorders

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Abstract

Introduction: Tics disorders and Tourette syndrome are commonly encountered in clinical practice. Currently, a vast number of behavioural, pharmacological and surgical treatments are available. **Methods:** Relevant and recent articles about clinical features, neurobiology and treatment of tic disorders and Tourette syndrome were reviewed and summarized. **Results:** Tic disorders and Tourette syndrome are frequently associated with comorbid conditions such as obsessive compulsive symptoms, attention deficit and hyperactivity disorder, anxiety and depression, behavioural disorders and sleep difficulties. Frontostriatal circuits and the dopaminergic system are believed to be involved in the pathophysiology of TS and tics. Pharmacological options that have been studied for treatment of tic disorders are reviewed. Behavioural therapy such as habit reversal training, and surgical treatment are other options. It is essential to identify and address comorbid conditions such as attention deficit disorder, obsessive-compulsive symptoms, depression, behavioural disorders and sleep disturbances, as they often cause more distress and disability than the tics themselves. **Conclusion:** Tic disorders frequently do not require pharmacological treatment, but if required, first line treatment options include dopamine modulators, tetrabenazine, clonidine and behavioural therapy.

Key words: tics, tourette, TS, obsessive-compulsive, ADHD

Résumé

Introduction: Les tics et le syndrome de la Tourette se retrouvent fréquemment dans la pratique clinique. Il existe actuellement un grand nombre de traitements comportementaux, pharmacologiques et chirurgicaux. **Méthodologie:** Les auteurs analysent et résumant les articles récents sur les aspects cliniques, la neurobiologie et le traitement des tics et du syndrome de la Tourette. **Résultats:** Les tics et le syndrome de la Tourette s'accompagnent souvent de troubles obsessionnels compulsifs, du trouble de déficit d'attention avec hyperactivité (TDAH), d'anxiété, de dépression, de troubles comportementaux et de problèmes de sommeil. On pense que les réseaux fronto-striataux et le système dopaminergique sont impliqués dans la pathophysiologie du syndrome de la Tourette et des tics. L'article présente les différentes médications utilisées pour traiter les tics, ainsi que d'autres options comme la thérapie comportementale orientée vers une modification des habitudes, et la chirurgie. Il est essentiel de détecter les comorbidités (déficit d'attention avec hyperactivité, troubles obsessionnels compulsifs, dépression, troubles du comportement et problèmes de sommeil), car elles causent souvent une plus grande détresse et sont plus handicapantes que les tics eux-mêmes. **Conclusion:** Bien que les tics exigent rarement de traitement pharmacologique, les traitements de première intervention incluent les modulateurs de la dopamine, la tétrabénazine, la clonidine et la thérapie comportementale.

Mots clés: tics, Tourette, syndrome de la Tourette, trouble obsessionnel compulsif, TDAH

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Introduction

Tic disorders including Tourette syndrome (TS) are common. Approximately 5% (range 4-19%) of school-aged children are estimated to have tics and 1% (range 0.5 to 4%) have Tourette syndrome. However, prevalence estimates are extremely variable due to the wide spectrum of severity, fluctuations of the symptoms, and lack of consensus regarding the syndrome definition. Establishing the presence of tics and differentiating these from other movement disorders is usually a simple task. Priorities are to classify the tics and to seek the presence of comorbid conditions, as these are often the major contributor to patient distress. Many pharmacologic and behavioural treatments are currently available, and it becomes the clinician's challenge to decide whether treat-

ment is required, and if so, to choose between the large amounts of treatments available.

This review summarises the clinical features of tics and associated comorbid conditions, presents briefly the neurobiology and discusses the treatment options.

Phenomenology of Tics

Tics are repetitive, sudden, rapid, non-rhythmic, stereotyped movements which usually occur in response to a sensation or an urge and often occur in bouts. Motor tics usually manifest first in the head and face and then migrate to more distal regions. The most frequent motor tics are eye blinking and orofacial grimaces. Throat clearing, shouting and simple non-verbal sound are most the common vocal tics. Tics are considered complex when

they involve several segments or when they appear goal-directed. Examples include touching, smelling, hitting, imitating actions (echopraxia) or repeating words (echolalia). Coprolalia, an involuntary verbalization of obscene or scatological words, appears only within a minority of subjects and it is often a temporary manifestation (Erenberg et al, 1986).

Tics are usually preceded by a localized sensation or a general discomfort which is relieved by production of the tic. Tics can be briefly inhibited voluntarily, but at the expense of an increasing urge to express them. This suppressibility and urge are important characteristics in helping to differentiate tics from other movement disorders such as tremor, dystonia, chorea or myoclonus.

Tics can be reduced by concentration on voluntary tasks, which activate fronto-striatal circuits. They can also be exacerbated by stress and fatigue (Hoekstra et al, 2004; Lin et al, 2007). Tics are suggestible and evolve over time; new tics replace old ones, can be evoked by discussing them with the patient, and can develop through observation of other people's tics (Woods et al, 2001).

Natural History of Tics

Transient tics are frequent among young children (Banaschewski et al, 2003; Gaze et al, 2006). The median age of tic onset in TS patients is 5-7 years and 96% of patients will have symptoms by age 11 (Robertson et al, 2001). Despite the fact that diagnostic criteria require onset before age 21, tics can uncommonly commence during adulthood (Chouinard et al, 2000).

An irregular evolution is characteristic of tic disorders, with exacerbation periods interspersed with remissions. Tic severity generally peaks between 8 and 15 years (Leckman et al, 1998). In the majority, symptoms subside during adolescence and are much less noticeable by adulthood; however, a majority of affected adults still have very mild tics (Bloch et al, 2005).

Classification of Tic Disorders

Tics disorders are classified as TS, chronic motor or vocal tic disorder, or transient tic disorder. According to the *Diagnostic and*

Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), transient tic disorder involves single or multiple motor or vocal tics which are present for at least 4 weeks, but no longer than 12 consecutive months. Tics must be present for over 12 months for the diagnosis of chronic motor (CMTD) or vocal tic disorder. The diagnosis of TS depends on multiple motor tics and at least one vocal tic with a fluctuating course during at least one year (Leckman et al, 1999). However, the requirement for a vocal tic may be somewhat arbitrary, since CMTD often shows the same evolution and co-morbidities as TS (Diniz et al, 2006; Saccomani et al, 2005). CMTD should be included in the family of Tourette spectrum disorders (TSD) to insure adequate attention and care for all individuals with primary tic disorders.

Comorbid Conditions

Tic disorders, especially TS, are associated with multiple comorbid conditions. These include obsessive and compulsive symptoms (OCS), attention deficit and hyperactivity disorder (ADHD), conduct disorder, oppositional defiant disorder, rage attacks, anxiety, depression and sleep disturbances. It is critical to identify and address these, as they are usually the source of more distress and disability than the tics themselves.

Obsessive-compulsive symptoms

Obsessive-compulsive symptoms (OCS) involve sudden, intrusive and repetitive thoughts or desires to act. OCS often increase in severity several years after tic severity has peaked (Bloch et al, 2005). Prevalence of OCS in TS has been reported as high as 80% (Gaze et al, 2006). In TS, obsessions are often vivid, imposed images or brief thoughts of violence or sex that have more variable accompanying distress than in idiopathic OCS (Cath et al, 2001).

Distinguishing tics from compulsions can occasionally be challenging, as the purposefulness of an action and its reduction of anxiety are hallmarks of a compulsion. Touching both legs with a finger may be a complex tic if it seems purposeless. However, the same gesture would be classified as a simple compulsion if done in response to a symmetry/just right obsession. These compulsions may be more responsive to dopamine antagonists than

to serotonergic antidepressants (Mataix-Cols et al, 1999).

ADHD and Cognition

Attention deficit hyperactivity disorder (ADHD) is found in 40 to 60% of children with TS. As with idiopathic ADHD, TS+ADHD subjects experience distractibility, emotional reactivity and impulsivity that lead to difficulty performing tasks which require sustained attention. Impulsivity in particular can often make answers and actions more approximate and poorly planned. This can result in academic performance below cognitive potential.

Rage outbursts, oppositional behaviours, depression and anxiety

Explosive outbursts are seen in up to 50% of TS patients (Budman et al, 2000; Richer et al, submitted). During these outbursts, the patient "loses control" and is usually shameful when the crisis subsides. Although they may be part of impulsivity/ADHD, oppositional-defiant disorder (ODD) or OCS (frustration over unmet needs), they often represent one of the most disabling manifestations.

Antisocial and oppositional behaviours are frequently encountered in TS, although psychosocial, familial and economic settings may be more relevant in understanding these pathological relational behaviours. Some patients show symptoms of anti-social behaviours (conduct disorder in children, anti-social personality disorder in adults) such as lying, stealing, and fighting. Again, overlap with OCS, ADHD and impulse-control disorder probably plays a significant role in these behaviours.

Although the list of possible contributing factors is long, anxiety and depression symptoms may be increased in TS (Coffey et al, 2000; Comings et al, 1987), and anxiety symptoms and psychosocial distress seem particularly relevant since they may predict future tic severity (Lin et al, 2007).

Sleep disturbances

Sleep studies have repeatedly described insomnia and inefficient sleep, parasomnias (sleep walking, sleep terrors), and agitated sleep in TS. (Kostanecka-Endress et al, 2003). Tics may be seen during sleep. Studies on the impact of sleep problems in children are rare.

However, a recent study with an experimental design showed that sleep deprivation can have a profound impact on children's behaviour and academic achievement (Fallone et al, 2005). These preliminary data suggest that improving sleep quality in TS may improve symptoms.

Restless legs

Restless legs syndrome (RLS) is an urge to move a limb, usually one or both legs, associated with focal dysesthesia, which is increased by rest, reduced by movement, mostly in the evening. We have previously described increased RLS symptoms in children with TS (10%) (Lesperance et al, 2004) independent of ADHD co-morbidity, which is a reported risk factor for adult RLS (Cortese et al, 2005). There may be parallels between premonitory urges, relieved by tics and the dysesthesia/urge to move relieved by leg movements in RLS.

Etiology

Several studies demonstrate an important genetic component in tic disorders. Whereas more than 50% of identical twins show a concordance for TS, less than 10% of fraternal twins are concordant (Price et al, 1985). Family studies indicate that the relative risk in first-degree relatives is 8.3% for TS and 16.3% for chronic tics. No major vulnerability gene has been identified for TS, but several genes show a significant statistical association. TS is probably a complex trait which involves several genes (Walkup et al, 1996; State et al, 2001). Several non-genetic factors are also associated with TS, including prenatal and perinatal events, hormones, immune responses and stressors. PANDAS (post-infectious autoimmune neuropsychiatric disorders associated with streptococcal infection) is a controversial entity in which a patient suddenly develops an explosion of tics and compulsions following a streptococcal infection (Swedo et al, 1998).

Neurobiology

There is mounting evidence that circuits linking frontal and striatal regions are involved in tic disorders. Lesions of the pallidum and of orbitofrontal cortex have been associated with TS (Laplaine, 1994; Demirkol et al, 1999; McAbee et al, 1999). MRI volumetric studies

show significant differences in the striatum and pallidum of TS patients in comparison with healthy volunteers (Hyde et al, 1995; Peterson et al, 2003; Singer et al, 1993). Functional neuroimaging data shows decreased resting activity in the basal ganglia, especially in ventral striatum (Braun et al, 1993; Diler et al, 2002; Klieger et al, 1997). In adults, the severity of tics may be linked to the reduction of glucose metabolism in the frontal cortex (Chase et al, 1984).

At the neurochemical level, TS may be associated with dysfunction of dopaminergic modulation of striatal and/or frontal activity. Presynaptic dopaminergic activity may be abnormally high in TS, especially in ventral striatum (Peterson et al, 2001; Albin et al, 2003; Ernst et al, 1999; Serra-Mestres et al, 2004; Singer et al, 2002; Cheon et al, 2004). Changes in the serotonin, noradrenaline and neuropeptide systems are also observed (Muller-Vahl et al, 2005; Leckman 2003). Pathophysiological models of TS have emphasized the role of striato-cortical circuits in the selection of voluntary responses and the concurrent inhibition of competing responses (Mink 2001). Some models propose an imbalance between motor and limbic striatal circuits (Groenewegen et al, 2003).

Treatment of Tic Disorders

The first therapeutic approach in tic disorders is education and demystification of symptoms. Persons in frequent contact with the child should be informed about tics, fluctuations and possible co-morbidities. It is important to emphasize the uselessness of constantly asking the child to control his/her tics. Such requests create tension which often exacerbates symptoms. The goal is to improve the tolerance of symptoms, and avoid situations that will augment stress or embarrassment. Following a complete evaluation, the treatment of tics and comorbidities should be prioritized according to the impairment caused by each problem. Physicians considering pharmacological treatments should be aware of the fluctuating nature of tics and the effect of comorbidities on outcome.

Pharmacological Treatment of Tics

The vast majority of affected people will not

require pharmacologic treatment for their tics. On the other hand, if tics cause interference with daily function, pain or social difficulties, medical treatment should be considered.

Dopamine Modulating Agents

Traditionally dopamine-blockers have been the first line treatment for tics and have the most compelling evidence for effectiveness in double-blind controlled studies. The three most studied agents are haloperidol, pimozide and risperidone (Gilbert 2006). One double-blinded placebo controlled study showed haloperidol as slightly more effective than pimozide in controlling tics (Shapiro et al, 1989), whereas a second study (Sallee et al, 1997) favoured pimozide. Starting doses of haloperidol and pimozide are 0.25-0.5 mg/day and 0.5-1 mg/day respectively, with usual maintenance doses ranging between 1-4 mg/day and 2-8 mg/day. Dopamine modulators have important but variable side effects such as weight gain, sedation, anxiety, electrographic changes (tachycardia and QTc prolongation) and extrapyramidal symptoms. With pimozide, medications that prolong the QTc interval should be used with caution, and the concomitant use of 3A4 inhibitors is contra-indicated.

Because of their presumed lower long-term side effects profile, atypical neuroleptics such as risperidone (0.5-4 mg) (Bruun et al, 1996; Scahill et al, 2003) or olanzapine (2.5-10 mg) are preferred. The risk of tardive syndromes in people with TS is unknown, so these agents should be given at the lowest dose possible and periodic attempts to taper medications should be made. The atypical anti-psychotics are also associated with the metabolic syndrome, defined as a cluster of clinical and laboratory abnormalities which include obesity, insulin resistance, hypertension, low levels of high density lipoprotein cholesterol and high levels of triglycerides (Sarafidis & Nilsson 2006). Individuals with the metabolic syndrome are at a two to three fold increased risk of cardiovascular mortality and a two fold increased risk of all-cause mortality, though it is still controversial as to whether this is simply due to the risk associated to the individual components of the syndrome (Lakka et al, 2002). The role of other atypical neuroleptics such as quetiapine (Mukaddes et al, 2003; Schaller et al,

2002) in the treatment of TS still need to be studied in larger trials. A number of small studies have demonstrated the efficacy of aripiprazole (not yet available in Canada at the time of publication) with a favourable side-effect profile (Seo et al, 2008; Davies et al, 2006). A small pilot study showed that ziprazidone, a new atypical antipsychotic available in Canada, was effective in reducing tics with minimal side effects and weight gain, though caution regarding prolongation of QTc interval must still be taken (Sallee et al, 2000; Blair et al, 2005).

Tetrabenazine (given as 12.5-25 mg TID) is a monoamine depletor which operates mainly by inhibiting dopamine liberation. This drug may be effective for the treatment of tics and unlike neuroleptics, does not pose any major risk of tardive dyskinesia at lower doses (Jankovic et al, 1984). The exact role of tetrabenazine in the therapeutic arsenal of tics, however, must be studied further. The most important side effects are depression and parkinsonism at high doses.

Alpha-2-Adrenergic Agonists

Because of contradictory results, the role of alpha-2-adrenergic agents (clonidine and guanfacine) in the treatment of tics is debatable. However, in practice, because of a better side effect profile and no long term potential risk, they are often a first line treatment option especially in patients with co-morbid symptoms of ADHD (Leckman et al, 1991; Scahill et al, 2001; Tourette's syndrome study group 2002; Goetz et al, 1987; Singer et al, 1995; Shapiro et al, 1984).

Other Agents

Numerous other agents have been studied for control of tics. However, it is difficult to derive strong conclusions since most studies have been either open-label or double-blind with few patients and have not been replicated. Other potential agents include flunarizine (Micheli et al, 1990), naloxone (Sandyk et al, 1985), delta-9-tetrahydrocannabinol (Muller-Vahl et al, 1999) baclofen, (Awaad 1999; Singer et al 2001), ondansetron (Toren et al, 2005), levetiracetam (Awaad et al, 2005) and dopamine agonists (Gilbert et al, 2003). Although sometimes used in children and adults, there has been no controlled study of

benzodiazepines (Gonce et al, 1977). Botulinum toxin may be a good treatment for highly-localized motor tics (Marras et al, 2001; Vincent 2006) – interestingly, some patients treated with botulinum toxin for a single focal tic notice spread of the tic to an adjacent non-injected muscle.

Behaviour Therapy

There is strong evidence from randomized controlled trials to support the use of behaviour therapy, specifically habit reversal training, as an alternative or adjunct treatment in tic disorders. (Himle et al, 2006; O'Connor et al, 2001; Deckersbach et al, 2006; Wilhelm et al 2003). In habit reversal training, participants learn to increase their awareness of tics and to perform a competing response when they sense an urge. The competing responses often involve antagonist muscles to those that produce the tic. However, this therapy requires a substantial time investment and the long term effectiveness is still unknown.

Response prevention is another tic reduction therapy which requires participants to suppress their tics during prolonged periods, thus exposing them to premonitory sensory experiences. In a recent study, repetitive periods of tic suppression resulted in tic reduction, and interestingly, the commonly reported phenomenon of tic rebound after suppression was not observed (Verdellen et al, 2007), suggesting that tic suppression training may have long term benefits.

Neurosurgical Treatment

Multiple neurosurgical procedures including frontal lobe bimedial frontal leucotomy and prefrontal lobotomy, limbic system anterior cingulotomy and limbic leucotomy, have been tried in patients with severe tics with variable results. None of these procedures have been studied in a large control-case studies (Temel & Visser-Vandewalle, 2004). More recently, because of a lower side effect profile and potential access to deeper regions, deep brain stimulation has been advocated as an alternative for cases with severe uncontrolled tics (Vandewalle et al, 1999, Shahed et al, 2007). A recent review has found very good effectiveness in select cases (Neimat et al, 2006). Nevertheless, to fully understand the utility of brain stimulation in TS better pathophysiological models and

larger trials need to be completed in order to specify which sites and approaches work best for different phenotypes.

Treatment of Comorbid Conditions

Treatment of Anxiety/Depression and OCS

Even if tic reduction is the initial expressed goal for the patient, targeting co-morbid conditions may prove to be more beneficial overall. For OCS, behaviour therapy such as exposure and response prevention has evidence of efficacy (Hembree et al, 2003). When anxiety is severe, selective serotonin re-uptake inhibitors (SSRIs) (such as escitalopram, fluoxetine, sertraline, etc...) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (venlafaxine, duloxetine) should be tried. It may be advisable to start at a very low dose and titrate slowly upwards, to prevent paradoxical agitation at the onset of treatment. Antidepressants may reduce anxiety and irritability, and therefore indirectly ameliorate tic severity. Low dose benzodiazepines (such as clonazepam 0.25-0.5 BID) may also reduce both anxiety and tic severity, but impulse-control symptoms should be closely monitored, since they may be exacerbated (Dietch & Jennings, 1988). For depression, SSRIs or SNRIs are usual first line treatments (American Psychiatric Association, 2000), but in children, only fluoxetine has clearly shown benefit over placebo (Emslie et al, 2002). SSRIs and SNRIs have been studied in idiopathic OCD where distress, doubt and anxiety are significantly more intense than in Tourette-related OCS. In fact, hoarding/symmetry OCS, mostly seen in TS, is predictive of poorer treatment response to SSRIs (Shavitt et al, 2006). Nevertheless, they should be tried, with the usual caveats of a possible increase in suicidal ideation, especially in children. Atypical antipsychotics may be beneficial in OCS, alone or in combination with SSRIs, especially in the TS hoarding-just right subtype: such compulsions may be predictors of better response to neuroleptics than SSRIs, as would be expected of tics (Mataix-Cols et al, 1999).

Treatment of Impulse-Control Problems

Familial intervention should be tried first when facing difficult impulse-control problems in TS patients. Pharmacological interventions

may be tried, but efficacy and safety data in children are scant (Ipser & Stein, 2006). For rage outbursts and self-injurious behaviour, atypical antipsychotics may be considered, but with regular monitoring of potential metabolic and tardive motor complications.

Treatment of Anti-Social Behaviour, Oppositional Behaviour and ADHD

Again, social and familial interventions are key for patients showing relational behavioural problems such as antisocial and severe oppositional behaviours. If oppositional behaviours are intertwined with OCS, the logical step is to start with the OCS algorithm. If suspecting comorbid ADHD, then ADHD treatment may be beneficial.

A consensus ADHD algorithm for Tourette's patients has been recently published that suggests starting with psychostimulants (methylphenidate or amphetamines) followed by atomoxetine and clonidine/guanfacine (Pliszka et al, 2006). Slow-release or extended-release bupropion may also be useful. Although there have been concerns that tic severity may increase with psychostimulants, a recent study has actually documented, on average, less tics on psychostimulants (Kurlan et al, 2002).

Treatment of Sleep Disturbances and RLS

Many drugs used for tic reduction will show hypnotic or sedative properties. On the other hand, psychostimulants and antidepressants, especially SSRIs and SNRIs, may reduce sleep continuity or cause insomnia. Benzodiazepines typically reduce the severity of non-rapid eye movement sleep parasomnias, sometimes encountered in TS children. Finally, in children with developmental delay, melatonin may stabilize sleep and may be useful especially in patients with sleep patterns suggestive of phase-delay or free-running sleep/wake cycles (Aremour & Paton, 2004).

If associated RLS is severe, dopamine agonists are particularly effective (Chahine & Chemali, 2006), but should be given at the lowest effective dose to avoid augmentation. Of interest, low doses of dopamine agonists may also have anti-tic properties (Anca et al, 2004; Gilbert et al, 2000). Levodopa may be considered in the treatment of RLS, but augmentation and morning rebound develop in

more than 50% of patients (Paulus & Trenkwalder, 2006). Clonazepam is helpful for light to moderate night-time RLS associated with insomnia. Gabapentin has shown some effectiveness and opiates are effective for refractory patients (see Vignatelli et al, 2006 for treatment guidelines).

Conclusion

Tic disorders are relatively common with an estimated prevalence of 5%. Identification of comorbidities such as anxiety/depression, OCS, impulse control disorders, ADHD behavioural disorders, sleep disturbances and RLS is an essential step in the treatment plan. Tic disorders frequently do not require pharmacologic treatment. If treatment is required, first-line options include dopamine modulators, tetrabenazine, clonidine and behavioural therapy.

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