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Meta-Analysis: Risk of Tics with Psychostimulant Use in Randomized, Placebo-Controlled Trials.

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Stephanie Celeste Cohen

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META-ANALYSIS: RISK OF TICS WITH PSYCHOSTIMULANT USE IN RANDOMIZED, PLACEBO-CONTROLLED TRIALS.

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Clinical practice currently restricts the use of psychostimulant medications in children with tics or a family history of tics for fear that tics will develop or worsen as a side effect of treatment. Our goal was to conduct a meta-analysis to examine the risk of new onset or worsening of tics as an adverse event of psychostimulants in randomized, placebo-controlled trials.

We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). We used a fixed effects meta-analysis with risk ratio of new onset or worsening tics in children treated with psychostimulants compared to placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dose, duration of treatment, recorder of side effect data, trial design, and mean age of participants on the measured risk of tics.

We identified 22 studies involving 2,385 children with ADHD for inclusion in our meta-analysis. New onset tics or worsening of tic symptoms were commonly reported in the psychostimulant (event rate=5.7% (95% CI: 3.7% to 8.6%), I^2 =72%, p<0.001) and placebo groups (event rate=6.5% (95% CI: 4.4% to 9.5%), I^2 =64%, p<0.001). The risk of new onset or worsening of tics associated with psychostimulant treatment was similar to that observed with placebo (risk ratio=0.99 (95% CI: 0.78 to 1.27), z=-0.05, p=0.96). Type of psychostimulant, dose, duration of treatment, recorder of side effects, and participant age did not affect risk of new onset or worsening of tics. Crossover studies were associated with a significantly greater measured risk of tics with psychostimulant use compared to parallel group trials.

Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. Clinicians may want to consider re-challenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.

Acknowledgements

First and foremost I would like to acknowledge and thank my mentor, Michael Bloch, for his continued support of me and this work throughout my years as a medical student. He was always available for questions big and small and encouraged me throughout the entire process. I could not have asked for a better research adviser and mentor.

I also acknowledge and thank the support of my entire family, especially my youngest brother, Elijah Cohen, who inspired me to work on this project.

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Of note, the following introduction is based on a review I wrote with my research mentors of the clinical assessment of Tourette syndrome and tic disorders [1]. The remainder of the thesis is also based on our published work [2]. Please see Appendix A and Appendix B for a full copy of each article.

Introduction

Section 1. Background on Tics & Tourette Syndrome

Tourette syndrome (TS) was first described by the French neurologist, Gilles de la Tourette, in 1885 as a "maladie des tics." In his original case series describing the syndrome that now bears his name, Gilles de la Tourette wrote about many of the characteristics of the syndrome including: involuntary movements and sounds, markedly enhanced startle reactions, a tendency to repeat both vocalizations (echolalia) and movements (echopraxia), and uncontrollable verbal obscenities (coprolalia) [3]. Since then, our knowledge of TS has progressed significantly, including advances in our understanding of tics, their surrounding sensory phenomena, and the central role that other co-occurring diseases, such as Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD), have on the overall clinical course of the disorder. This introduction will focus on our current understanding of the diagnosis, clinical characterization and assessment of tics as well as their clinical course. Because of the large overlap between TS and ADHD, a background on use of psychostimulants and tics will be provided as well.

Definition of tics:

Tics appear as sudden, rapid, purposeless motor movements or sounds that involve discrete muscle groups. They are also stereotyped in that they will occur in a similar manner each time they are performed. In comparison to some movement

disorders or psychiatric conditions (e.g. Sterotypies, Chorea, or Dyskinesia), patients with tics report the ability to suppress them, even if only for a short duration. However, they report that suppression often causes discomfort. Almost any movement, sound, or combination therein that the body can make can become a tic. Although some tics are more mild (i.e. eye blinking), others can be more severe to the point of causing pain to the patient (i.e. head or neck jerk). Apart from the physical consequences incurred by them, tics and their associated neuropsychiatric symptoms can diminish patients' quality of life, social and academic function, and lifetime achievements. They can also be very troubling and disruptive to the patients' family, and many times the entire family needs care and counseling [4]. Oftentimes, the tics themselves have less adverse effects than the co-occurring disorders. For instance, a 2011 study measuring quality of life (QoL) in fifty youth with TS found that symptoms of depression, OCD, and ADHD appeared to have a widespread negative impact on QoL; however, increased tic severity and poor QoL were not associated [5].

Tourette Syndrome and other tic disorders:

The prevalence of TS varies based on study design and location. An international prevalence of 0.6% – 1% has been reported for mainstream schoolchildren, with the disorder being 3–4 times more common in males than in females [6]. Data from the 2007 National Survey of Children's Health (NSCH) showed an estimated prevalence of 0.3% among U.S. children aged 6–17 years [7]. This number may represent an underestimate of TS prevalence since data were gathered from a parent- reported survey, and detection might be imperfect for children with fluctuating levels of symptoms or limited access to specialty health-care services [7]. Alternatively, TS prevalence may differ in prevalence

worldwide due to either genetic or environmental differences. For example, TS has been reported to be less common in African-American people and has been reported only very rarely in sub-Saharan black African people [8]. Regardless, the phenomenology of TS is similar in all cultures in which it has been reported [8].

TS is defined by the pediatric onset of both motor and vocal tics, lasting for at least one year. Although TS is the most notorious cause of chronic tics, there are types of tic disorders that are more common in children. Based on the Diagnostic and Statistical Manual–5 (DSM-5) of the American Psychiatric Association, other tic disorders include: Persistent (Chronic) Motor or Vocal Tic disorder (CMT), which is defined as having motor or vocal tics (but not both) for more than one year; and Provisional Tic Disorder, which is characterized by single or multiple motor and/or vocal tics for a duration of less than one year [9]. Transient tics affect 15–25% of school-aged children with the majority experiencing resolution of tics within several months [8, 10-12]. Other Specified Tic Disorder or Other Unspecified Tic Disorder are the diagnostic terms used for tic disorders that begin after age 18, are secondary to other factors such as substance use (e.g. cocaine), toxins (e.g. carbon monoxide poisoning), or head trauma (e.g. physical trauma, stroke, or encephalitis), or do not fit in the above-mentioned categories [9].

Table 1. Tic Disorders according to DSM-5

Diagnosis	Type of Tics	Description of Tics	Age of Onset
Tourette's Disorder	Multiple motor and one or more vocal tics	Tics may wax and wane in frequency but have persisted for >1 year since first tic onset	<18 years of age
Persistent (Chronic) Motor or Vocal Tic Disorder	Single or multiple motor or vocal tics (but not both)	Tics may wax and wane in frequency but have persisted for >1 year since first tic onset	<18 years of age

Provisional Tic Disorder	Single or multiple motor and/or vocal tics	Tics have been present for <1 year since first tic onset	<18 years of age
Other Specified Tic Disorder	Motor or vocal	Tic disorder symptoms present, which cause clinically significant distress or impairment, but do not meet full criteria for a tic disorder for a *specific reason* (e.g., "with onset after age 18 years")	Often used for individuals that have onset at >18 years of age
Unspecified Tic Disorder	Motor or vocal	Tic disorder symptoms present, which cause clinically significant distress or impairment, but do not meet full criteria for a tic disorder for a reason that is *not specified* by the clinician, often because there is insufficient information to do so	N/A

Tics also exhibit several characteristics that distinguish them from other common childhood movement disorder such as stereotypies, choreas and dystonias. The distinguishing characteristics of tics include (1) they wax-and-wane in severity, (2) the character of the movements changes over time, (3) they are temporarily suppressible and (4) they are typically associated with sensory phenomena. Table 2 contrasts TS with other common movement and childhood psychiatric disorders confused with TS.

Table 2. Differential Diagnosis of Tic Disorders

Movement	Description	Common Causes
Tics	- Abrupt, stereotyped coordinated movements or vocalizations that often mimic aspects of regular behavior - Wax and Wane - The character of the movements changes over time - Temporarily suppressible - Premonitory urges are common - Exacerbated by stress and relieved by distraction	- Tourette's Disorder - Persistent (Chronic) Motor or Vocal Tic Disorder - Provisional Tic Disorder
Stereotypies	Repetitive, purposeless, and apparently voluntary movements	- Autism - Pervasive Developmental Disorder - Mental Retardation - Stereotyped Movement Disorder

Chorea	• Simple, random, irregular, and non-stereotyped movements • Has no premonitory component and increases when the person is distracted • Often flows from one body part to another	• Normal in children less than 8 months of age • Cerebral Palsy • Sydenham's Chorea • Hereditary choreas • Kernicteris • Lesch-Nyhan syndrome • hypoxia or stroke
Dyskinesia	• Slow, protracted twisting movements interspersed with prolonged states of muscular tension	• Drug-induced • Idiopathic torsion dystonia • Anoxia or stroke • Wilson's disease • Huntington's Disease • Parkinson's Disease
Athetoid	• Slow, irregular, writhing movements. Usually involving fingers and toes but occasionally the neck • A "slow chorea"	• See section on "chorea"
Myoclonia	• Brief, simple, shock-like muscle contractions that may affect individualized muscles or muscle groups.	• Physiologic: hiccups, anxiety, or exercise- induced • Pathologic: Juvenile Myoclonic Epilepsy, Metabolic encephalopathies, Creutzfeldt-Jakob Disease, Wilson's disease, and hypoxia
Synkinesis	• Involuntary movement associated with a specific voluntary act, i.e. raising corner of mouth when closing one's eyes	• Physiologic

Characterization of Tics:

Tics are characterized by their anatomical location, number, frequency, and

duration. They are also further described by their forcefulness or intensity and by their

complexity (ranging from simple to complex). The most widely-used rating scale of tic

severity is the Yale Global Tic Severity Scale (YGTSS), which includes separate scores

from 0–5 for number, frequency, intensity, complexity, and interference (the degree to

which planned actions or speech are interrupted by tics) of both motor and phonic tics

[13]. This tool has allowed for the standardization of tic severity across different studies

and research groups, aiding in the characterization and quantification of symptoms.

Additionally, because the clinical characteristics of TS make it hard for clinicians to diagnose and assess the severity of the condition, the Tourette Syndrome Diagnostic Confidence Index (DCI) was created through a collaborative effort of an expert group of clinicians. Based on the range and complexity of tics, their changeable nature, the temporal features of tic expression, and associated subjective and cognitive experiences, the DCI assigns a score from 0 to 100, which reflects the likelihood of having or ever having had TS [14].

Other rating scales include the Shapiro Tourette Syndrome Severity Scale, Tourette's Syndrome-Clinical Global Impression Scale, and the Hopkins Motor and Vocal Tic Scale [15]. Standardized video recordings can also be used to count tics [16]. See Table 3 for a detailed comparison of various rating scales. For a detailed discussion on these rating scales, please refer to a recently published review [17].

Table 3. Tic Rating Scales

Scale	Citation	Informants	Items	Domains Probed	Strengths	Weaknesses
Yale Global Tic Severity Scale (YGTSS)	[13]	Clinician-rated; Semi-structured interview	10	Number, frequency, intensity, complexity, and interference from motor and vocal tics, and overall impairment	• Most widely used measure. • Has tic symptom checklist • Gives separate severity for motor and vocal tics • Good inter-rater reliability • Sensitive to change with treatment	• Insensitive to change in patients with frequent and severe tics. • In individuals with few phonic tics small changes in symptomatology can cause large fluctuations in ratings

Tourette's Syndrome Severity Scale (TSSS)	[18]	Patients and collaterals asked to give ratings	5	How much tics are noticed, commented on, seen as odd by others and degree of impairment	• Reliable • Short administra-tion time	• Focuses primarily on social impact from tics and not on the severity of tics themselves
Tourette's Disorder Scale-Clinician Rated (TODS-CR)	[19, 20]	Clinician-rated; semi-structured interview of parent and child	15	Motor and Phonics Tics as well as common comorbid conditions (such as obsessions, compulsions, inattention, hyperactivity, aggression, and emotional disturbances)	• Provides ratings of common comorbid behavioral symptoms.	• Severity ratings include symptoms classified in other DSM-5 disorders such as ADHD, OCD, MDD, anxiety disorders, and IED
Tourette's Disorder Scale-Patient Rated (TODS- PR)		Parent-rated; self-report regarding child				
Hopkins Motor and Vocal Tic Scale	[15, 21]	Separate ratings by family member and observer	N/A	Measures overall severity of each individual tic on a visual scale	• Can follow separately improve-ment in specific tics • Easy to administer	• Difficult to aggregate data across patients • Does not have separate measures for frequency, intensity and interference from tics
Tourette's Syndrome Questionna ire (TSQ)	[22]	Self-report involving parent and child	35 pages	Tic history, prenatal and developmental history and family history.	• Provides assessment of many potential risk factors for Tourette syndrome	• Time intensive • Problems with recall bias for many parent report items
Child Tourette Syndrome Impairment Scale	[23]	Parent-rated, self-report	37	Overall impairment (and impairment from tics) in school, home and social activities.	• Provides more nuanced with of impairmen t than single-item measures	• Most useful when performed in conjunction with tic severity measure

Videotape Ratings and Tic Counts	[24, 25]	Videotape subject for at least 5 minutes. Count motor and vocal and total tic frequency.	N/A	Tic frequency	• Objective measure of tic severity	• Labor-intensive • Vulnerable to sampling bias because tics wax-and-wane in severity • Requires significant amount of equipment • Does not measure impairment and interference from tics

Note: ADHD = Attention-Deficit Hyperactivity Disorder; OCD = Obsessive Compulsive Disorder; MDD = Major Depressive Disorder; IED = Intermittent Explosive Disorder

Natural History of Tourette Syndrome:

The natural history of TS has been established based on clinical observations. There is a clear progression of the disorder from the onset of symptoms to, in most cases, full or partial regression of symptoms. Tics usually begin around 6–8 years of age, and 90–95% of TS cases have an onset of tics between the ages of 4–13 [26]. Simple motor tics involving the eyes or face are usually the first to appear in a child with TS. They are called simple because they involve a single contraction, such as a shoulder shrug or neck stretch. Motor tics will typically progress in a rostral-caudal fashion and over time they have a tendency to become more complex, involving contractions of groups of muscles in a stereotyped, repetitive way [26]. As such, complex motor tics are often difficult to distinguish from compulsive behaviors.

Phonic tics usually appear after the onset of motor tics and can also progress from simple vocalizations to more complex ones. Although a distinction is made between phonic and motor tics, it is a tenuous one as the sounds produced are a result of contractions of laryngeal, respiratory, oral, or nasal musculature [27]. Simple phonic tics are brief, meaningless vocalizations that often consist of a single sound, such as grunting,

squeaking, or sniffing, while complex phonic tics can include uttering different words or phrases. In the same category, echolalia (repeating the words or sounds of others), palilalia (repeating oneself), and coprolalia (saying obscene words or phrases) are types of complex phonic tics. Table 4 describes and gives examples of simple and complex motor and phonic tics.

Table 4. Types of Tics

	Motor	Phonic
Simple	Sudden, brief, short (usually <1 second), one group of muscles (e.g. eye blinking, facial grimacing, head jerk, shoulder shrug)	Fast, meaningless sounds/noises (e.g. sniffing, throat clearing, grunting, or high-pitched squeaks)
Complex	Sudden, appear purposive, stereotyped, longer duration, coordinated movements	Syllables, words, or phrases; odd patterns of speech with changes in rate, volume, or rhythm
	Echopraxia: copying gestures of others	Echolalia: repeating words or phrases of others
	Palipraxia: repeating one's own gestures	Palilalia: repeating one's own words or phrases
	Copropraxia: lewd and obscene gestures with hands or tongue	Coprolalia: socially inappropriate syllables, words, or phrases expressed in a loud, explosive manner
	Dystonic: sustained, gyrating, bending, or twisting movement or posture (e.g. blepharospasm, oculogyric movements, mouth opening, shoulder rotation)	
	Tonic: sustained, isometric contraction (e.g. abdominal or limb tensing)	
	Self-injurious Behavior: tics that involve injuring oneself (e.g. tongue or lip biting, or hitting one's face)	

Tics tend to wax and wane in severity and frequency. Both motor and phonic tics arise in bouts over the course of the day, and they change in severity over weeks and months. Thus, the amount and length of tic-free intervals throughout the day determines to some extent the severity of the symptom. The tic itself can be more or less forceful, which characterizes its intensity [28].

By contrast, there are no factors known to affect the long-term course of tics. However, the vast majority of children with tics improve. The severity of tics usually peaks at about 10–12 years of age, and in one half to two thirds of cases, symptoms will drastically reduce during adolescence [29] (Fig. 1). In the rare cases in which tic severity persists into adulthood, tic symptoms are most severe, characterized by self-injurious motor tics or coprolalic utterances [28].
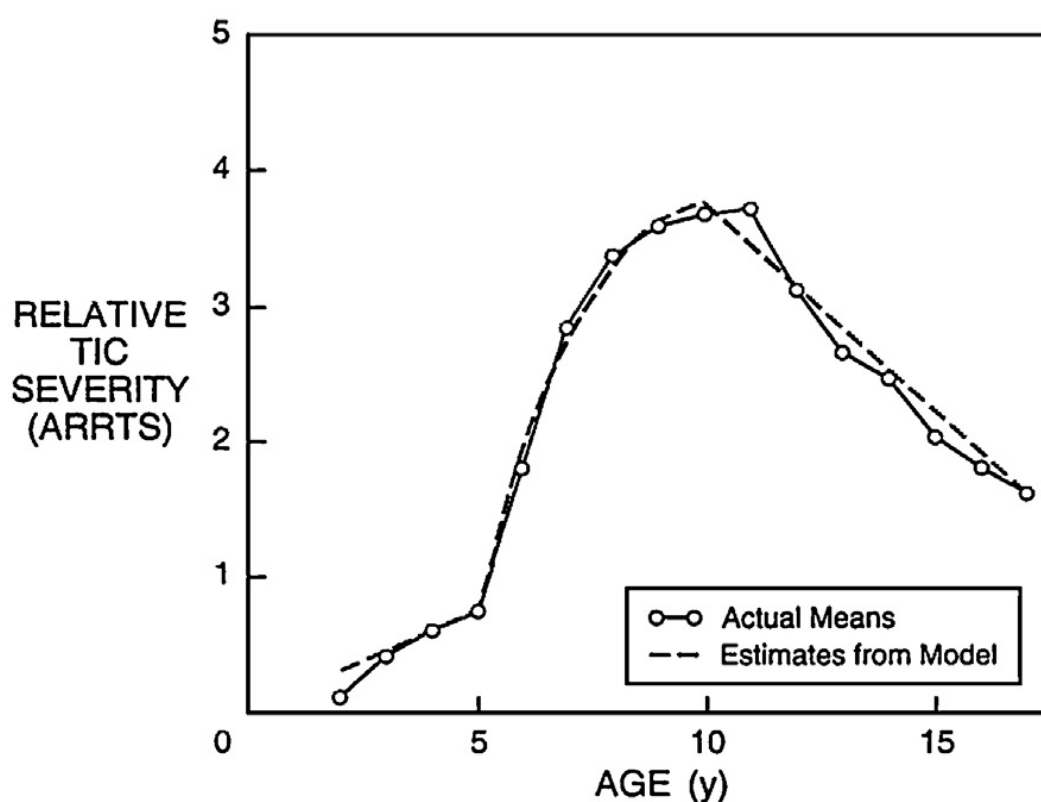
Fig. 1. Average tic severity from age 2 to 18 years. Adapted with permission from [26].

In fact, in a recent study by Freeman et al., the overall prevalence of coprophenomena was 19.3% in an international cross-sectional sample of 597 patients. Only 15 of 220 individuals who had mildly-rated tics had coprolalia; whereas 42.6% of the 108 patients with severe tics had coprolalia. The mean age of onset of coprolalia and copropraxia was 5 years 4 months and 4 years 10 months, respectively, after the onset of

tics. This delayed onset and greater percentage of coprolalia seen in patients with severe tics is not surprising, as coprophenomena reflects more complex tics and comorbidity patterns [30].

Other studies have also associated the presence of certain types of tics with clinical course. A recent study by Martino et al. looked at the prevalence of eye tics in TS patients. They found that of 212 patients, 201 or 94.8%, reported ever having eye tics in their lifetime. They also discovered that overall tic severity positively correlated to lifetime history of eye and/or eyelid/eyebrow movement tics. Furthermore, they found that regardless of the type of tic at onset, patients with a lifetime history of eye movement tics had an earlier onset of TS than those who had never had eye movement tics. These findings suggest the possibility for a difference in the natural history of patients with and without ocular tics [31].

Few studies have examined predictors of long-term outcome on neuropsychological assessment and neuroimaging. One cohort that examined 43 children with TS followed to young adulthood demonstrated that smaller childhood caudate volume and poor Purdue Pegboard performance were associated with increased tic severity in early adulthood [32, 33]. Purdue pegboard performance is a test of fine-motor skill, and poor performance may be a sign of deficits in complex, visually guided or coordinated movement that is likely mediated by circuits involving the basal ganglia. Reduced caudate volume has been previously demonstrated to be a morphological trait of TS on structural MRI [34, 35].

Sensory Phenomena surrounding tics:

The outward manifestation of TS represents only a part of the symptomatology experienced by most of our patients. In 1980, Joseph Bliss, articulately described his careful observations from 35 years of self-study of the feelings and subjective events surrounding his own tics. Much of what he described became the basis for future research surrounding the sensory phenomena associated with tics. The term, "sensory phenomena," is now used as an all- encompassing term to describe such subjective experiences as premonitory urges, "just- right" perceptions, or somatic hypersensitivity in an effort to unify terminology across the literature [36].

Premonitory Urges:

Premonitory urges (PU) are uncomfortable sensory phenomena that typically precede and are subjectively experienced as being the initiators of tics. Premonitory urges, formerly deemed, "sensory tics," can be experienced by individuals with tics and are likened to the need to sneeze or itch or an inner feeling of restlessness, pressure or mounting tension [37]. In a questionnaire administered to 135 patients with tic disorders, it was shown that the anatomical regions with the greatest density of urges were the palms, shoulders, midline abdomen, and throat [38]. Thus, premonitory urges are focal in character and limited to specific anatomical locations. They can also vary in frequency, intensity, and location. The performance of the tic itself is usually associated with a momentary feeling of relief from this uncomfortable urge.

The premonitory urge has been studied in comparison with other normal physiological urges, such as the urge to urinate, cough, blink or sleep. An urge is one mode of processing internal or external sensory input into motor output. However, an urge is not always perceived. Often the motor action can be triggered by sensory input

alone outside of our awareness, and the action would thus be perceived as involuntary [39].

Similarly, Bliss writes when describing the process of a tic that: "the inception and emergence of a single action and its passage into the overt phase is so faint, subtle, surreptitious, and lightening fast that rarely is it known to the subject that it exists at all" [40].

If the action is delayed, an urge develops. This feeling of a need to act is different from the sensation of the sensory input itself. Typically, the discomfort associated with the premonitory urge builds up until the tic is performed. Some patients state that they will voluntarily make tics in response to the urge in order to relieve themselves of the mounting discomfort.

In 1994, Kane, then a graduate student with TS, wrote in reference to premonitory urges, "these sensations are not mere precursors to tics; […] more than providing a signal of imminence, the pre-tic sensation acts as the aversive stimulus toward which tics are directed" [41].

Patients with TS have the ability to suppress tics temporarily but only at the expense of mounting discomfort like suppressing a sneeze, itch, or the urge to urinate. In fact, with prolonged suppression, the urge to tic can become so great that the action occurs beyond the patients' control. In this way, tics have been called "un-voluntary," since they are neither voluntary nor involuntary. In contrast to normal urges, the urge to tic is different in that the sensory input that generates the urge to tic is unknown, tics are not key to survival – in fact, they are both nonessential and nonproductive –, and the execution of a tic only temporarily reduces the intensity of the urge to tic [39]. Also,

individuals with tics sometimes report the need to perform tics until they get the feeling associated with it being "just right."

It remains possible that abnormal perception or filtering of these sensory phenomena may be central to the pathogenesis of TS (see "Sensorimotor gating" below). Several individuals with tics have suggested that these premonitory urges may be as characteristic of TS and as disruptive and distracting as the tics themselves. Some individuals perceive premonitory urges and other sensory phenomena as being the "core" of TS [42].

Furthermore, patients have reported an awareness of the premonitory urge helps them suppress imminent tics because they are fore-warned of their arrival and can take measures to suppress them. Along these lines, certain types of behavioral therapies have been developed in order to take advantage of this awareness. Premonitory urges are utilized in cognitive-behavioral interventions that include empirically supported behavioral therapy [43] and exposure and response prevention [44].

Awareness of premonitory urges typically increases as children with TS become older [45]. Individuals with TS have reported that they first became aware of their premonitory urges on average 3.1 years after the onset of tic symptoms [38]. The delayed onset of awareness of urges most likely represents the normal development self-awareness and the fact that younger children are less able to recognize and describe bodily urges. Premonitory urges are experienced by most adolescents and adults with TS. Eighty-two to ninety-two percent of patients will report experiencing premonitory urges prior to motor and vocal tics [46, 47].

Whether a tic is voluntary or involuntary has been the topic of much study. Some have said, the tic is a voluntary action performed in an attempt to relieve an involuntary urge [40]. Furthermore, in a 2003 study, 68% of 50 TS subjects described a motor tic as a voluntary motor response to an involuntary sensation, as opposed to a completely involuntary movement [47]. Also, in a study involving 135 individuals with TS, 92% of individuals indicated that their tics were either fully or partially a voluntary response to their premonitory urges. Also, in the same study, 84% of these subjects reported that their tics were associated with a momentary feeling of relief [38].

The Premonitory Urge for Tics Scale (PUTS) is a rating scale designed to measure the strength of these premonitory urges in tic disorders. Although premonitory urges have been difficult to recognize and consistently report for youth under the age of 10, the scale was found to have excellent psychometric properties for children above the age of 10 years, with PUTS scores correlating with tic severity as measured by the YGTSS [48].

Table 5. Sensory Phenomena Rating Scales

Measure	Citation(s)	# Items	Domains Probed	Strengths	Limitations
Premonitory Urge for Tics Scale (PUTS)	[48]	9 items	Frequency of specific pre-tic related sensory symptoms along with relief after tic completion	• Easy to administer and complete	• Difficult to administer with younger children who may not recognize or understand urges • Does not capture other common sensory phenomenon in TS besides premonitory urges

University of Sao Paulo Sensory Phenomena Scale (USP-SPS)	[49]	2 parts: checklist and severity scale	Frequency, interference and distress of sensory phenomena that precede, accompany, or follow tics and other obsessive-compulsive spectrum behaviors	• Probes other sensory phenomena such as "just right" feelings, feelings of incompleteness, inner restlessness. • Has symptom checklist to identify common symptoms	• Does not have separate domains for different types of sensory phenomena
Sensory Gating Inventory (SGI)	[50]	124 items	6-point Likert ratings assessing 4 factors: perceptual modulation, distractibility, over- inclusion or hyper-attention, and fatigue and stress vulnerability	• Has 4 subscales related to different types of sensorimotor gating deficits	• Not designed specifically to detect sensory phenomena associated with tics
Structured Interview for Assessing Perceptual Anomalies (SIAPA)	[51]	15 items	5-point Likert ratings of: hypersensitivity, inundation and flooding, and selective attention to external sensory stimuli for each of the 5 sensory modalities	• Easier to complete than SGI	• Not designed specifically to detect sensory phenomena associated with tics • Has not been demonstrate d to be elevated in tic disorder patients

Somatic Hypersensitivity:

Sensorimotor gating describes the neurological processes of filtering out redundant or unnecessary sensory stimuli from all possible environmental stimuli. Individuals with TS (and schizophrenia) have consistently demonstrated deficits in sensorimotor gating as compared to healthy controls. Prepulse inhibition (PPI) of startle to a high-intensity stimulus is an experimentally measurable indication of sensorimotor

gating. Prepulse inhibition of startle is defined as the inhibitory effect of a low-intensity

stimulus or "prepulse," on the startle response to the subsequent same, but high-intensity

stimulus [52]. The prepulse is believed to activate brain mechanisms which suppress or

"gate" the processing of that stimulus for a brief window of time. Impaired PPI has been

shown in patients with TS, and recently lesions in the dorsomedial striatum have been

implicated in their diminished capacity for PPI [52]. Swerdlow has demonstrated PPI is

regulated by both norepinephrine and dopamine substrates, and clonidine can repair PPI

disrupted by cirazoline [53].

As hypothesized by these sensorimotor gating deficits observed in patients with

TS, many individuals describe hypersensitivity as being an important phenomenon

intertwined with other aspects of the disorder. A salient example of this phenomenon is

the extreme sensitivity to tags in new clothing experienced by some children with TS.

These experiences are described well in the following quotes:

> "Because of the state of sensitization (combined with memory recall and attention targeting), this site is the most difficult to extinguish. Paradoxically, for the same reasons it is the one most likely to be extinguished first in any period of remission" [40].

> "All these sensory actions can dart from one to another with great speed and varying intensities, at times escalating to a fever pitch of intensity and at other times fading quickly away, to recur some other time. Often the effort to control these wild sensations seems to be more than the human spirit can bear; there are really only two choices: let it all hang out or keep fighting. However great the confusion and diversity of sensory-related actions and sensations, only one of these is active at any given moment. All others, residual and secondary, stand in the wings, with their entrances and exits following so quickly on after the other that it is very hard at times to be aware of their single movements" [40].

> "Perhaps the best description for the sensory state of TS is a somatic hyper-attention: It is not as itch-like as it is an enduring somatosensory bombardment. I experience the TS state as one of keen bodily awareness, or a continual consciousness of muscle, joint, and skin sensations. For example, when sitting in a chair, I do not lose awareness of the tactile sensation of the seat against my

body, nor can I ignore the deeper somatic sensations of what my back and legs feel like" [41].

"How does a new tic get started? The activation of TS sites is dependent on a combination of (1) attention direction and (2) various precipitants such as stress, tactile and kinesthetic perceptions, previous sensitization of a site, inadvertent pressure points anywhere on the body, memory recall of the earlier sites, and phantom fixations. […] The subject's attention, for any of a multitude of chance reasons, can fall on any potential site. Over seconds, minutes, or hours, the attention shifts to numberless places via sounds, sights, touch, pressure, discomfort, pain, temperature, or thoughts. In the normal person, these attention-exciting events can go relatively unnoticed. In the person with TS, anyone can set off a TS action even though that person may be completely unaware of the stimulating factor" [40].

In 2011, Belluscio et al. studied in detail the experience of sensitivity to external stimuli in a case-control study of 19 TS patients and 19 age-matched healthy volunteers. An in-depth interview and questionnaire revealed that 80% of TS patients reported heightened sensitivity to external stimuli, with examples among all sensory modalities, but with statistically significant heightened sensitivity to 4 of 5 sensory modalities (sound, light, smell, and touch) as compared to the healthy volunteers [54]. They found bothersome stimuli were characterized as "faint, repetitive or constant, and nonsalient, whereas intense stimuli were well tolerated" [54]. Examples of such bothersome stimuli include: rough fabrics, the constant pressure exerted by a shirt collar or a waistband, the pressure of a chair or another person's arm. Patients also described a preference for strong tactile stimuli such as having their skin scratched or receiving a massage. Furthermore, these investigators did not observe in TS patients any greater ability to detect different intensities of olfactory and tactile stimuli as compared to healthy volunteers. This led them to suggest that the perceived sensitivities were the result of altered or impaired central processing [54].

Several rating scales have been designed to measure this hypersensitivity experienced by those with TS. The University of Sao Paulo Sensory Phenomena Scale (USP-SPS) was designed in 2005 in order to assess the severity and frequency of sensory phenomena that precede, accompany, or follow tics and other repetitive behaviors, such as compulsions or rituals [55]. Furthermore, in 2009 it was validated against other established scales, such as the Yale-Brown Obsessive-Compulsive Scale, Dimensional Yale-Brown Obsessive-Compulsive Scale, Yale Global Tic Severity Scale, Beck Anxiety Inventory, and Beck Depression Inventory, as a reliable instrument for measuring the presence and severity of sensory phenomena in individuals with OCD [49].

In addition to PPI as an experimental measure of sensorimotor gating, the Structured Interview for Assessing Perceptual Anomalies (SIAPA) and the Sensory Gating Inventory (SGI) are rating scales that were developed in order to quantify sensorimotor gating impairment seen in TS and schizophrenic patients. SIAPA was developed in 1999 as a way to measure perceptual anomalies, such as flooding or inundation of sensory stimuli in individuals with schizophrenia. The interview employs Likert ratings of perceived hypersensitivity, inundation, and selective attention to external sensory stimuli [51].

Furthermore, Hetrick et al. created the self-report rating scale, Sensory Gating Inventory (SGI) in an effort to expand upon the SIAPA scale by employing an empirical, factor analytic procedure to assess and systematically identify the phenomenology and major dimensions of sensory gating. The self-report rating scale also employs Likert ratings of subjective experiences, such as: perceptions of heightened stimulus sensitivity, sensory inundation, disturbances in the processes of focal and radial attention, and

exacerbation of sensory gating-like anomalies by fatigue and stress. The SGI scale demonstrated strong reliability and validity [50].

Exacerbating/Alleviating Factors:

Tic symptoms vary in frequency and intensity, and in addition to potential neurological variation, it has been shown that certain environmental or contextual factors will either exacerbate or alleviate tic symptoms in individuals with TS.

The results of 6 different descriptive studies looking at the effects of different antecedent variables on tic severity show stress and anxiety appear to be the most common factors associated with an increase in TS symptoms, while fatigue and boredom also rank high on the list [56]. On the other hand, relaxation, concentration, and physical exercise were antecedent factors shown to contribute to tic attenuation [56]. These studies are limited by the fact that they describe aggregate data, thus removing individual experiences from the descriptions, and they are subject to bias because data were collected by self report and parental observation.

Experimental designs studying the impact of various antecedent factors on tic expression show tic expression occurs more frequently in cases of direct, overt observation, during easy reading assignments, and when the tics themselves are spoken about. For instance, more tics were observed when children were overtly, as opposed to covertly, observed by a video camera; and the presence of another person in the room did not affect overall tic counts [57]. Also, direct observation revealed tics are aggravated by easy reading assignments, reading in a quiet classroom, and by the period between assignments [58]. Conversely, it has been shown that periods of focused attention to tasks and reduced peripheral sympathetic tone inhibit tic expression [59]. Another study

revealed tic-related conversations increase the frequency of phonic tics (not motor tics) as compared to conversations that do not have to do with tics [60]. Additionally, instructions to suppress tics have been shown to modestly reduce tic frequency, at least for 30 minutes, with adults demonstrating suppression more frequently. In this same study of 7 adults and children, tic suppression did not lead to the rebound effect of increased tic frequency after the period of suppression, but the impact of suppression instructions on strength of premonitory urges ratings remains unclear [61].

Furthermore, taken together, multiple studies have suggested stress, anxiety, frustration, and tension are emotional variables often associated with an increase in tics [56]. However, it remains unclear as to why certain emotions exacerbate tics and what their effect is on premonitory urges. With regard to consequent factors that affect tic expression, it has been shown reinforcing tic-free periods acts to reduce tic frequency, while paying attention to the tics themselves or publicly commenting on tics increases these symptoms [56].

Table 6. Exacerbating and Alleviating Factors

Tic Attenuation	Tic Exacerbation
Relaxation	Stress, anxiety, worry, frustration
Physical exercise, sports	Fatigue, tiredness
Concentration, study activity	Returning to school
Habitual, automatic actions	Boredom, waiting
Reading for pleasure	Emotional trauma
Leisure activity	Holidays, birthdays
Talking to friends	Working under pressure
Doctor visits	Overstimulation, multitasking
Verbal instructions to suppress tics and rewarding/reinforcing tic-free periods	Tic-related conversation
Interaction with familiar people	Being alone
Socialization (30%), social gatherings (25%)	Social gatherings (42%), socialization (50%) (presence of others/overt observation)
	Transportation

Adapted from data in (Conelea and Woods, 2008) [56].

Suppressing Tics:

One of the characteristics of tic symptoms is that they are suppressible, even if only for a short while. However, as stated earlier, the act of suppression can lead to the build-up of uncomfortable premonitory urges. In one study, 3 of 4 children who demonstrated reliable suppression showed a pattern of higher subjective urge ratings during suppression as compared to baseline [62].

Although tics can be suppressed, to do so requires more attention and energy from the individual. For instance, in a study involving 9 children with TS, ages 9–15, accuracy and performance on a distraction task was reduced while children were simultaneously told to suppress tics as compared to free-to-tic conditions [63]. However, no significant difference was demonstrated between tic frequencies during periods of reinforced suppression and reinforced suppression plus a distraction task. This study demonstrates accuracy on an attention-demanding task may be impacted if a child is simultaneously trying to suppress their tics: a finding that has strong implications on school performance for children with TS. This finding suggests school performance of children with TS may be impacted not only by tics but by the attention devoted to suppressing tics and highlights the importance of a supportive environment where negative feedback from their peers and teachers in response to tics is minimized.

Stress has been shown to be one of the major factors associated with tic exacerbation. In a study involving 10 youth with TS, ages 9–17, it was demonstrated that stress impacts children's ability to suppress tics but not necessarily their baseline tic frequency. Tic frequency was greater during periods of reinforced suppression plus a stressor as compared to just reinforced suppression [64]. However, tic frequency was not

different between free-to-tic baseline levels and periods when applied stress was added to this condition [64].

Additionally, it has been shown that tic suppression rewarded for tic-free intervals is more successful at reducing tic frequency than is just being told to suppress tics. For instance, in a study design in which tokens were delivered both contingently on the absence of tics and non-contingently, tic frequency was lower in 3 of 4 children during the former condition. The success of reinforced tic suppression could be one of the reasons children are seen to tic more at home than in the classroom because tic absence is reinforced in the classroom by the avoidance of teasing from peers [65]. Alternatively, it is possible tic frequency is greater at home than in the classroom because children become more tired by the end of the day when they return home from school.

Finally, one concern with the use of reinforced tic suppression as a model for therapy is the potential for a tic rebound effect, which describes an increase in frequency of tics after suppression. However, studies have not supported such concerns. Although tic frequencies have been shown to increase post-suppression as compared to during suppression, they do not increase above pre-suppression levels [66]. Another study demonstrated similar findings after repeated 2-hour sessions of Exposure and Response Prevention (ER), a behavioral treatment program, consisting of habituation to premonitory sensory experiences during prolonged tic suppression. The study demonstrated successful ER as this treatment resulted in a reduction of tics by 91% as compared to baseline. However, comparison of 15 minute pre- and post-suppression measurements did not result in a significant increase in tic frequency [67]. Additionally,

one study noted the absence of the rebound effect in the 5 minutes following reinforced tic suppression during periods of up to 40 consecutive minutes [68].

Comorbidities:

The description of behavioral and emotional disturbances in patients with TS has occurred since 1899, around the time the disorder was first described by Georges Gilles de la Tourette himself [69]. In fact, comorbid neuropsychiatric disorders, the majority being ADHD and OCD, have been shown to occur in up to 90% of TS patients in both clinic and community settings [70]. Figure 2 depicts the time course of common comorbidities in relation to tic symptoms, as experienced by patients with TS (Fig. 2).
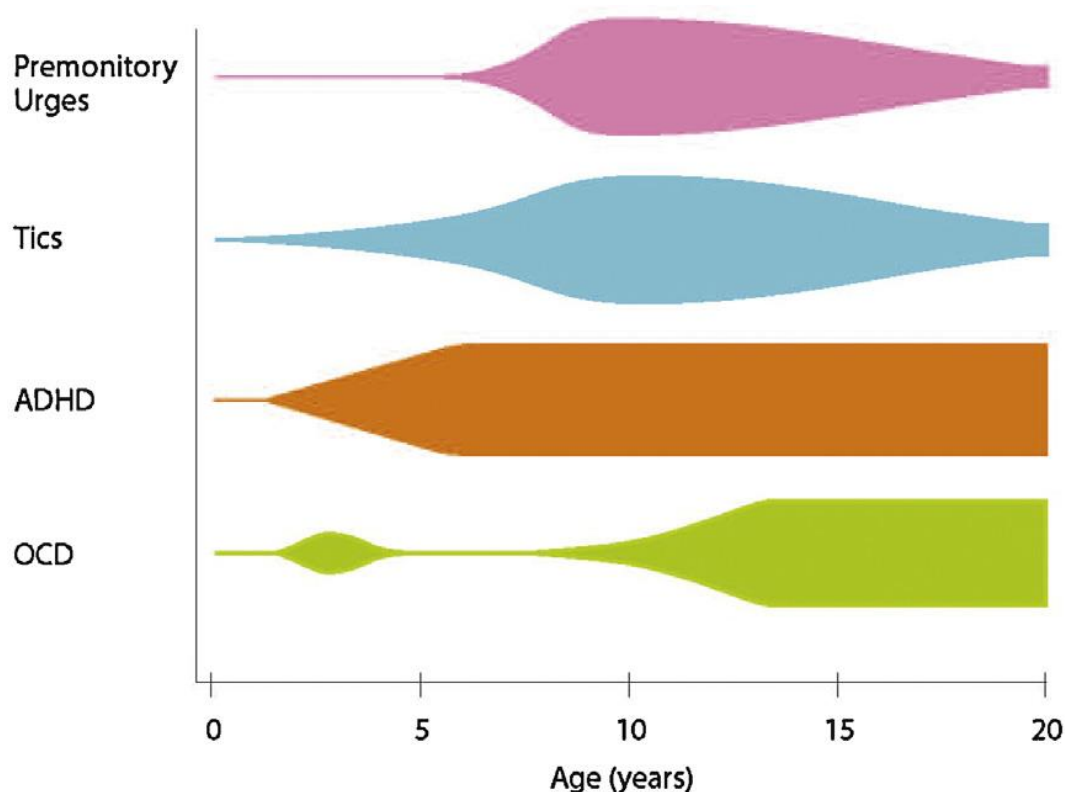
Fig. 2. Clinical course of Tourette syndrome and associated conditions. Figure depicts severity of premonitory urges, tics, or comorbid conditions symptoms associated with Tourette syndrome. Width bars correspond to severity of symptoms of each condition over time. Adapted with permission from [28].

Obsessive-Compulsive Disorder:

Roughly one-third to one-half of individuals with TS experience recurrent obsessive- compulsive (OC) symptoms [71-73]. Genetic, neurobiological, and treatment response studies suggest there may be qualitative differences between tic-related forms of OCD and cases of OCD not related to tics. Specifically, tic-related OCD has a male preponderance, an earlier age of onset, a poorer level of response to standard anti-obsessional medications, and a greater likelihood of first-degree family members with a tic disorder [74]. Symptomatically the most common obsessive-compulsive symptoms encountered in TS patients are obsessions concerning a need for symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions [73]. Also, obsessive-compulsive symptoms, when present, in children with TS, appear more likely to persist into adulthood than the tics themselves [29]. OCD with comorbid tics is less responsive to SSRI pharmacotherapy and more responsive to antipsychotic augmentation than OCD in patients without tics [75, 76]. OCD patients with and without tic disorders appear equally responsive to cognitive-behavioral therapy [76].

Baseline data from a study of 158 youth with a chronic tic disorder (TD) showed children with comorbid OCD (53% of subjects) experienced more severe tics, increased levels of depressive and anxious symptoms, heightened psychosocial stress and poorer global functioning [77]. The authors concluded TD with OCD is a more severe subtype of TD and describes children with more internalizing disorders than those without OCD [77]. By contrast, another exploratory study involving 306 children with TD, OCD, or TD + OCD, failed to show that those with TD + OCD exhibited increases in tic severity as compared to those with TD alone [78].

Attention-Deficit Hyperactivity Disorder:

Roughly 30–50% of children with TS are diagnosed with comorbid ADHD [72]. This rate of comorbid ADHD is higher in clinical samples. Although the etiological relationship between TS and ADHD is unclear, it is clear individuals with both TS and ADHD are at a much greater risk for a variety of poor outcomes including greater academic and social impairment [79-83]. Children with TS are often regarded as more aggressive, more withdrawn, and less popular than their classmates, and comorbidity with ADHD is associated with these difficulties [84]. Surprisingly, levels of tic severity are less predictive of peer acceptance than is the presence of ADHD [83]. Comorbid ADHD symptoms in children with tics are responsive to similar pharmacological treatment as are ADHD symptoms in children without tics [85]. Therefore, prompt screening of ADHD symptoms in children with tic disorders is imperative. We suggest examination of recent practice parameters for a thorough review of the diagnosis, assessment, and treatment of ADHD [86, 87].

Impulse Control Disorders:

In addition to the high frequency of such comorbid conditions as ADHD and OCD, many children with TS have been noted to exhibit rage attacks, self-injurious behavior, inappropriate sexual activity, discipline problems, sleep disturbances, and other forms of impulse control disorders. Disruptive, Impulse-Control, and Conduct Disorders are currently listed as a category within the DSM-V [9]. "Impulsivity is defined as the failure to resist an impulse, drive, or temptation that is potentially harmful to oneself or others. It is evidenced behaviorally as carelessness; an underestimated sense of harm; extroversion; impatience, including the inability to delay gratification; and a tendency

toward risk-taking and pleasure- and sensation-seeking" [70]. Wright et al. review TS as it relates to impulse-control disorders, specifically, intermittent explosive disorder (IED), self-injurious behavior (SIB), and other forms of impulse-control disorder.

This type of disinhibited behavior is inextricably linked to tics. For instance, some individuals will have the urge to make a loud vocal tic in a quiet library upon seeing the sign, "Quiet Please." Similarly, one can feel the need to jerk his shoulder after someone lightly puts their hand on it. This type of behavior could represent the disrupted sensory gating in that the light stimulus is bothersome and can create a site of unpleasant urge. Furthermore, there is the example of a physicist during WWII, who had to relinquish his job in a high energy physics laboratory because whenever he saw the sign, "Danger High Voltage," he had the strong urge to touch the apparatus. These types of tics are seen as reflexive tics to specific sensory clues, but often appear as disinhibited or impulsive behavior.

It is estimated between 23% and 40% of clinically-referred TS subjects report distressing behavioral symptoms, such as sudden unpredictable anger, irritability, temper outbursts, and aggression [70]. A part of intermittent explosive disorder, rage attacks have been linked to TS since as early as 1998, when it was suggested individuals with TS and another comorbid condition, such as ADHD or OCD, are more likely to also experience rage attacks [88]. Since then, a study in 2008 showed that of 314 children in a Danish cohort of TS patients, 109 experienced rage attacks. Interestingly, when examining the presence of rage attacks within different subgroups, it was noted rage attacks were present in the greatest percentage (70.6%) of children who have TS with both ADHD and OCD. In those with TS and ADHD, 56.7% experienced rage, which is

similar to the 50.9% of children with TS and OCD who experience rage. In those children who have TS alone, 36.7% exhibited rage attacks [89]. These data could support the suggestion that impulsivity and compulsivity are interlinked. Another hypothesis as to why OCD is linked to rage attacks in TS patients is that the sudden, impulsive outbursts of anger are a result of a disruption to routines that are linked to the compulsivity present in these patients [70]. In 2003, a questionnaire was developed in order to screen TS patients for episodic rage according to their symptoms. In this study, 48 children with TS, ages 7–17, were screened to explore rage attack phenomenology, and the investigators used a cluster analysis to identify four potential subgroups of TS with rage: specific urge resolution, environmentally secure reactivity, nonspecific urge resolution, or labile non-resolving [90].

Furthermore, self-injurious behavior (SIB) has been consistently associated with a subgroup of TS patients. Of the 9 patients described by Gilles de la Tourette in 1885, 2 of them were described as exhibiting SIB. Self-injurious behavior has been reported in anywhere between 14.8% and 29% of TS subjects [91, 92]. Additionally, the proportion of SIB present in those with TS is higher in those with comorbid ADHD and who are older in age. In those patients with ADHD and TS, age of onset of SIB was 7.4 years, as compared to 10 years in those without ADHD [91]. Examples of types of SIB noted are biting one's tongue or lip, head-banging, body punching/slapping, head or face punching/slapping, body-to-hard-object banging, and poking sharp objects into one's body [70].

The co-occurrence of impulse-control disorders and TS has further implications on the cognitive aspects of these individuals. They can exhibit the inability to delay

gratification, the tendency toward making decisions based on immediate reward, they are

distractible, and they are generally disinhibited, all of which can lead to behavior that

does not comply with cultural norms. If impulsivity and compulsivity are thought to be

opposite ends of a spectrum, TS would be considered a mixture of the two. While

compulsions are driven by an attempt to reduce anxiety, impulsions are driven by an

attempt to obtain arousal and gratification [70].

Concluding Thoughts:

Tourette syndrome is a neuropsychiatric disorder characterized by multiple motor

and vocal tics. In the majority of children with TS, tic symptoms diminish significantly

during adolescence. Most individuals with TS experience associated sensory phenomena

such as premonitory urges and somatic hypersensitivity that are often as distressing as the

tics themselves. On the other hand, for many individuals with TS, the tics are neither the

most prominent nor distressing part of the disorder. The majority of individuals with TS

reaching clinical attention have common comorbid conditions such as ADHD, OCD and

impulse control disorders. Proper diagnosis and treatment of TS involves appropriate

evaluation and recognition, not only of tics, but also of these associated conditions.

Section 2. Psychostimulants and tics:

Psychostimulants are recommended as the first line pharmacologic treatment for

children with ADHD [87]. Psychostimulants have demonstrated a larger effect size when

compared to placebo, as compared to alternative pharmacological treatments for ADHD

[85]. Randomized controlled trials have demonstrated that psychostimulants are more

effective than behavioral treatments for ADHD for at least 14 months after the start of

treatment [93]. When ADHD is present in children with tics, the symptoms of ADHD typically cause greater impairment in academic performance, social relationships, and neuropsychological performance, especially executive functioning, than the tics themselves [81-83, 94, 95]. Psychostimulants have been shown to be equally efficacious in treating ADHD symptoms in children with ADHD and comorbid tics as in children with ADHD alone [85].

Clinical practice currently restricts the use of psychostimulant medications in children with ADHD and comorbid tics. The limited use of psychostimulants in patients with ADHD and comorbid tic symptoms is likely partially attributable to warnings placed on the medications by regulatory agencies. The Food and Drug Administration (FDA) currently requires that psychostimulants list tics and/or a family history of a tic disorder as a contraindication (methylphenidate) or significant adverse reaction (methylphenidate and amphetamines) to their use [96, 97]. FDA labeling warns parents that psychostimulants "should not be taken by their child" (methylphenidate) and/or "may not be right for your child" (amphetamines) if they have tics [98, 99]. Amphetamine/Dextroamphetamine labeling also warns the public to "use with caution in patients with Tourette's syndrome; stimulants may unmask tics" [100]. The FDA warnings resulted largely from a series of case reports and case series, which were published in the 1970s and 1980s [101-111]. A particularly influential case series of 15 children who developed tics while on psychostimulants helped lead the FDA in 1983 to require listing contraindications and significant adverse reactions to psychostimulant medications [112].

Since then, however, multiple randomized controlled trials (RCTs) have demonstrated no effect of psychostimulants on tics [113-116]. In fact, an NIH- and Tourette Syndrome Association-funded trial examining treatment of ADHD in children with tics concluded "that prior concerns that MPH worsens tics and that the drug should be avoided in patients with tics may be unwarranted" [113]. Recent meta-analyses examining pharmacological treatment of children with tics and ADHD demonstrated that methylphenidate did not significantly worsen tic symptoms and was beneficial in treating ADHD symptoms in children with both conditions [85, 117].

There is, however, strong biological rationale to suggest that psychostimulants might exacerbate tics. Methylphenidate and dextroamphetamine induce stereotypies in rats in a dose-dependent manner [118-120]. Stimulant-induced stereotypies in rodents are hypothesized to be an animal model for tic disorders [121]. Furthermore, psychostimulants have been demonstrated to increase dopamine in the synaptic cleft [122] whereas the most effective anti-tic medications available, antipsychotic medications, act as dopamine antagonists [28, 123, 124].

On the other hand, the timing of onset of ADHD and Tourette syndrome represents a possible confounder. Roughly 20% of children with ADHD go on to develop a chronic tic disorder [125]. When ADHD and tics co-occur in an individual, the onset of ADHD typically precedes that of tic symptoms by 2 to 3 years [28]. Therefore, it is difficult to determine whether the tics are a result of a side-effect of psychostimulants or if they were to occur anyway, as children with ADHD are at higher risk of developing tics regardless of medication use. Also, tics in Tourette syndrome typically wax and

wane in severity, so it is unclear whether a patient's tics are going to naturally increase at a given time or if the increase is a result of psychostimulant side-effects.

Clinicians are uncertain regarding use of psychostimulants in children with existing tics or a family history of tics because of conflict between strong FDA labeling contradicting psychostimulant use in this population and randomized, controlled trial and meta-analysis data suggesting efficacy without any apparent risk in the same population.

Statement of Purpose and Hypothesis

The goal of this meta-analysis is to provide an evidence base for future guidelines, warnings, and clinical decisions for the use of psychostimulants in children who develop tics after psychostimulant use or are judged to be at increased risk of developing tics prior to psychostimulant use. We will examine all available data on side-effects in previous randomized, placebo-controlled trials of psychostimulants in childhood ADHD to determine the risk of new-onset or worsening of tics associated with psychostimulants compared to placebo. We will conduct secondary analyses to examine the effects of psychostimulant type (methylphenidate vs. mixed amphetamine salt derivatives, long versus short-acting formulations), dose, duration, recorder of side-effects, trial design, and participant age on the risk of tics with psychostimulant treatment.

Methods

Search Strategy for Identification of Studies:

Two reviewers (JMM and EFO) searched the electronic database of PubMed on August 18, 2013 for relevant studies using the search: (Attention deficit disorder with hyperactivity OR ADHD OR ADDH OR hyperactiv* OR hyperkin* OR "attention

deficit*" OR "brain dysfunction") AND (methylphenidate OR Ritalin OR Metadate OR Equasym OR Daytrana OR Concerta OR Dextroamphetamine OR amphetamine OR Adderall OR Vyvanse OR Dexedrine OR Dextrostat). The search only utilized randomized controlled trials. The references of appropriate papers on the safety and efficacy of psychostimulant medications were also searched (by SCC) for citations of further relevant published and unpublished research.

Selection of Studies:

The titles and abstracts of studies obtained by this search strategy were examined by two reviewers (JMM and EFO) to determine inclusion in this meta-analysis. Any discrepancies were resolved by a final reviewer (MHB). Authors (SCC, CGC, and JMM) re-checked this work to make sure the database created was accurate. Eligibility for the study was based upon analysis of the full articles for the following criteria (1) they are randomized, double-blind, placebo-controlled clinical trials of psychostimulant medications (methylphenidate or dextroamphetamine derivatives) compared with placebo and (2) participants included are children and adolescents less than 18 years of age diagnosed with ADHD or hyperkinetic disorder by explicit criteria i.e. DSM or ICD criteria. Exclusion criteria for the studies included if (1) the study was not published in English, (2) the study population included only patients with ADHD plus another primary comorbidity i.e. mental retardation, pervasive developmental disorder, oppositional defiant disorder, tics, or anxiety, (3) the medication of interest was given for less than 7 days in duration, (4) there were fewer than 10 subjects (crossover design) or fewer than 20 subjects (parallel design), and (5) the primary goal of the trial was not treatment for ADHD (e.g. studies which were primarily concerned with neuroimaging or

neuropsychological measures were excluded). We required medication/placebo each to be given for at least 7 days in trial because the authors *a priori* decided that this was the minimum required time needed in order to be confident regarding a change in tic symptoms. A 7-day assessment period is similar to that utilized for common clinical rating scales of tic symptoms such as the Yale Global Tic Severity Scale [13]. We additionally restricted trials to treatment trials as studies utilizing non-treatment related outcome measures such as MRI, EEG or neuropsychological testing were less likely to systematically assess side-effects of medications.

Meta-Analytic Procedures:

Data was extracted by independent reviewers (SCC, JMM, CGC, and ZDS) on specially designed Microsoft Excel spreadsheets. Our primary outcome measure was the proportion of children reporting tics as a side-effect of medication. When possible, clinician-rated side-effect measures were utilized as the main outcome measure. When this information was unavailable, participant-rated, parent-rated, or teacher-rated side-effect measures were used. Reviewers additionally gathered data on trial medication, trial design, maximum daily medication dose, number of participants, mean age of participants, duration of active treatment in trials, who recorded side-effect ratings, and other relevant attributes and results of the studies. Any disagreement among reviewers was mitigated through discussion and the procurement of more information from the study investigators when possible. When agreement could not be attained between the initial reviewers, the senior investigator (MHB) resolved all disputes. When information about proportion of tics was not available in the original manuscripts, the corresponding author was contacted (by SCC and CGC) for further information. If contacting the

corresponding author was ineffective, pharmaceutical company databases were searched (by CGC) for the data.

All statistical analyses were completed (by MHB) in Comprehensive Meta-Analysis Version 2.   For our outcome measures of interest, proportion of subjects experiencing tics was analyzed using pooled risk ratio (RR). Absolute risk difference (ARD) and number needed to harm (NNH) were also reported for the primary outcome as both the absolute and relative risks are clinically relevant when considering the use of medications. For all outcome measures, 95% confidence intervals (CIs) were conveyed. A fixed-effects model for meta-analysis was used, as well as a random-effects model in sensitivity analysis. Publication bias was assessed by plotting the effect size against standard error for each included trial (i.e., funnel plot). In addition, publication bias was statistically tested by the Egger's test and by determining the association between sample size and effect size in meta-regression. We additionally reported the risk of new-onset or worsening of tics in both the psychostimulant and placebo groups in order to assist clinicians in decision-making. We report results of a random effects model for these data as it is clear there was significant heterogeneity in how tics were assessed and the frequency that tics were reported within the placebo and psychostimulant groups based on trial methodology.

For secondary analyses several subgroup analyses and meta-regressions were accomplished. Stratified subgroup analyses were conducted based on (1) type of psychostimulant (methylphenidate vs. mixed-amphetamine derivatives), (2) duration of action of medications (long-acting vs. short-acting psychostimulants), (3) recorder of side-effect data, and (4) trial design (crossover vs. parallel group trials). We utilized the

test for subgroup differences (between group heterogeneity chi-square) in the mixed-effects model of CMA to test for subgroup differences. Meta-regression analysis was used to examine the effect of (1) maximum daily dose of psychostimulants utilized in trials, (2) length of active psychostimulant treatment, and (3) age of participants on the risk of developing new-onset or worsening of tics with psychostimulants compared to placebo. All daily doses of psychostimulants were converted into methylphenidate equivalents using previously described methodology [126]. Our threshold for statistical significance was p<0.05 for the primary analysis, as well as for all stratified subgroup analyses and meta-regression.

Results

Included Trials:

Fig. 3 depicts the selection of trials for this meta-analysis. A total of 815 references were identified in PubMED. A total of 92 trials were eligible for inclusion. Of these 92 trials, 16 trials published data on tics as a side-effect of psychostimulant medication. Authors of 6 additional trials responded to email requests with unpublished data regarding the risks of tics in psychostimulant trials. Therefore, a total of 22 trials, involving 2385 participants, were included in our meta-analysis [127-148]. The characteristics of included trials are depicted in Table 7.
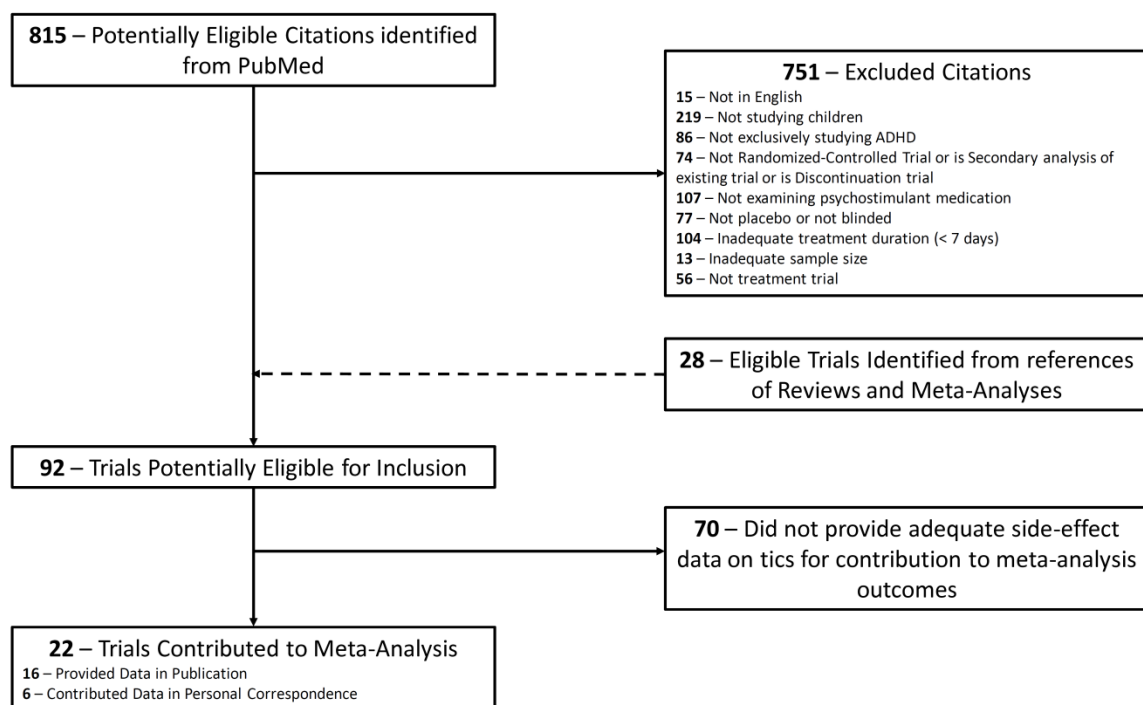
Fig. 3. Selection of studies. Note: ADHD = attention-deficit/hyperactivity disorder

Table 7. Characteristics of Included Trials in the Meta-Analysis of the Risk of Tics with Psychostimulants.

Authors	Year	Medication	Stimulant Class	Duration of Action	Maximum Dose	Design	Duration of Active Treatment	N	Mean Age (years)
Werry et al. [127]	1974	MPH IR	MPH	Short	0.5 - 1 mg/kg/day	Crossover	4 week	37	8.9
Gittelman-Klein et al. [128]	1976	MPH IR	MPH	Short	60 mg/day	Parallel	4 weeks	80	8.6
Werry et al. [129]	1980	MPH IR	MPH	Short	0.4 mg/kg/day	Crossover	3-4 weeks	30	8.4
Rapport et al. [130]	1985	MPH IR	MPH	Short	15 mg/day	Crossover	1 week	12	6-10
Barkley et al. [131]	1990	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7-10 days	82	8.2
Buitelaar et al. [132]	1996	MPH IR	MPH	Short	10 mg BID	Parallel	4 weeks	21	9.2
Stein et al. [133]	1996	MPH IR	MPH	Short	20 mg TID	Crossover	1 week	25	8.0
Gillberg et al. [134]	1997	MAS IR	AMP	Short	45 mg/day	Parallel	3 months	56	9
Firestone et al. [135]	1998	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7-10 days	32	4.8
Pliszka et al. [136]	2000	MPH IR	MPH	Short	50 mg/day	Parallel	3 weeks	58	8.1
		MAS IR	AMP	Short	30 mg/day				
Pelham et al. [137]	2001	OROS® MPH	MPH	Long	54 mg/day	Crossover	1 week	68	9.1
		MPH IR	MPH	Short	15 mg TID				

Wolraich et al. [138]	2001	OROS® MPH	MPH	Long	54 mg/day	Parallel	4 weeks	282	9.0
		MPH IR	MPH	Short	15 mg TID				
Greenhill et al. [139]	2002	MPH MR	MPH	Long	60 mg/day	Parallel	3 weeks	316	9
McCracken et al. [140]	2003	MAS XR	AMP	Long	30 mg/day	Crossover	1 week	49	9.5
		MAS IR	AMP	Short	10 mg/day				
Stein et al. [141]	2003	OROS® MPH	MPH	Long	54 mg/day	Crossover	1 week	47	9
Findling et al. [142]	2006	EqXL	MPH	Long	60 mg/day	Parallel	3 weeks	318	9.5
		MPH IR	MPH	Short	30 mg BID				
Gorman et al. [143]	2006	MPH IR	MPH	Short	1 mg/kg divided daily	Crossover	3 weeks	41	9.1
Findling et al. [144]	2008	MPH Patch	MPH	Short	30 mg 9hr/day	Parallel	2 weeks	274	8.7
		OROS® MPH	MPH	Long	54 mg/day				
Newcorn et al. [145]	2008	OROS® MPH	MPH	Long	54 mg/day	Parallel	6 weeks	293	10.2
Silva et al. [146]	2008	dMPH ER	MPH	Long	30 mg/day	Crossover	1 week	82	9.4
		MPH MR	MPH	Long	54 mg/day				
Solanto et al. [147]	2009	MPH IR	MPH	Short	50 mg/day	Crossover	1 week	25	8.8
Lee et al. [148]	2011	MPH IR	MPH	Short	0.5 mg/kg/day	Crossover	1 week	157	9.0

Note: AMP = amphetamine; BID = twice daily; dMPH = dexmethylphenidate; EqXL = Equasym XL; IR = immediate release; MAS = mixed amphetamine salts; MPH = methylphenidate; MR = modified-release; MTS = methylphenidate transdermal system; OROS = trademarked acronym denoting Osmotic Controlled-Release Oral Delivery System; Ref = reference; TID = 3 times daily; XR/ER = extended-release.

Risk of new-onset or worsening of tics with psychostimulants:

Meta-analysis of 22 studies involving 2385 participants demonstrated no significant increase in the risk of new-onset or worsening of tics when comparing psychostimulant to placebo (Fig. 4), RR=0.99 (95% CI: 0.78 to 1.27), z=-0.05, p=0.96. There was no significant heterogeneity between trials (I^2 =12.7%, p=0.28) or evidence of publication bias (Egger's test: p=0.88). A random effects model produced similar estimates of risk when examined in a sensitivity analysis (RR=0.97 (95%CI: 0.72 to 1.32), z=-0.18, p=0.86).
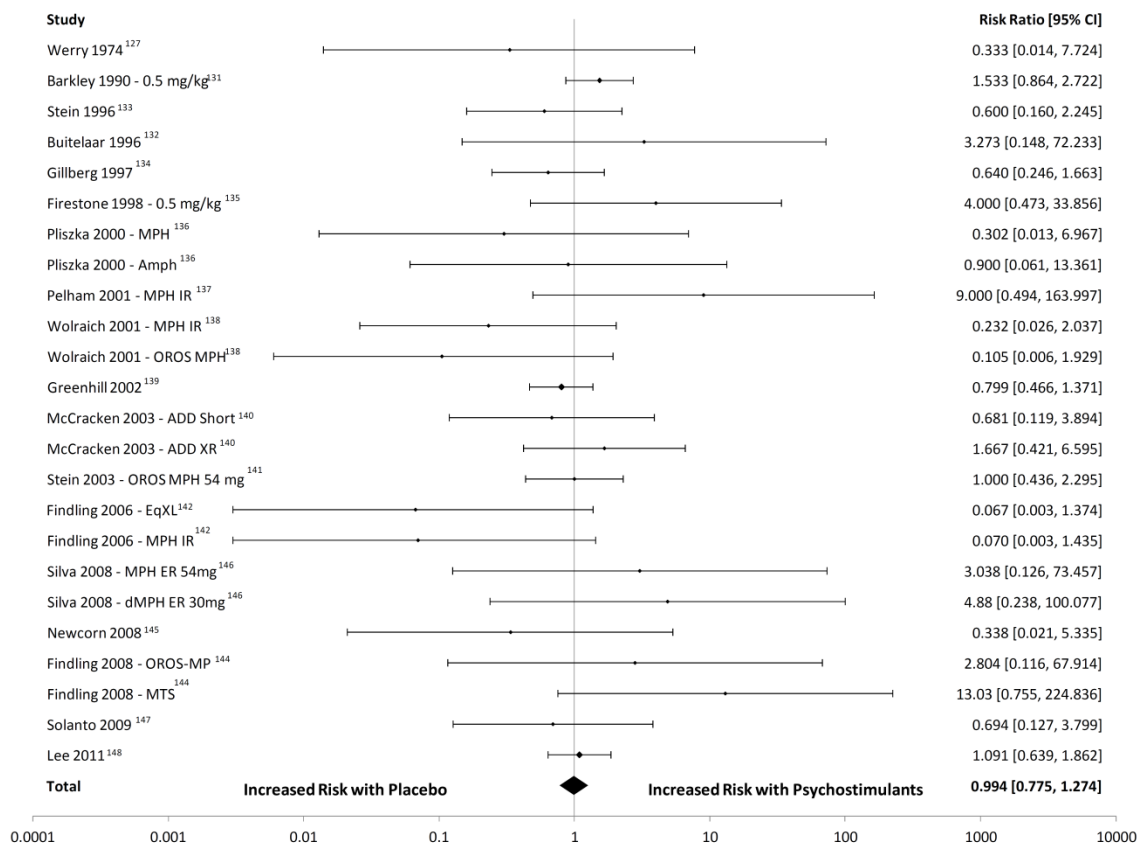
Fig. 4. Relative risk of tics with psychostimulants compared to placebo. Note: Forest plot comparing the relative risk of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (risk ratio = 0.99, 95% confidence interval = 0.78 to 1.27, z = -0.05, p = 0.96).

There was also no evidence of increased risk of new-onset or worsening of tics when examining absolute risk difference of tics with psychostimulants compared to placebo (Fig. 5), ARD=0.001 (95% CI: -0.009 to 0.011), z=0.18, p=0.86). There was no significant heterogeneity among trials (I^2 = 9.6%, p=0.32) or evidence of publication bias (egger's test: p=0.88). A random effects model produced similar estimates of risk when examined in a sensitivity analysis (ARD=0.001 (95% CI: -0.011 to 0.013), z=0.16, p=0.88.
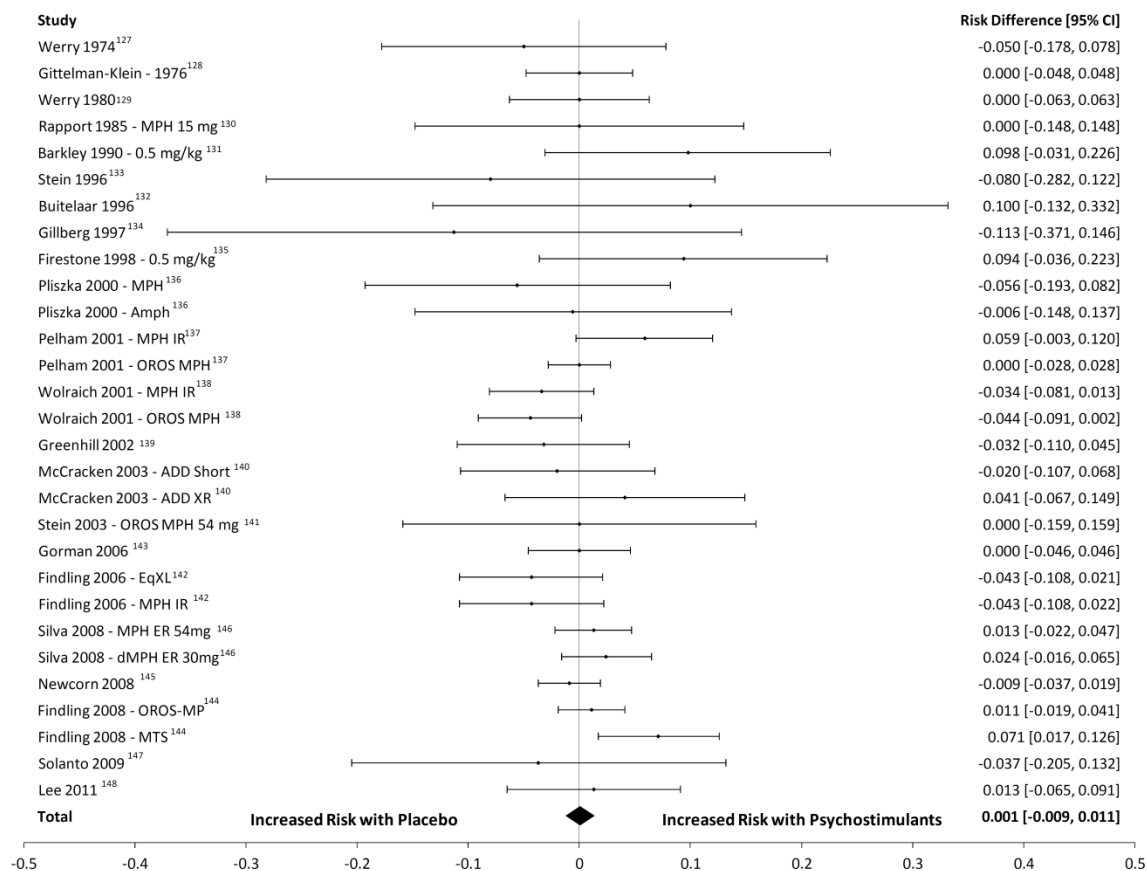
Fig. 5. Absolute risk difference of tics between psychostimulants and placebo. Note: Forest plot depicting the absolute risk difference of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (absolute risk difference = 0.001, 95% confidence interval = -0.009 to 0.011, z = 0.18, p = 0.86).

In random effects meta-analysis, 5.7% of children in the psychostimulant arms of trials reported new onset or worsening of tics (event rate=5.7% (95% CI: 3.7% to 8.6%), I^2 = 72%, p<0.001). However, the event rate for new-onset or worsening of tics was higher in the placebo arms of included trials (event rate=6.5% (95% CI: 4.4% to 9.5%), I^2 = 64%, p<0.001).

Methylphenidate vs. Amphetamine Derivatives:

Stratified subgroup analysis demonstrated no significant difference in risk of new-onset or worsening of tics (test for subgroup differences χ^2=0.26, p=0.61) between methylphenidate derivatives (RR=1.02 (95% CI: 0.78 to 1.33), k=20, z=0.14, p=0.89) and amphetamine derivatives (RR=0.84 (95% CI: 0.42 to 1.68), k=4, z=-0.49, p=0.63).

Long- vs. Short-acting psychostimulants:

Stratified subgroup analysis demonstrated no significant difference in risk of new-onset or worsening of tics (test for subgroup differences χ^2=0.22, p=0.64) between short-acting (RR=1.04 (95% CI: 0.76 to 1.43), z=0.25, p=0.80) and long-acting psychostimulants (RR=0.92 (95% CI: 0.62 to 1.38), z=-0.40, p=0.69).

Psychostimulant Dose:

Meta-regression demonstrated no significant association between dosage of psychostimulants and the risk of new-onset or worsening of tics (β=-0.0023 (95% CI: -0.0142 to 0.0097), z=-0.37, p=0.71). There was no significant association between dosage of psychostimulants and risk of new-onset or worsening of tics when analysis was restricted to methylphenidate (β=-0.0005 (95% CI: -0.0159 to 0.0150), z=-0.06, p=0.95) or amphetamine derivatives (β=-0.0028 (95% CI: -0.0280 to 0.0224), z=-0.22, p=0.83).

Duration of Active Treatment:

Meta-regression demonstrated no significant association between duration of active treatment and the risk of new-onset or worsening of tics associated with psychostimulant medication (β=-0.010 (95% CI: -0.022 to 0.002), z=-1.69, p=0.09).

Recorder of Side-effect Data:

Stratified subgroup analysis demonstrated no significant difference in risk of new-onset or worsening of tics based on whether clinicians or non-clinical informants (parents and/or teachers) were rating tic outcomes (test for subgroup differences χ^2=1.49, p=0.22). The relative risk of tics was non-significantly lower when utilizing clinician recorders of tics (RR=0.72 (95% CI: 0.41 to 1.29), z=-1.10, p=0.28) rather than non-clinical report (RR=1.08 (95% CI: 0.82 to 1.42), z=0.53, p=0.59).

Trial Design:

Crossover studies reported a significantly greater association of new-onset or worsening of tics with psychostimulants compared to parallel-group studies (test for subgroup differences χ^2=5.3, p=0.02). However, neither crossover trials (RR=1.23 (95% CI: 0.90 to 1.68), z=1.3, p=0.19) nor parallel-group studies (RR=0.67 (95% CI: 0.44 to 1.02), z=-1.88, p=0.06) reported a significant association of tics with psychostimulant use.

Age of Participants:

Meta-regression demonstrated no significant association between participants' age and measured risk of new-onset or worsening of tics with psychostimulant medications (β=-0.39 (95% CI: -0.83 to 0.05), z=-1.75, p=0.08).

Discussion

Meta-analysis demonstrated no statistically significant relationship between psychostimulant use and new-onset or worsening of tics in children with ADHD. Specifically, the relative risk of new-onset or worsening of tics was 0.99 (95% CI: 0.78 to 1.27) indicating no evidence of an association between psychostimulants and tics.

Furthermore, we found no association between risk of new-onset or worsening of tics and

dosage, type or duration of use, psychostimulant agent, or recorder of side-effect data.

Taken together, data from this meta-analysis is most consistent with an absence of a risk

of new-onset or worsening of tics with psychostimulant medications. However, the

power of this meta-analysis is not sufficient to rule out the possibility of a small increased

risk of tics with psychostimulant use. However, based on the available data, it remains

equally likely that psychostimulants reduce the risk of tics as they do raise the risk of tics.

Current evidence from this meta-analysis and previous work examining the effects

of psychostimulants in children with tics and ADHD does not support the clinical practice

of restricting the use of psychostimulants in children with tics or at high risk of

developing tics [98, 99]. Previous meta-analysis examining the effects of

methylphenidate in children with ADHD and comorbid tics demonstrated that

psychostimulants appear to have a similar effect size in reducing ADHD symptoms in

children with comorbid tics as in children without comorbid tic disorders [85].

Furthermore, there was no evidence that psychostimulants worsened tic symptoms in

children with both ADHD and tics [85].   Randomized controlled trials in children with

ADHD and tics have further demonstrated that combination treatment with

methylphenidate and clonidine is more effective than either medication alone [113]. Our

meta-analysis extends upon these previous results by demonstrating that there is no

increased risk of new-onset or worsening tics with psychostimulant use compared to

placebo in meta-analysis of randomized, placebo-controlled trials in children with ADHD

alone.

The results of this meta-analysis also provide strong support for re-challenging children (or even continuing children on psychostimulants) who develop tics that are temporally related to the initiation of psychostimulants. Assuming the absolute risk difference of 0.001 observed in the meta-analysis, the number needed to harm for new-onset or worsening tics with psychostimulants is 1000 (95% CI: 77 to ∞). If additionally assuming the baseline risk of experiencing new-onset tics over short-term trials of medications is equivalent to the 6.5% observed in the placebo arms of randomized, controlled trials of psychostimulants then in a child who develops tics shortly after initiating psychostimulants, the tics are 65-fold more likely to be the result of coincidence than caused by the medication. Even assuming the highest risk of tics (0.011 -- at the upper bound of the 95% confidence interval of absolute risk difference), when new-onset or worsening of tics appear after the initiation of psychostimulants, the tics are 6-fold more likely to be a result of coincidence than be caused by the medications. Given the absence of data suggesting psychostimulants make existing tics worse [85, 113], re-challenging appears reasonable, whether or not the tics persist after discontinuation of the psychostimulant. Re-challenging appears particularly advisable in children whose ADHD does not respond sufficiently to other medications such as alpha-2 agonists and atomoxetine, which are used to help ADHD and may additionally help improve tics symptoms [124, 149, 150].

There are several limitations to this meta-analysis that may have affected its findings. Foremost among these limitations is the fact that a limited number of randomized, placebo-controlled trials of psychostimulants for children with ADHD actually reported on the frequency of tics as side-effects. The selective reporting of tics in

side-effect data, if it existed, could lead to publication bias that would likely exaggerate the association between tics and psychostimulants. Many trials only report side-effects that were above a certain percent threshold in the active treatment group or were statistically different between groups. This practice would also lead to an inflated estimate of the association between psychostimulants and tics, as trials with increased associations would be selectively published and included in our meta-analysis. In order to minimize this potential bias, we emailed authors of potentially eligible trials that did not include data on tics in order to obtain additional data to include in the meta-analysis. However, many authors were unresponsive or did not have available data from the trial, so this potential bias should not be discounted. Another potential limitation is the inclusion of crossover trials in addition to parallel group trials in this meta-analysis. We made the decision to include crossover trials to maximize power in our meta-analysis. Crossover trials of psychostimulants were designed using washout periods of sufficient time to eliminate any beneficial effects of psychostimulants before the start of the next phase of the trial. It remains quite possible that if tics occurred as an adverse event in crossover trials, they might still carryover to the next trial phase and thus dampen our ability to detect tics as an adverse effect of treatment. However, stratified analysis demonstrated an increased measured risk of tics with psychostimulants in crossover studies compared to parallel-group studies, arguing against this phenomenon occurring. An additional potential limitation is the heterogeneity in how tics were assessed as a side-effect between trials – some trials relied on parent-report, whereas others included direct observation of subjects. We conducted stratified subgroup analysis based on whether or not a clinician was rating side-effects. We did not observe any significant effect based on

who was rating side-effect symptoms. Additionally, some trials require significant impairment for side-effects to be reported while others do not. Because of the manner in which tics are reported as a side-effect in trials, we are unable to determine whether individual reported adverse events in trials were due to (1) a new-onset of tics or (2) worsening of pre-existing tics. We therefore are only able to comment on the aggregate risk of either of these two events occurring but not of each event individually. It should also be emphasized that our data only applies to use of psychostimulants within the recommended therapeutic dose range. Both data in animal models and children with tics has suggested that supratherapeutic doses of psychostimulant medications may worsen tics [114, 118-120]. Another limitation to this meta-analysis is the fact that the studies included in our meta-analysis do not have available data on whether tics resolve or persist after medication or placebo discontinuation.

Conclusion

In conclusion, this meta-analysis suggests that new-onset or worsening of tics appear to occur at a fairly high rate (5-7%) in the period immediately after starting psychostimulants. However, tics were no more likely to be associated with psychostimulant treatment than with placebo. When tics occur in temporal relationship to psychostimulant use, this relationship is much more often coincidental than causative. There are several potential confounding factors that may explain the high-rate of tics reported in children after starting psychostimulants. The high rate of tics observed in children with ADHD and the waxing-and-waning nature of tic symptoms may explain some of this phenomenon [151]. Additionally, tics have been demonstrated to worsen during periods of stress, excitement, and fatigue [151]. The initiation of psychostimulants

often coincides with the start of the academic year or in the face of increasing academic/social difficulties – natural periods of high stress, excitement and fatigue for children. Therefore, the temporal relationship between psychostimulant use and new-onset tics could be largely or completely attributable to confounding. Future research investigating side-effects associated with medications could be greatly enhanced by requiring pivotal trials to make side-effect data publically available. Additionally, this research would benefit from a standardized method of reporting and measuring tics and other side-effects in clinical trials of psychostimulants.

In summary, new-onset or worsening tics are commonly experienced by children with ADHD in both the active and placebo groups of psychostimulant trials. There is no evidence of an association between psychostimulant use and risk of new-onset or worsening tics in placebo-controlled trials. When new-onset or worsening of tics occurs after the initiation of a psychostimulant medication, it is much more likely to be a result of coincidence than caused by the medication. Using psychostimulant medications in children with ADHD and comorbid tics (or with a family history of tics) should be considered, especially when agents that target both ADHD and tic symptoms (e.g. alpha-2 agonists) have failed. Re-challenging children who experience new-onset or worsening tics on psychostimulants appears to be a reasonable treatment strategy if ADHD symptoms remain impairing.

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Appendix A

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Review

Clinical assessment of Tourette syndrome and tic disorders

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ARTICLE INFO

ABSTRACT

Tourette syndrome (TS) is a neuropsychiatric disorder involving multiple motor and phonic tics. Tics, which usually begin between the ages of 6 and 8, are sudden, rapid, stereotyped, and apparently purposeless movements or sounds that involve discrete muscle groups. Individuals with TS experience a variety of different sensory phenomena, including premonitory urges prior to tics and somatic hypersensitivity due to impaired sensorimotor gating. In addition to other conditions, stress, anxiety, fatigue, or other heightened emotional states tend to exacerbate tics, while relaxation, playing sports, and focused concentration on a specific task tend to alleviate tic symptoms. Ninety percent of children with TS also have comorbid conditions, such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or an impulse control disorder. These disorders often cause more problems for the child both at home and at school than tics do alone. Proper diagnosis and treatment of TS involves appropriate evaluation and recognition, not only of tics, but also of these associated conditions.

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Contents

1. Introduction

Tourette syndrome (TS) was first described by the French neurologist, Gilles de la Tourette, in 1885 as a "maladie des tics." In his original case series describing the syndrome that now bears his name, Gilles de la Tourette wrote about many of the characteristics of the syndrome including: involuntary movements and

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sounds, markedly enhanced startle reactions, a tendency to repeat both vocalizations (echolalia) and movements (echopraxia), and uncontrollable verbal obscenities (coprolalia) (Lajonchere et al., 1996). Since then, our knowledge of TS has progressed significantly, including advances in our understanding of tics, their surrounding sensory phenomena, and the central role that other co-occurring diseases, such as attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), have on the overall clinical course of the disorder. This review will focus on our current understanding of the diagnosis, clinical characterization and assessment of tics as well as their clinical course. Other reviews will focus on the evidence-based treatment and neurobiology of tic disorders.

2. Definition of tics

Tics appear as sudden, rapid, purposeless motor movements or sounds that involve discrete muscle groups. They are also stereotyped in that they will occur in a similar manner each time they are performed. In comparison to some movement disorders or psychiatric conditions (e.g. sterotypies, chorea, or dyskinesia), patients with tics report the ability to suppress them, even if only for a short duration. However, they report that suppression often causes discomfort. Almost any movement, sound, or combination therein that the body can make can become a tic. Although some tics are more mild (i.e. eye blinking), others can be more severe to the point of causing pain to the patient (i.e. head or neck jerk). Apart from the physical consequences incurred by them, tics and their associated neuropsychiatric symptoms can diminish patients' quality of life, social and academic function, and lifetime achievements. They can also be very troubling and disruptive to the patients' family, and many times the entire family needs care and counseling (Leckman, 2012). Oftentimes, the tics themselves have less adverse effects than the co-occurring disorders. For instance, a 2011 study measuring quality of life (QoL) in fifty youth with TS found that symptoms of depression, OCD, and ADHD appeared to have a widespread negative impact on QoL; however, increased tic severity and poor QoL were not associated (Eddy et al., 2011).

3. Tourette syndrome and other tic disorders

The prevalence of TS varies based on study design and location. An international prevalence of 0.6–1% has been reported for mainstream schoolchildren, with the disorder being 3–4 times more common in males than in females (Cavanna and Termine, 2012). Data from the 2007 National Survey of Children's Health (NSCH) showed an estimated prevalence of 0.3% among U.S. children aged 6–17 years (Scahill et al., 2009). This number may represent an underestimate of TS prevalence since data were gathered from a parent-reported survey, and detection might be imperfect for children with fluctuating levels of symptoms or limited access to specialty health-care services (Scahill et al., 2009). Alternatively, TS prevalence may differ in prevalence worldwide due to either genetic or environmental differences. For example, TS has been reported to be less common in African-American people and has been reported only very rarely in sub-Saharan black African people (Robertson, 2008a). Regardless, the phenomenology of TS is similar in all cultures in which it has been reported (Robertson, 2008a).

TS is defined by the pediatric onset of both motor and vocal tics, lasting for at least one year. Although TS is the most notorious cause of chronic tics, there are types of tic disorders that are more common in children. Based on the Diagnostic and Statistical Manual – IV (DSM-IV) of the American Psychiatric Association, other tic disorders include: chronic motor tic disorder (CMT) and chronic vocal tic disorder (CVT), which are defined as having motor

or phonic tics (but not both) for at least one year; and transient tic disorder (TTD), which is characterized by tics (either motor and/or vocal) for a duration of less than one year (DSM-IV-TR, 2000). Transient tics affect 15–25% of school-aged children with the majority experiencing resolution of tics within several months (Khalifa and von Knorring, 2003; Scahill et al., 2005; Robertson, 2008a,b). With the advent of DSM-V, the category of TTD is likely to be replaced by "Provisional Tic Disorder," as this designation is more accurate than TTD for patients with ongoing tic symptoms of less than one-year duration since onset (Walkup et al., 2010). Tic Disorders Not Otherwise Specified is the diagnostic term used for tic disorders that begin after age 18 or are secondary to other factors such as substance use (e.g. cocaine), toxins (e.g. carbon monoxide poisoning), or head trauma (e.g. physical trauma, stroke, or encephalitis) (Table 1).

Tics also exhibit several characteristics that distinguish them from other common childhood movement disorder such as stereotypies, choreas and dystonias. The distinguishing characteristics of tics include (1) they wax-and-wane in severity, (2) the character of the movements changes over time, (3) they are temporarily suppressible and (4) they are typically associated with sensory phenomena. Table 2 contrasts TS with other common movement and childhood psychiatric disorders confused with TS.

4. Characterization of tics

Tics are characterized by their anatomical location, number, frequency, and duration. They are also further described by their forcefulness or intensity and by their complexity (ranging from simple to complex). The most widely-used rating scale of tic severity is the Yale Global Tic Severity Scale (YGTSS), which includes separate scores from 0 to 5 for number, frequency, intensity, complexity, and interference (the degree to which planned actions or speech are interrupted by tics) of both motor and phonic tics (Leckman et al., 1989). This tool has allowed for the standardization of tic severity across different studies and research groups, aiding in the characterization and quantification of symptoms.

Additionally, because the clinical characteristics of TS make it hard for clinicians to diagnose and assess the severity of the condition, the Tourette Syndrome Diagnostic Confidence Index (DCI) was created through a collaborative effort of an expert group of clinicians. Based on the range and complexity of tics, their changeable nature, the temporal features of tic expression, and associated subjective and cognitive experiences, the DCI assigns a score from 0 to 100, which reflects the likelihood of having or ever having had TS (Robertson et al., 1999).

Other rating scales include the Shapiro Tourette Syndrome Severity Scale, Tourette's Syndrome-Clinical Global Impression Scale, and the Hopkins Motor and Vocal Tic Scale (Walkup et al., 1992). Standardized video recordings can also be used to count tics (Tanner et al., 1982). See Table 3 for a detailed comparison of various rating scales. For a detailed discussion on these rating scales, we suggest reading a recently published review (McGuire et al., 2012).

5. Natural history

The natural history of TS has been established based on clinical observations. There is a clear progression of the disorder from the onset of symptoms to, in most cases, full or partial regression of symptoms. Tics usually begin around 6–8 years of age, and 90–95% of TS cases have an onset of tics between the ages of 4 and 13 (Leckman et al., 1998). Simple motor tics involving the eyes or face are usually the first to appear in a child with TS. They are called simple because they involve a single contraction, such as a shoulder shrug or neck stretch. Motor tics will typically progress

Table 1
Tic disorders according to DSM IV.

Diagnosis	Type of tics	Timing of tics	Age of onset
Tourette's syndrome (TS)	Multiple motor and one or more vocal tics	Nearly every day for >1 year, with no more than 3 consecutive months tic free	<18 years of age
Chronic motor tic disorder (CMT)	Single or multiple motor tics	Nearly every day for >1 year, with no more than 3 consecutive months tic free	<18 years of age
Chronic vocal tic disorder (CVT)	Single or multiple vocal tics	Nearly every day for >1 year, with no more than 3 consecutive months tic free	<18 years of age
Transient tic disorder (TTD)	Single or multiple motor and/or vocal tics	Nearly every day for at least 4 weeks, but no more than 12 consecutive months	<18 years of age
Tic disorder NOS	Motor or vocal	Not specified; often used when current tics have been present for less than a year	Not specified, often used for individuals that have onset at >18 years of age

in a rostral-caudal fashion and over time they have a tendency to become more complex, involving contractions of groups of muscles in a stereotyped, repetitive way (Leckman et al., 1998). As such, complex motor tics are often difficult to distinguish from compulsive behaviors.

Phonic tics usually appear after the onset of motor tics and can also progress from simple vocalizations to more complex ones. Although a distinction is made between phonic and motor tics, it is a tenuous one as the sounds produced are a result of contractions of laryngeal, respiratory, oral, or nasal musculature (Jankovic, 1997). Simple phonic tics are brief, meaningless vocalizations that often consist of a single sound, such as grunting, squeaking, or sniffing, while complex phonic tics can include uttering different words or phrases. In the same category, echolalia (repeating the words or sounds of others), palilalia (repeating oneself), and coprolalia (saying obscene words or phrases) are types of complex phonic tics. Table 4 describes and gives examples of simple and complex motor and phonic tics.

Tics tend to wax and wane in severity and frequency. Both motor and phonic tics arise in bouts over the course of the day, and they change in severity over weeks and months. Thus, the amount and length of tic-free intervals throughout the day determines to some extent the severity of the symptom. The tic itself can be more or less forceful, which characterizes its intensity (Leckman, 2002).

By contrast, there are no factors known to affect the long-term course of tics. However, the vast majority of children with tics improve. The severity of tics usually peaks at about 10–12 years of age, and in one half to two thirds of cases, symptoms will drastically reduce during adolescence (Bloch et al., 2006b). In the rare cases in which tic severity persists into adulthood, tic symptoms are most severe, characterized by self-injurious motor tics or coprolalic utterances (Leckman, 2002) (Fig. 1).

In fact, in a recent study by Freeman et al., the overall prevalence of coprophenomena was 19.3% in an international cross-sectional sample of 597 patients. Only 15 of 220 individuals who had mildly-rated tics had coprolalia; whereas 42.6% of the 108 patients with

Table 2
Differential diagnosis of tic disorders.

Movement	Description	Common causes
Tics	• Abrupt, stereotyped coordinated movements or vocalizations that often mimic aspects of regular behavior • Wax and Wane • The character of the movements changes over time • Temporarily suppressible • Premonitory urges are common • Exacerbated by stress and relieved by distraction	• Tourette syndrome • Chronic tic disorder • Transient tic disorder
Stereotypies	• Repetitive, purposeless, and apparently voluntary movements	• Autism • Pervasive developmental disorder • Mental retardation • Stereotyped movement disorder
Chorea	• Simple, random, irregular, and non-stereotyped movements • Has no premonitory component and increases when the person is distracted • Often flows from one body part to another	• Normal in children less than 8 months of age • Cerebral palsy • Sydenham's chorea • Hereditary choreas • Kernicteris • Lesch–Nyhan syndrome • Hypoxia or stroke
Dyskinesia	• Slow, protracted twisting movements interspersed with prolonged states of muscular tension	• Drug-induced • Idiopathic torsion dystonia • Anoxia or stroke • Wilson's disease • Huntington's disease • Parkinson's disease
Athetoid	• Slow, irregular, writhing movements. Usually involving fingers and toes but occasionally the neck • A "slow chorea"	• See chorea
Myoclonia	• Brief, simple, shock-like muscle contractions that may affect individualized muscles or muscle groups	• Physiologic: hiccups, anxiety, or exercise-induced • Pathologic: juvenile myoclonic epilepsy, metabolic encephalopathies, CJD, Wilson's disease, and hypoxia
Synkinesis	• Involuntary movement associated with a specific voluntary act, i.e. raising corner of mouth when closing one's eyes	• Physiologic

Table 3
Tic rating scales.

Scale	Citation	Informants	Items	Domains Probed	Strengths	Weaknesses
Yale Global Tic Severity Scale (YGTSS)	Leckman et al. (1989)	Clinician-rated; semi-structured interview	10	Number, frequency, intensity, complexity, and interference from motor and vocal tics, and overall impairment	• Most widely used measure • Has tic symptom checklist • Gives separate severity for motor and vocal tics • Good inter-rater reliability • Sensitive to change with treatment	• Insensitive to change in patients with frequent and severe tics • In individuals with few phonic tics small changes in symptomatology can cause large fluctuations in ratings
Tourette's Syndrome Severity Scale (TSSS)	Shapiro and Shapiro (1984)	Patients and collaterals asked to give ratings	5	How much tics are noticed, commented on, seen as odd by others and degree of impairment	• Reliable • Short administration time	• Focuses primarily on social impact from tics and not on the severity of tics themselves
Tourette's Disorder Scale-Clinician Rated (TODS-CR)	Shytle et al. (2003), Storch et al. (2007b)	Clinician-rated; semi-structured interview of parent and child	15	Motor and Phonics Tics as well as common comorbid conditions (such as obsessions, compulsions, inattention, hyperactivity, aggression, and emotional disturbances)	• Provides ratings of common comorbid behavioral symptoms	• Severity ratings include symptoms currently classified in other DSM-IV disorders such as ADHD, OCD, MDD, anxiety disorders and IED
Tourette's Disorder Scale-Patient Rated (TODS-PR)		Parent-rated; self-report regarding child				
Hopkins Motor and Vocal Tic Scale	Walkup et al. (1992), Singer and Rosenberg (1989)	Separate ratings by family member and observer	N/A	Measures overall severity of each individual tic on a visual scale	• Can follow separately improvement in specific tics • Easy to administer	• Difficult to aggregate data across patients • Does not have separate measures for frequency, intensity and interference from tics
Tourette's Syndrome Questionnaire (TSQ)	Jagger et al. (1982)	Self-report involving parent and child	35 pages	Tic history, prenatal and developmental history and family history	• Provides assessment of many potential risk factors for Tourette syndrome	• Time intensive • Problems with recall bias for many parent report items
Child Tourette Syndrome Impairment Scale	Storch et al. (2007a)	Parent-rated, self-report	37	Overall impairment (and impairment from tics) in school, home and social activities	• Provides more nuanced with of impairment than single-item measures	• Most useful when performed in conjunction with tic severity measure
Videotape Ratings and Tic Counts	Himle et al. (2006), Chappell et al. (1994)	Videotape subject for at least 5 min. Count motor and vocal and total tic frequency	N/A	Tic frequency	• Objective measure of tic severity	• Labor-intensive • Vulnerable to sampling bias because tics wax-and-wane in severity • Requires significant amount of equipment • Does not measure impairment and interference from tics

Table 4
Types of tics.

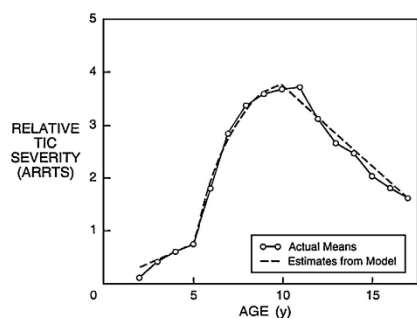|	Motor	Phonic
Simple	Sudden, brief, short (usually ≤1 second), one group of muscles (e.g. eye blinking, facial grimacing, head jerk, shoulder shrug)	Fast, meaningless sounds/noises (e.g. sniffing, throat clearing, grunting, or high-pitched squeaks)
Complex	Sudden, appear purposive, stereotyped, longer duration, coordinated movements	Syllables, words, or phrases; odd patterns of speech with changes in rate, volume, or rhythm
	Echopraxia: copying gestures of others *Palipraxia*: repeating one's own gestures *Copropraxia*: lewd and obscene gestures with hands or tongue	*Echolalia*: repeating words or phrases of others *Palilalia*: repeating one's own words or phrases *Coprolalia*: socially inappropriate syllables, words, or phrases expressed in a loud, explosive manner
	Dystonic: sustained, gyrating, bending, or twisting movement or posture (e.g. blepharospasm, oculogyric movements, mouth opening, shoulder rotation) *Tonic*: sustained, isometric contraction (e.g. abdominal or limb tensing) *Self-injurious behavior*: tics that involve injuring oneself (e.g. tongue or lip biting, or hitting one's face)	

Fig. 1. Average tic severity from age 2 to 18 years.
Adapted with permission from Leckman et al. (1998).

severe tics had coprolalia. The mean age of onset of coprolalia and copropraxia was 5 years 4 months and 4 years 10 months, respectively, after the onset of tics. This delayed onset and greater percentage of coprolalia seen in patients with severe tics is not surprising, as coprophenomena reflects more complex tics and comorbidity patterns (Freeman et al., 2009).

Other studies have also associated the presence of certain types of tics with clinical course. A recent study by Martino et al. looked at the prevalence of eye tics in TS patients. They found that of 212 patients, 201 or 94.8%, reported ever having eye tics in their lifetime. They also discovered that overall tic severity positively correlated to lifetime history of eye and/or eyelid/eyebrow movement tics. Furthermore, they found that regardless of the type of tic at onset, patients with a lifetime history of eye movement tics had an earlier onset of TS than those who had never had eye movement tics. These findings suggest the possibility for a difference in the natural history of patients with and without ocular tics. (Martino et al., 2012).

Few studies have examined predictors of long-term outcome on neuropsychological assessment and neuroimaging. One cohort that examined 46 children with TS followed to young adulthood demonstrated that smaller childhood caudate volume and poor Purdue Pegboard performance were associated with increased tic severity in early adulthood (Bloch et al., 2005, 2006c). Purdue pegboard performance is a test of fine-motor skill, and poor performance may be a sign of deficits in complex, visually guided or coordinated movement that is likely mediated by circuits involving the basal ganglia. Reduced caudate volume has been previously demonstrated to be a morphological trait of TS on structural MRI (Catafau et al., 2000; Peterson et al., 2003).

6. Sensory phenomena surrounding tics

The outward manifestation of TS represents only a part of the symptomatology experienced by most of our patients. In 1980, Joseph Bliss, articulately described his careful observations from 35 years of self-study of the feelings and subjective events surrounding his own tics. Much of what he described became the basis for future research surrounding the sensory phenomena associated with tics. The term, "sensory phenomena," is now used as an all-encompassing term to describe such subjective experiences as premonitory urges, "just-right" perceptions, or somatic hypersensitivity in an effort to unify terminology across the literature (Prado et al., 2007).

6.1. Premonitory urges

Premonitory urges (PU) are uncomfortable sensory phenomena that typically precede and are subjectively experienced as being the initiators of tics. Premonitory urges, formerly deemed, "sensory tics," can be experienced by individuals with tics and are likened to the need to sneeze or itch or an inner feeling of restlessness, pressure or mounting tension (Kurlan et al., 1989). In a questionnaire administered to 135 patients with tic disorders, it was shown that the anatomical regions with the greatest density of urges were the palms, shoulders, midline abdomen, and throat (Leckman et al., 1993). Thus, premonitory urges are focal in character and limited to specific anatomical locations. They can also vary in frequency, intensity, and location. The performance of the tic itself is usually associated with a momentary feeling of relief from this uncomfortable urge.

The premonitory urge has been studied in comparison with other normal physiological urges, such as the urge to urinate, cough, blink or sleep. An urge is one mode of processing internal or external sensory input into motor output. However, an urge is not always perceived. Often the motor action can be triggered by sensory input alone outside of our awareness, and the action would thus be perceived as involuntary (Belluscio et al., 2011b).

Similarly, Bliss writes when describing the process of a tic that, "*the inception and emergence of a single action and its passage into the overt phase is so faint, subtle, surreptitious, and lightening fast that rarely is it known to the subject that it exists at all*" (Bliss, 1980).

If the action is delayed, an urge develops. This feeling of a need to act is different from the sensation of the sensory input itself. Typically, the discomfort associated with the premonitory urge builds up until the tic is performed. Some patients state that they will voluntarily make tics in response to the urge in order to relieve themselves of the mounting discomfort.

In 1994, Kane, then a graduate student with TS, wrote in reference to premonitory urges, "*these sensations are not mere precursors to tics; [. . .] more than providing a signal of imminence, the pre-tic sensation acts as the aversive stimulus toward which tics are directed*" (p. 806) (Kane, 1994).

Patients with TS have the ability to suppress tics temporarily but only at the expense of mounting discomfort like suppressing a sneeze, itch, or the urge to urinate. In fact, with prolonged suppression, the urge to tic can become so great that the action occurs beyond the patients' control. In this way, tics have been called "un-voluntary," since they are neither voluntary nor involuntary. In contrast to normal urges, the urge to tic is different in that the sensory input that generates the urge to tic is unknown, tics are not key to survival – in fact, they are both nonessential and nonproductive –, and the execution of a tic only temporarily reduces the intensity of the urge to tic (Belluscio et al., 2011b). Also, individuals with tics sometimes report the need to perform tics until they get the feeling associated with it being "just right."

It remains possible that abnormal perception or filtering of these sensory phenomena may be central to the pathogenesis of TS (see "Sensorimotor gating" below). Several individuals with tics have suggested that these premonitory urges may be as characteristic of TS and as disruptive and distracting as the tics themselves. Some individuals perceive premonitory urges and other sensory phenomena as being the "core" of TS (Hollenbeck, 2001).

Furthermore, patients have reported an awareness of the premonitory urge helps them suppress imminent tics because they are fore-warned of their arrival and can take measures to suppress them. Along these lines, certain types of behavioral therapies have been developed in order to take advantage of this awareness. Premonitory urges are utilized in cognitive-behavioral interventions that include empirically supported behavioral therapy (Piacentini

et al., 2010) and exposure and response prevention (Verdellen et al., 2008).

Awareness of premonitory urges typically increases as children with TS become older (Banaschewski et al., 2003). Individuals with TS have reported that they first became aware of their premonitory urges on average 3.1 years after the onset of tic symptoms (Leckman et al., 1993). The delayed onset of awareness of urges most likely represents the normal development self-awareness and the fact that younger children are less able to recognize and describe bodily urges. Premonitory urges are experienced by most adolescents and adults with TS. Eighty-two to ninety-two percent of patients will report experiencing premonitory urges prior to motor and vocal tics (Cohen and Leckman, 1992; Kwak et al., 2003).

Whether a tic is voluntary or involuntary has been the topic of much study. Some have said, the tic is a voluntary action per-formed in an attempt to relieve an involuntary urge (Bliss, 1980). Furthermore, in a 2003 study, 68% of 50 TS subjects described a motor tic as a voluntary motor response to an involuntary sen-sation, as opposed to a completely involuntary movement (Kwak et al., 2003). Also, in a study involving 135 individuals with TS, 92% of individuals indicated that their tics were either fully or partially a voluntary response to their premonitory urges. Also, in the same study, 84% of these subjects reported that their tics were associated with a momentary feeling of relief (Leckman et al., 1993).

The Premonitory Urge for Tics Scale (PUTS) is a rating scale designed to measure the strength of these premonitory urges in tic disorders. Although premonitory urges have been difficult to recognize and consistently report for youth under the age of 10, the scale was found to have excellent psychometric properties for children above the age of 10 years, with PUTS scores correlating with tic severity as measured by the YGTSS (Woods et al., 2005).

6.2. Somatic hypersensitivity

Sensorimotor gating describes the neurological processes of filtering out redundant or unnecessary sensory stimuli from all possible environmental stimuli. Individuals with TS (and schizophrenia) have consistently demonstrated deficits in sensor-imotor gating as compared to healthy controls. Prepulse inhibition (PPI) of startle to a high-intensity stimulus is an experimentally measurable indication of sensorimotor gating. Prepulse inhibition of startle is defined as the inhibitory effect of a low-intensity stim-ulus or "prepulse," on the startle response to the subsequent same, but high-intensity stimulus (Baldan Ramsey et al., 2011). The pre-pulse is believed to activate brain mechanisms which suppress or "gate" the processing of that stimulus for a brief window of time. Impaired PPI has been shown in patients with TS, and recently lesions in the dorsomedial striatum have been implicated in their diminished capacity for PPI (Baldan Ramsey et al., 2011). Swerd-low has demonstrated PPI is regulated by both norepinephrine and dopamine substrates, and clonidine can repair PPI disrupted by cirazoline (Swerdlow et al., 2006).

As hypothesized by these sensorimotor gating deficits observed in patients with TS, many individuals describe hypersensitivity as being an important phenomenon intertwined with other aspects of the disorder. A salient example of this phenomenon is the extreme sensitivity to tags in new clothing experienced by some children with TS. Bliss and Kane describe their sensory phenomena in the following quotes:

"Because of the state of sensitization (combined with memory recall and attention targeting), this site is the most difficult to extinguish." (Bliss, 1980).

"All these sensory actions can dart from one to another with great speed and varying intensities, at times escalating to a fever pitch of intensity and at other times fading quickly away, to recur some other time. Often the effort to control these wild sensations seems to be more than the human spirit can bear; there are really only two choices: let it all hang out or keep fighting. However great the confusion and diversity of sensory-related actions and sensations, only one of these is active at any given moment. All others, residual and secondary, stand in the wings, with their entrances and exits following so quickly on after the other that it is very hard at times to be aware of their single movements." (Bliss, 1980, p. 1345).

"Perhaps the best description for the sensory state of TS is a somatic hyper-attention: It is not as itch-like as it is an enduring somatosensory bombardment. I experience the TS state as one of keen bodily awareness, or a continual consciousness of muscle, joint, and skin sensations. For example, when sitting in a chair, I do not lose awareness of the tactile sensation of the seat against my body, nor can I ignore the deeper somatic sensations of what my back and legs feel like" (Kane, 1994).

"How does a new tic get started? The activation of TS sites is dependent on a combination of (1) attention direction and (2) various precipitants such as stress, tactile and kinesthetic per-ceptions, previous sensitization of a site, inadvertent pressure points anywhere on the body, memory recall of the earlier sites, and phantom fixations. [. . .] The subject's attention, for any of a multitude of chance reasons, can fall on any potential site. Over seconds, minutes, or hours, the attention shifts to number-less places via sounds, sights, touch, pressure, discomfort, pain, temperature, or thoughts. In the normal person, these attention-exciting events can go relatively unnoticed. In the person with TS, any one can set off a TS action *even though that person may be completely unaware of the stimulating factor*" p. 1346 (Bliss, 1980).

In 2011, Belluscio et al. studied in detail the experience of sen-sitivity to external stimuli in a case-control study of 19 TS patients and 19 age-matched healthy volunteers. An in-depth interview and questionnaire revealed that 80% of TS patients reported heightened sensitivity to external stimuli, with examples among all sensory modalities, but with statistically significant heightened sensitiv-ity to 4 of 5 sensory modalities (sound, light, smell, and touch) as compared to the healthy volunteers (Belluscio et al., 2011a). They found bothersome stimuli were characterized as "faint, repetitive or constant, and nonsalient, whereas intense stimuli were well tolerated" (Belluscio et al., 2011a). Examples of such bothersome stimuli include: rough fabrics, the constant pressure exerted by a shirt collar or a waistband, the pressure of a chair or another per-son's arm. Patients also described a preference for strong tactile stimuli such as having their skin scratched or receiving a massage. Furthermore, these investigators did not observe in TS patients any greater ability to detect different intensities of olfactory and tactile stimuli as compared to healthy volunteers. This led them to sug-gest that the perceived sensitivities were the result of altered or impaired central processing (Belluscio et al., 2011a).

Several rating scales have been designed to measure this hyper-sensitivity experienced by those with TS. The University of Sao Paulo Sensory Phenomena Scale (USP-SPS) was designed in 2005 in order to assess the severity and frequency of sensory phenomena that precede, accompany, or follow tics and other repetitive behav-iors, such as compulsions or rituals (Sutherland Owens et al., 2011). Furthermore, in 2009 it was validated against other estab-lished scales, such as the Yale-Brown Obsessive-Compulsive Scale, Dimensional Yale-Brown Obsessive-Compulsive Scale, Yale Global Tic Severity Scale, Beck Anxiety Inventory, and Beck Depression Inventory, as a reliable instrument for measuring the presence and severity of sensory phenomena in individuals with OCD (Rosario et al., 2009).

Table 5
Sensory phenomena rating scales.

Measure	Citation(s)	# Items	Domains Probed	Strengths	Limitations
Premonitory Urge for Tics Scale (PUTS)	Woods et al. (2005)	9 items	Frequency of specific pre-tic related sensory symptoms along with relief after tic completion	• Easy to administer and complete	• Difficult to administer with younger children who may not recognize or understand urges • Does not capture other common sensory phenomenon in TS besides premonitory urges
University of Sao Paulo Sensory Phenomena Scale (USP-SPS)	Rosario et al. (2009)	2 parts: checklist and severity scale	Frequency, interference and distress of sensory phenomena that precede, accompany, or follow tics and other obsessive-compulsive spectrum behaviors	• Probes other sensory phenomena such as "just right" feelings, feelings of incompleteness, inner restlessness • Has symptom checklist to identify common symptoms	• Does not have separate domains for different types of sensory phenomena
Sensory Gating Inventory (SGI)	Hetrick et al. (2012)	124 items	6-point Likert ratings assessing 4 factors: perceptual modulation, distractibility, over-inclusion or hyper-attention, and fatigue and stress vulnerability	• Has 4 subscales related to different types of sensorimotor gating deficits	• Not designed specifically to detect sensory phenomena associated with tics
Structured Interview for Assessing Perceptual Anomalies (SIAPA)	Bunney et al. (1999)	15 items	5-point Likert ratings of hypersensitivity, inundation and flooding, and selective attention to external sensory stimuli for each of the 5 sensory modalities	• Easier to complete than SGI	• Not designed specifically to detect sensory phenomena associated with tics • Has not been demonstrated to be elevated in tic disorder patients

In addition to PPI as an experimental measure of sensorimotor gating, the Structured Interview for Assessing Perceptual Anomalies (SIAPA) and the Sensory Gating Inventory (SGI) are rating scales that were developed in order to quantify sensorimotor gating impairment seen in TS and schizophrenic patients. SIAPA was developed in 1999 as a way to measure perceptual anomalies, such as flooding or inundation of sensory stimuli in individuals with schizophrenia. The interview employs Likert ratings of perceived hypersensitivity, inundation, and selective attention to external sensory stimuli (Bunney et al., 1999).

Furthermore, Hetrick et al. created the self-report rating scale, Sensory Gating Inventory (SGI) in an effort to expand upon the SIAPA scale by employing an empirical, factor analytic procedure to assess and systematically identify the phenomenology and major dimensions of sensory gating. The self-report rating scale also employs Likert ratings of subjective experiences, such as: perceptions of heightened stimulus sensitivity, sensory inundation, disturbances in the processes of focal and radial attention, and exacerbation of sensory gating-like anomalies by fatigue and stress. The SGI scale demonstrated strong reliability and validity (Hetrick et al., 2012) (Table 5).

7. Exacerbating/alleviating factors

Tic symptoms vary in frequency and intensity, and in addition to potential neurological variation, it has been shown that certain environmental or contextual factors will either exacerbate or alleviate tic symptoms in individuals with TS.

The results of 6 different descriptive studies looking at the effects of different antecedent variables on tic severity show stress and anxiety appear to be the most common factors associated with an increase in TS symptoms, while fatigue and boredom also rank high on the list (Conelea and Woods, 2008b). On the other hand,

relaxation, concentration, and physical exercise were antecedent factors shown to contribute to tic attenuation (Conelea and Woods, 2008b). These studies are limited by the fact that they describe aggregate data, thus removing individual experiences from the descriptions, and they are subject to bias because data were collected by self-report and parental observation.

Experimental designs studying the impact of various antecedent factors on tic expression show tic expression occurs more frequently in cases of direct, overt observation, during easy reading assignments, and when the tics themselves are spoken about. For instance, more tics were observed when children were overtly, as opposed to covertly, observed by a video camera; and the presence of another person in the room did not affect overall tic counts (Piacentini et al., 2006). Also, direct observation revealed tics are aggravated by easy reading assignments, reading in a quiet classroom, and by the period between assignments (Watson et al., 2005). Conversely, it has been shown that periods of focused attention to tasks and reduced peripheral sympathetic tone inhibit tic expression (Nagai et al., 2009). Another study revealed tic-related conversations increase the frequency of phonic tics (not motor tics) as compared to conversations that do not have to do with tics (Woods et al., 2001). Additionally, instructions to suppress tics have been shown to modestly reduce tic frequency, at least for 30 min, with adults demonstrating suppression more frequently. In this same study of 7 adults and children, tic suppression did not lead to the rebound effect of increased tic frequency after the period of suppression, but the impact of suppression instructions on strength of premonitory urges ratings remains unclear (Meidinger et al., 2005).

Furthermore, taken together, multiple studies have suggested stress, anxiety, frustration, and tension are emotional variables often associated with an increase in tics (Conelea and Woods, 2008b). However, it remains unclear as to why certain emotions exacerbate tics and what their effect is on premonitory urges. With

Table 6
Exacerbating and alleviating factors for tics.

Tic attenuation	Tic exacerbation
Relaxation	Stress, anxiety, worry, frustration
Physical exercise, sports	Fatigue, tiredness
Concentration, study activity	Returning to school
Habitual, automatic actions	Boredom, waiting
Reading for pleasure	Emotional trauma
Leisure activity	Holidays, birthdays
Talking to friends	Working under pressure
Doctor visits	Overstimulation, multitasking
Verbal instructions to suppress tics and rewarding/reinforcing tic-free periods	Tic-related conversation
Interaction with familiar people	
Socialization (30%), social gatherings (25%)	Social gatherings (42%), socialization (50%) (presence of others/overt observation) Transportation
	Being alone

Adapted from data in Conelea and Woods (2008a,b).

regard to consequent factors that affect tic expression, it has been shown reinforcing tic-free periods acts to reduce tic frequency, while paying attention to the tics themselves or publicly commenting on tics increases these symptoms (Conelea and Woods, 2008b) (Table 6).

8. Suppressing tics

One of the characteristics of tic symptoms is that they are suppressible, even if only for a short while. However, as stated earlier, the act of suppression can lead to the build-up of uncomfortable premonitory urges. In one study, 3 of 4 children who demonstrated reliable suppression showed a pattern of higher subjective urge ratings during suppression as compared to baseline (Himle et al., 2007).

Although tics can be suppressed, to do so requires more attention and energy from the individual. For instance, in a study involving 9 children with TS, ages 9–15, accuracy and performance on a distraction task was reduced while children were simultaneously told to suppress tics as compared to free-to-tic conditions (Conelea and Woods, 2008a). However, no significant difference was demonstrated between tic frequencies during periods of reinforced suppression and reinforced suppression plus a distraction task. This study demonstrates accuracy on an attention-demanding task may be impacted if a child is simultaneously trying to suppress their tics: a finding that has strong implications on school performance for children with TS. This finding suggests school performance of children with TS may be impacted not only by tics but by the attention devoted to suppressing tics and highlights the importance of a supportive environment where negative feedback from their peers and teachers in response to tics is minimized.

Stress has been shown to be one of the major factors associated with tic exacerbation. In a study involving 10 youth with TS, ages 9–17, it was demonstrated that stress impacts children's ability to suppress tics but not necessarily their baseline tic frequency. Tic frequency was greater during periods of reinforced suppression plus a stressor as compared to just reinforced suppression (Conelea et al., 2011). However, tic frequency was not different between free-to-tic baseline levels and periods when applied stress was added to this condition (Conelea et al., 2011).

Additionally, it has been shown that tic suppression rewarded for tic-free intervals is more successful at reducing tic frequency than is just being told to suppress tics. For instance, in a study design in which tokens were delivered contingent on the absence of tics and non-contingently, tic frequency was lower in 3 of 4 children during the former condition. The success of reinforced

tic suppression could be one of the reasons children are seen to tic more at home than in the classroom because tic absence is reinforced in the classroom by the avoidance of teasing from peers (Himle et al., 2008). Alternatively, it is possible tic frequency is greater at home than in the classroom because children become more tired by the end of the day when they return home from school.

Finally, one concern with the use of reinforced tic suppression as a model for therapy is the potential for a tic rebound effect, which describes an increase in frequency of tics after suppression. However, studies have not supported such concerns. Although tic frequencies have been shown to increase post-suppression as compared to during suppression, they do not increase above pre-suppression levels (Himle and Woods, 2005). Another study demonstrated similar findings after repeated 2-h sessions of Exposure and Response Prevention (ER), a behavioral treatment program, consisting of habituation to premonitory sensory experiences during prolonged tic suppression. The study demonstrated successful ER as this treatment resulted in a reduction of tics by 91% as compared to baseline. However, comparison of 15 min pre- and post-suppression measurements did not result in a significant increase in tic frequency (Verdellen et al., 2007). Additionally, one study noted the absence of the rebound effect in the 5 min following reinforced tic suppression during periods of up to 40 consecutive minutes (Woods et al., 2008).

9. Comorbidities

The description of behavioral and emotional disturbances in patients with TS has occurred since 1899, around the time the disorder was first described by Georges Gilles de la Tourette himself (Coffey and Park, 1997). In fact, comorbid neuropsychiatric disorders, the majority being ADHD and OCD, have been shown to occur in up to 90% of TS patients in both clinic and community settings (Wright et al., 2012). Figure 2 depicts the time course of common comorbidities in relation to tic symptoms, as experienced by patients with TS (Fig. 2).

9.1. Obsessive-compulsive disorder

Roughly one-third to one-half of individuals with TS experience recurrent obsessive-compulsive (OC) symptoms (Leckman et al., 1994, 1997; Khalifa and von Knorring, 2005). Genetic, neurobiological, and treatment response studies suggest there may be qualitative differences between tic-related forms of OCD and cases
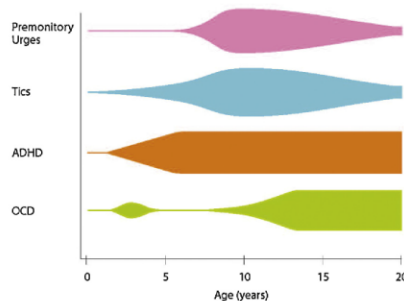
Fig. 2. Clinical course of Tourette syndrome and associated conditions. Figure depicts severity of tics and comorbid conditions associated with Tourette syndrome. Width of bars correspond to severity of symptoms.
Adapted with permission from Leckman (2002).

of OCD not related to tics. Specifically, tic-related OCD has a male preponderance, an earlier age of onset, a poorer level of response to standard anti-obsessional medications, and a greater likelihood of first-degree family members with a tic disorder (Hounie et al., 2006). Symptomatically the most common obsessive-compulsive symptoms encountered in TS patients are obsessions concerning a need for symmetry or exactness, repeating rituals, counting compulsions, and ordering/arranging compulsions (Leckman et al., 1997). Also, obsessive-compulsive symptoms, when present, in children with TS, appear more likely to persist into adulthood than the tics themselves (Bloch et al., 2006a,b,c). OCD with comorbid tics is less responsive to SSRI pharmacotherapy and more responsive to antipsychotic augmentation than OCD in patients without tics (Bloch et al., 2006a; March et al., 2007). OCD patients with and without tic disorders appear equally responsive to cognitive-behavioral therapy (March et al., 2007).

Baseline data from a study of 158 youth with a chronic TD showed children with comorbid OCD (53% of subjects) experienced more severe tics, increased levels of depressive and anxious symptoms, heightened psychosocial stress and poorer global functioning (Lebowitz et al., 2012). The authors concluded TD with OCD is a more severe subtype of TD and describes children with more internalizing disorders than those without OCD (Lebowitz et al., 2012). By contrast, another exploratory study involving 306 children with TD, OCD, or TD + OCD, failed to show that those with TD + OCD exhibited increases in tic severity as compared to those with TD alone (Lewin et al., 2010).

9.2. Attention-deficit hyperactivity disorder

Roughly 30–50% of children with TS are diagnosed with comorbid ADHD (Khalifa and von Knorring, 2005). This rate of comorbid ADHD is higher in clinical samples. Although the etiological relationship between TS and ADHD is unclear, it is clear individuals with both TS and ADHD are at a much greater risk for a variety of poor outcomes including greater academic and social impairment (Carter et al., 2000; Peterson et al., 2001; Sukhodolsky et al., 2003, 2005). They are often regarded as less likeable, more aggressive, and more withdrawn than their classmates (Stokes et al., 1991). These social difficulties are amplified in a child with TS who also has ADHD (Bawden et al., 1998; Sukhodolsky et al., 2003, 2005). Surprisingly, levels of tic severity are less predictive of peer acceptance than is the presence of ADHD (Bawden et al., 1998). Comorbid ADHD symptoms in children with tics are responsive to similar pharmacological treatment as ADHD in children without tics (Bloch et al., 2009). Therefore, prompt screening of ADHD symptoms in children with tic disorders is imperative. We suggest examination of recent practice parameters for a thorough review of the diagnosis, assessment, and treatment of ADHD (Pliszka, 2007; Wolraich et al., 2011).

9.3. Impulse control disorders

In addition to the high frequency of such comorbid conditions as ADHD and OCD, many children with TS have been noted to exhibit rage attacks, self-injurious behavior, inappropriate sexual activity, discipline problems, sleep disturbances, and other forms of impulse control disorders. Impulse-control disorders are currently classified as an individual category within the DSM-IV-TR (DSM-IV-TR, 2000). "Impulsivity is defined as the failure to resist an impulse, drive, or temptation that is potentially harmful to oneself or others. It is evidenced behaviorally as carelessness; an underestimated sense of harm; extroversion; impatience, including the inability to delay gratification; and a tendency toward risk-taking and pleasure- and sensation-seeking" (Wright et al., 2012). Wright et al. review TS as it relates to impulse-control disorders, specifically, intermittent

explosive disorder (IED), self-injurious behavior (SIB), and other forms of impulse-control disorder.

This type of disinhibited behavior is inextricably linked to tics. For instance, some individuals will have the urge to make a loud vocal tic in a quiet library upon seeing the sign, "Quiet Please." Similarly, one can feel the need to jerk his shoulder after someone lightly puts their hand on it. This type of behavior could represent the disrupted sensory gating in that the light stimulus is bothersome and can create a site of unpleasant urge. Furthermore, there is the example of a physicist during WWII, who had to relinquish his job in a high energy physics laboratory because whenever he saw the sign, "Danger High Voltage," he had the strong urge to touch the apparatus. These types of tics are seen as reflexive tics to specific sensory clues, but often appear as disinhibited or impulsive behavior.

It is estimated between 23% and 40% of clinically-referred TS subjects report distressing behavioral symptoms, such as sudden unpredictable anger, irritability, temper outbursts, and aggression (Wright et al., 2012). A part of intermittent explosive disorder, rage attacks, have been linked to TS as early as 1998, when it was suggested individuals with TS and another comorbid condition, such as ADHD or OCD, are more likely to also experience rage attacks (Budman et al., 1998). Since then, a study in 2008 showed that of 314 children in a Danish cohort of TS patients, 109 experienced rage attacks. Interestingly, when examining the presence of rage attacks within different subgroups, it was noted rage attacks were present in the greatest percentage (70.6%) of children who have TS with both ADHD and OCD. In those with TS and ADHD, 56.7% experienced rage, which is similar to the 50.9% of children with TS and OCD who experience rage. In those children who have TS without any other comorbidity, 36.7% exhibited rage attacks (Mol Debes et al., 2008). This data could support the suggestion that impulsivity and compulsivity are interlinked. Another hypothesis as to why OCD is linked to rage attacks in TS patients is that the sudden, impulsive outbursts of anger are a result of a disruption to routines that are linked to the compulsivity present in these patients (Wright et al., 2012). In 2003, a questionnaire was developed in order to screen TS patients for episodic rage according to their symptoms. In this study, 48 children with TS, ages 7–17, were screened to explore rage attack phenomenology, and the investigators used a cluster analysis to identify four potential subgroups of TS with rage: specific urge resolution, environmentally secure reactivity, nonspecific urge resolution, or labile non-resolving (Budman et al., 2003).

Furthermore, SIB has been consistently associated with a subgroup of TS patients. Of the 9 patients described by Gilles de la Tourette in 1885, 2 of them were described as exhibiting SIB. Self-injurious behavior has been reported in anywhere between 14.8% and 29% of TS subjects (Freeman, 2007; Mathews et al., 2004). Additionally, the proportion of SIB present in those with TS is higher in those with comorbid ADHD and who are older in age. In those patients with ADHD and TS, age of onset of SIB was 7.4 years, as compared to 10 years in those without ADHD (Freeman, 2007). Examples of types of SIB noted are biting one's tongue or lip, head-banging, body punching/slapping, head or face punching/slapping, body-to-hard-object banging, and poking sharp objects into one's body (Wright et al., 2012).

The co-occurrence of impulse-control disorders with those patients with TS has further implications on the cognitive aspects of these individuals. They can exhibit the inability to delay gratification, making decisions based on immediate reward, they are distractible, and they are generally disinhibited, which can lead to behavior that does not comply with cultural norms. If impulsivity and compulsivity are thought to be opposite ends of a spectrum, TS would be considered a mixture of the two. While compulsions are driven by an attempt to reduce anxiety, impulsions are driven by an attempt to obtain arousal and gratification (Wright et al., 2012).

10. Conclusions

Tourette's syndrome is a neuropsychiatric disorder characterized by multiple motor and vocal tics. However, for many individuals with TS, the tics are neither the most prominent nor distressing part of the disorder. In the majority of children with TS, tic symptoms diminish significantly during adolescence. Most individuals with TS experience associated sensory phenomena such as premonitory urges and somatic hypersensitivity that are often as distressing as the tics themselves. The majority of individuals with TS reaching clinical attention have common comorbid conditions such as ADHD, OCD and impulse control disorders. Proper diagnosis and treatment of TS involves appropriate evaluation and recognition, not only of tics, but also of these associated conditions.

Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix B

■■■ NEW RESEARCH ├────────────────────────────

Meta-Analysis: Risk of Tics Associated With Psychostimulant Use in Randomized, Placebo-Controlled Trials

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Zachary D. Stuckelman, Catherine G. Coughlin, BS,
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Objective: Clinical practice currently restricts the use of psychostimulant medications in children with tics or a family history of tics for fear that tics will develop or worsen as a side effect of treatment. Our goal was to conduct a meta-analysis to examine the risk of new onset or worsening of tics as an adverse event of psychostimulants in randomized, placebo-controlled trials.

Method: We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with attention-deficit/hyperactivity disorder (ADHD). We used a fixed effects meta-analysis with risk ratio of new onset or worsening tics in children treated with psychostimulants compared to placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dose, duration of treatment, recorder of side effect data, trial design, and mean age of participants on the measured risk of tics.

Results: We identified 22 studies involving 2,385 children with ADHD for inclusion in our meta-analysis. New onset tics or worsening of tic symptoms were commonly reported in the psychostimulant (event rate = 5.7%, 95% CI = 3.7%−8.6%) and placebo groups (event rate = 6.5%, 95% CI = 4.4%−9.5%). The risk of new onset or worsening of tics associated with psychostimulant treatment was similar to that observed with placebo (risk ratio = 0.99, 95% CI = 0.78−1.27, $z = -0.05$, $p = .962$). Type of psychostimulant, dose, duration of treatment, recorder, and participant age did not affect risk of new onset or worsening of tics. Crossover studies were associated with a significantly greater measured risk of tics with psychostimulant use compared to parallel group trials.

Conclusion: Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and psychostimulant use. Clinicians may want to consider rechallenging children who report new onset or worsening of tics with psychostimulant use, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.

Key Words: tics, psychostimulants, methylphenidate, amphetamine, meta-analysis

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Psychostimulants are recommended as the first-line pharmacologic treatment for children with attention-deficit/hyperactivity disorder (ADHD).[1] Psychostimulants have demonstrated a larger effect size when compared to placebo, as compared to alternative pharmacological treatments for ADHD.[2] Randomized controlled trials have demonstrated that psychostimulants are more effective than behavioral treatments for ADHD for at least 14 months after the start of treatment.[3] When ADHD is present in children with tics, the symptoms of ADHD typically cause greater impairment in academic performance, social relationships, and neuropsychological performance, especially executive functioning, than the tics themselves.[4-8] Psychostimulants have been shown to be equally efficacious in treating ADHD symptoms in children with ADHD and comorbid tics as in children with ADHD alone.[2]

Clinical practice currently restricts the use of psychostimulant medications in children with ADHD and comorbid tics. The limited use of psychostimulants in patients with ADHD and comorbid tic symptoms is likely partially attributable to warnings placed on the medications by regulatory agencies. The Food and Drug Administration (FDA) currently requires that psychostimulants list tics and/or a family history of a tic disorder as a contraindication (methylphenidate) or significant adverse reaction (methylphenidate and amphetamines) to their use.[9,10] FDA labeling warns parents that psychostimulants "should not be taken by their child" (methylphenidate) and/or "may not be right for your child" (amphetamines) if they have tics.[11,12] Amphetamine/dextroamphetamine labeling also warns the public to "use with caution in patients with Tourette's syndrome; stimulants may unmask tics."[13] The FDA warnings resulted

CG Clinical guidance is available at the end of this article.

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largely from a series of case reports and case series that were published in the 1970s and 1980s.[14-24] A particularly influential case series of 15 children who developed tics while on psychostimulants helped lead the FDA in 1983 to require listing contraindications and significant adverse reactions to psychostimulant medications.[25]

Since then, however, multiple randomized controlled trials (RCTs) have demonstrated no effect of psychostimulants on tics.[26-29] In fact, a National Institutes of Health (NIH)– and Tourette Syndrome Association–funded trial examining treatment of ADHD in children with tics concluded "that prior concerns that methylphenidate worsens tics and that the drug should be avoided in patients with tics may be unwarranted."[26] Recent meta-analyses examining pharmacological treatment of children with tics and ADHD demonstrated that methylphenidate did not significantly worsen tic symptoms and was beneficial in treating ADHD symptoms in children with both conditions.[2,30] In fact, as mentioned above psychostimulants appear to be equally efficacious in treating ADHD symptoms in children with ADHD and comorbid tics as in children with ADHD alone.[2]

There is, however, a strong biological rationale to suggest that psychostimulants might exacerbate tics. Methylphenidate and dextroamphetamine induced stereotypies in rats in a dose-dependent manner.[31-33] Stimulant-induced stereotypies in rodents are hypothesized to be an animal model for tic disorders.[34] Furthermore, psychostimulants have been demonstrated to increase dopamine in the synaptic cleft,[35] whereas the most effective anti-tic medications available, antipsychotic medications, act as dopamine antagonists.[36-38]

On the other hand, the timing of onset of ADHD and Tourette syndrome represents a possible confounder. Roughly 20% of children with ADHD go on to develop a chronic tic disorder.[39] When ADHD and tics co-occur in an individual, the onset of ADHD typically precedes that of tic symptoms by 2 to 3 years.[37] Therefore, it is difficult to determine whether the tics are a result of a side effect of psychostimulants or if they were to occur anyway, as children with ADHD are at higher risk for developing tics regardless of medication use. Also, tics in Tourette syndrome typically wax and wane in severity, so it is unclear whether a patient's tics are going to naturally increase at a given time or whether the increase is a result of psychostimulant side effects.

Clinicians are uncertain regarding the use of psychostimulants in children with existing tics or a family history of tics because of conflict between strong FDA labeling advising against psychostimulant use in this population and randomized, controlled trial and meta-analysis data suggesting efficacy without any apparent risk in the same population. The goal of this meta-analysis was to provide an evidence base for future guidelines, warnings, and clinical decisions for the use of psychostimulants in children who develop tics after psychostimulant use or are judged to be at increased risk for developing tics before psychostimulant use. We examined all available data on side effects in previous randomized, placebo-controlled

trials of psychostimulants in childhood ADHD to determine the risk of new onset or worsening of tics associated with psychostimulants compared to placebo. We conducted secondary analyses to examine the effects of psychostimulant type (long- versus short-acting formulations, methylphenidate versus mixed amphetamine salt derivatives), dose, duration of treatment, recorder of side effects, trial design (parallel versus crossover trial), and participant age on the risk of tics with psychostimulant treatment.

METHOD

Search Strategy for Identification of Studies
Two reviewers searched the electronic database of PubMed on August 18, 2013, for relevant studies using the search: (Attention deficit disorder with hyperactivity OR ADHD OR ADDH OR hyperactiv* OR hyperkin* OR "attention deficit*" OR "brain dysfunction") AND (methylphenidate OR Ritalin OR Metadate OR Equasym OR Daytrana OR Concerta OR Dextroamphetamine OR amphetamine OR Adderall OR Vyvanse OR Dexedrine OR Dextrostat). The search used only randomized controlled trials. The references of appropriate papers on the safety and efficacy of psychostimulant medications were searched for citations of further relevant published and unpublished research.

Selection of Studies
The titles and abstracts of studies obtained by this search strategy were examined by 2 reviewers to determine inclusion in this meta-analysis. Any discrepancies were resolved by a final reviewer. Eligibility for the study was based upon analysis of the full articles for the following criteria: they were randomized, double-blind, placebo-controlled clinical trials of psychostimulant medications (methylphenidate or dextroamphetamine derivatives) compared with placebo; and participants included were children and adolescents who were less than 18 years of age and were diagnosed with ADHD or hyperkinetic disorder by explicit criteria, namely, *DSM* or *International Classification of Diseases* (ICD) criteria. Studies were excluded if the following were true: the study was not published in English; the study population included only patients with ADHD plus another primary comorbidity, namely, mental retardation, pervasive developmental disorder, oppositional defiant disorder, tics, or anxiety; the medication of interest was given for less than 7 days; there were fewer than 10 participants (crossover design) or fewer than 20 participants (parallel design); or the primary goal of the trial was not treatment for ADHD (e.g., studies that were primarily concerned with neuroimaging or neuropsychological measures were excluded). We required medication/placebo each to be given for at least 7 days during the trial, because the authors a priori decided that this was the minimum required time needed to be confident regarding a change in tic symptoms. A 7-day assessment period is similar to that used for common clinical rating scales of tic symptoms such as the Yale Global Tic Severity Scale.[40] We additionally restricted trials to treatment trials, as studies using non-treatment-related outcome measures such as magnetic resonance imaging (MRI), electroencephalography (EEG), or neuropsychological testing were less likely to systematically assess side effects of medications.

Meta-Analytic Procedures
Data were extracted by independent reviewers (Z.D.S., S.C.C., J.M.M., and C.G.C.) on specially designed Microsoft Excel

spreadsheets. Our primary outcome measure was the proportion of children reporting tics as a side effect of medication. When possible, clinician-rated side effect measures were used as the main outcome measure. When this information was unavailable, participant-, parent-, or teacher-rated side effect measures were used. Reviewers also gathered data on trial medication, trial design, maximum daily medication dose, number of participants, mean age of participants, duration of active treatment in trials, who recorded side effect ratings (i.e., clinician versus parent/teacher), and other relevant attributes and results of the studies. Any disagreement among reviewers was mitigated through discussion and the procurement of more information from the study investigators if possible. When agreement could not be attained between the initial reviewers, the senior investigator (M.H.B.) resolved all disputes. When information about proportion of tics was not available in the original manuscripts, the corresponding author was contacted for further information. If contacting the corresponding author was ineffective, we also searched pharmaceutical company databases for the data.

All statistical analyses were completed in Comprehensive Meta-Analysis Version 2. For our outcome measures of interest, proportion of participants experiencing tics was analyzed using pooled risk ratio (RR). Absolute risk difference (ARD) and number needed to harm (NNH) were also reported for the primary outcome, as both the absolute and relative risks are clinically relevant when considering the use of medications. For all outcome measures, 95% CIs were conveyed. A fixed-effects model for meta-analysis was used, as well as a random effects model in sensitivity analysis. Publication bias was assessed by plotting the effect size against standard error for each included trial (i.e., funnel plot). In addition, publication bias was statistically tested by the Egger test and by determining the association between sample size and effect size in meta-regression. We additionally reported the risk of new onset or worsening of tics in both the psychostimulant and placebo groups to assist clinicians in decision making. We report results of a random effects

model for these data, as it is clear there was significant heterogeneity in how tics were assessed and the frequency that tics were reported within the placebo and psychostimulant groups based on trial methodology.

For secondary analyses, several subgroup analyses and meta-regressions were accomplished. Stratified subgroup analyses were conducted based on the following: type of psychostimulant (methylphenidate vs. mixed-amphetamine derivatives); duration of action of medications (long-acting versus short-acting psychostimulants); recorder of side effect data; and trial design (crossover versus parallel group trials). We used the test for subgroup differences (between-group heterogeneity χ^2) in the mixed-effects model of comprehensive meta-analysis to test for subgroup differences. Meta-regression analysis was used to examine the effects of maximum daily dose of psychostimulants used in trials, duration of active psychostimulant treatment, and mean age of participants on the risk of developing new onset or worsening of tics with psychostimulants compared to placebo. All daily doses of psychostimulants were converted into methylphenidate equivalents using previously described methodology.[41] Our threshold for statistical significance was $p < .05$ for the primary analysis, as well as for all stratified subgroup analyses and meta-regression.

RESULTS

Included Trials

Figure 1 depicts the selection of trials for this meta-analysis. A total of 815 references were identified in PubMed. In all, 92 trials were eligible for inclusion. Of these 92 trials, 16 trials published data on tics as a side effect of psychostimulant medication. Authors of 6 additional trials responded to electronic mail requests with unpublished data regarding

FIGURE 1 Selection of studies. Note: ADHD = attention-deficit/hyperactivity disorder.
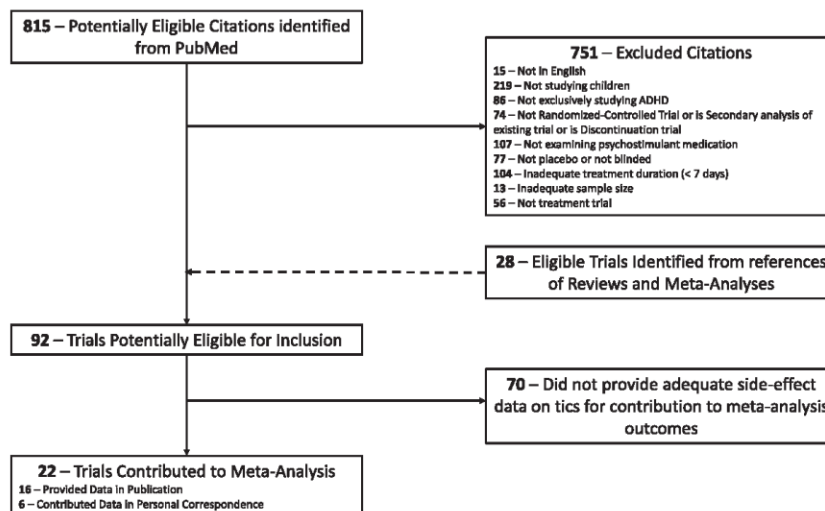
TABLE 1   Characteristics of Included Trials in the Meta-Analysis of the Risk of Tics With Psychostimulants

Authors [Ref]	Year	Medication	Stimulant Class	Duration of Action	Maximum Dose	Design	Duration of Active Treatment	n	Mean Age (y)
Werry et al. [42]	1974	MPH IR	MPH	Short	0.5–1 mg/kg/d	Crossover	4 wk	37	8.9
Gittelman-Klein et al. [43]	1976	MPH IR	MPH	Short	60 mg/d	Parallel	4 wk	80	8.6
Werry et al. [44]	1980	MPH IR	MPH	Short	0.4 mg/kg/d	Crossover	3-4 wk	30	8.4
Rapport et al. [45]	1985	MPH IR	MPH	Short	15 mg/d	Crossover	1 wk	12	6-10
Barkley et al. [46]	1990	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7–10 days	82	8.2
Buitelaar et al. [47]	1996	MPH IR	MPH	Short	10 mg BID	Parallel	4 wk	21	9.2
Stein et al. [48]	1996	MPH IR	MPH	Short	20 mg TID	Crossover	1 wk	25	8.0
Gillberg et al. [49]	1997	MAS IR	AMP	Short	45 mg/d	Parallel	3 months	56	9
Firestone et al. [50]	1998	MPH IR	MPH	Short	0.5 mg/kg BID	Crossover	7–10 days	32	4.8
Pliszka et al. [51]	2000	MPH IR	MPH	Short	50 mg/d	Parallel	3 wk	58	8.1
		MAS IR	AMP	Short	30 mg/d				
Pelham et al. [52]	2001	OROS MPH	MPH	Long	54 mg/d	Crossover	1 wk	68	9.1
		MPH IR	MPH	Short	15 mg TID				
Wolraich et al. [53]	2001	OROS MPH	MPH	Long	54 mg/d	Parallel	4 wk	282	9.0
		MPH IR	MPH	Short	15 mg TID				
Greenhill et al. [54]	2002	MPH MR	MPH	Long	60 mg/d	Parallel	3 wk	316	9
McCracken et al. [55]	2003	MAS XR	AMP	Long	30 mg/d	Crossover	1 wk	49	9.5
		MAS IR	AMP	Short	10 mg/d				
Stein et al. [56]	2003	OROS MPH	MPH	Long	54 mg/d	Crossover	1 wk	47	9.0
Findling et al. [57]	2006	EqXL	MPH	Long	60 mg/d	Parallel	3 wk	318	9.5
		MPH IR	MPH	Short	30 mg BID				
Gorman et al. [58]	2006	MPH IR	MPH	Short	1 mg/kg divided daily	Crossover	3 wk	41	9.1
Findling et al. [59]	2008	MPH Patch	MPH	Short	30 mg 9 h/d	Parallel	2 wk	274	8.7
		OROS MPH	MPH	Long	54 mg/d				
Newcorn et al. [60]	2008	OROS MPH	MPH	Long	54 mg/d	Parallel	6 wk	293	10.2
Silva et al. [61]	2008	dMPH ER	MPH	Long	30 mg/d	Crossover	1 wk	82	9.4
		MPH MR	MPH	Long	54 mg/d				
Solanto et al. [62]	2009	MPH IR	MPH	Short	50 mg/d	Crossover	1 wk	25	8.8
Lee et al. [63]	2011	MPH IR	MPH	Short	0.5 mg/kg/d	Crossover	1 wk	157	9.0

Note: AMP = amphetamine; BID = twice daily; dMPH= dexmethylphenidate; EqXL = Equasym XL; IR = immediate release; MAS = mixed amphetamine salts; MPH = methylphenidate; MR = modified-release; MTS = methylphenidate transdermal system; OROS = trademarked acronym denoting Osmotic Controlled-Release Oral Delivery System; Ref = reference; TID = 3 times daily; XR/ER = extended-release.

the risks of tics in psychostimulant trials. Therefore, a total of 22 trials, involving 2,385 participants, was included in our meta-analysis (Table 1).[42-63]

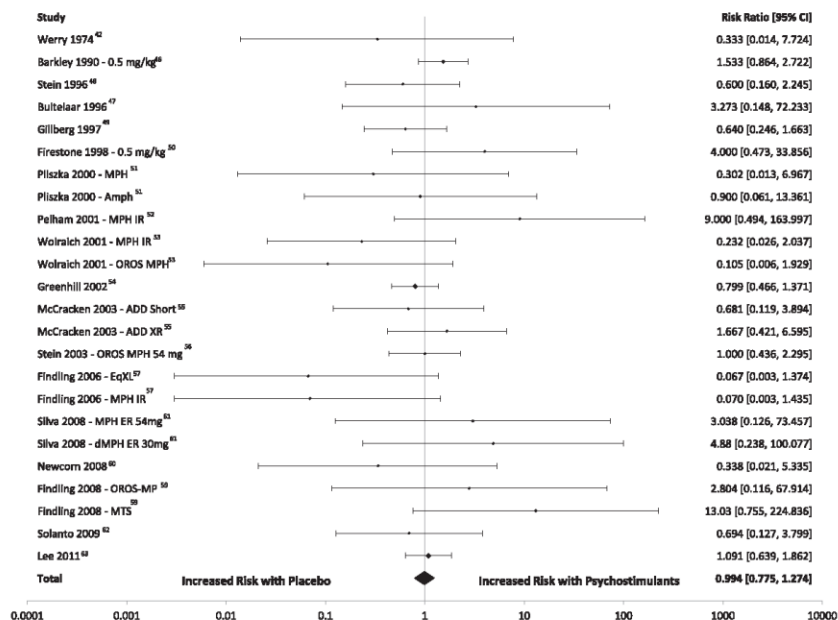### Risk of New Onset or Worsening of Tics With Psychostimulants

Meta-analysis of 22 studies involving 2,385 participants demonstrated no significant increase in the risk of new onset or worsening of tics when comparing psychostimulant to placebo (RR = 0.99, 95% CI = 0.78–1.27, z = −0.05, p = .96; Figure 2). There was no significant heterogeneity between trials (I^2 = 12.7%, p = 0.28) or evidence of publication bias (Egger test: p = 0.88). A random effects model

produced similar estimates of risk when examined in a sensitivity analysis (RR = 0.97, 95% CI = 0.72–1.32, z = −0.18, p = .86).

There was also no evidence of increased risk of new onset or worsening of tics when examining absolute risk difference of tics with psychostimulants compared to placebo (ARD = 0.001, 95% CI = −0.009 to 0.011, z = 0.18, p = .86; Figure 3). There was no significant heterogeneity among trials (I^2 = 9.6%, p = .32) or evidence of publication bias (Egger test, p = .88). A random effects model produced similar estimates of risk when examined in a sensitivity analysis (ARD = 0.001, 95% CI = −0.011 to 0.013, z = 0.16, p = .88).

In a random effects meta-analysis, 5.7% of children in the psychostimulant arms of trials reported new onset or worsening

FIGURE 2   Relative risk of tics with psychostimulants compared to placebo. Note: Forest plot comparing the relative risk of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (risk ratio $= 0.99$, 95% confidence interval $= 0.78$–1.27, $z = -0.05$, $p = .96$).

Study	Risk Ratio [95% CI]
Werry 1974[42]	0.333 [0.014, 7.724]
Barkley 1990 - 0.5 mg/kg[46]	1.533 [0.864, 2.722]
Stein 1996[48]	0.600 [0.160, 2.245]
Buitelaar 1996[47]	3.273 [0.148, 72.233]
Gillberg 1997[49]	0.640 [0.246, 1.663]
Firestone 1998 - 0.5 mg/kg[50]	4.000 [0.473, 33.856]
Pliszka 2000 - MPH[51]	0.302 [0.013, 6.967]
Pliszka 2000 - Amph[51]	0.900 [0.061, 13.361]
Pelham 2001 - MPH IR[52]	9.000 [0.494, 163.997]
Wolraich 2001 - MPH IR[53]	0.232 [0.026, 2.037]
Wolraich 2001 - OROS MPH[53]	0.105 [0.006, 1.929]
Greenhill 2002[54]	0.799 [0.466, 1.371]
McCracken 2003 - ADD Short[55]	0.681 [0.119, 3.894]
McCracken 2003 - ADD XR[55]	1.667 [0.421, 6.595]
Stein 2003 - OROS MPH 54 mg[56]	1.000 [0.436, 2.295]
Findling 2006 - EqXL[57]	0.067 [0.003, 1.374]
Findling 2006 - MPH IR[57]	0.070 [0.003, 1.435]
Silva 2008 - MPH ER 54mg[61]	3.038 [0.126, 73.457]
Silva 2008 - dMPH ER 30mg[61]	4.88 [0.238, 100.077]
Newcorn 2008[60]	0.338 [0.021, 5.335]
Findling 2008 - OROS-MP[59]	2.804 [0.116, 67.914]
Findling 2008 - MTS[59]	13.03 [0.755, 224.836]
Solanto 2009[62]	0.694 [0.127, 3.799]
Lee 2011[63]	1.091 [0.639, 1.862]
Total	0.994 [0.775, 1.274]

Increased Risk with Placebo   —   Increased Risk with Psychostimulants

0.0001   0.001   0.01   0.1   1   10   100   1000   10000

of tics (event rate $= 5.7\%$, 95% CI $= 3.7\%$–8.6%, $I^2 = 72\%$, $p < .001$). However, the event rate for new onset or worsening of tics was higher in the placebo arms of included trials (event rate $= 6.5\%$, 95% CI $= 4.4\%$–9.5%, $I^2 = 64\%$, $p < .001$).

Methylphenidate Versus Amphetamine Derivatives
Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics (test for subgroup differences $\chi^2 = 0.26$, $p = .61$) between methylphenidate derivatives (RR $= 1.02$, 95% CI $= 0.78$–1.33, $\kappa = 20$, $z = 0.14$, $p = .89$) and amphetamine derivatives (RR $= 0.84$, 95% CI $= 0.42$–1.68, $\kappa = 4$, $z = -0.49$, $p = .63$).

Long-Acting Versus Short-Acting Psychostimulants
Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics (test for subgroup differences $\chi^2 = 0.22$, $p = .64$) between short-acting (RR $= 1.04$, 95% CI $= 0.76$–1.43, $z = 0.25$, $p = .80$) and long-acting (RR $= 0.92$, 95% CI $= 0.62$–1.38, $z = -0.40$, $p = .69$) psychostimulants.

Psychostimulant Dose
Meta-regression demonstrated no significant association between dosage of psychostimulants and the risk of new onset or worsening of tics ($\beta = -0.0023$, 95% CI $= -0.0142$ to 0.0097, $z = -0.37$, $p = .71$). There was no significant association between dosage of psychostimulants and risk of new onset or worsening of tics when analysis was restricted to methylphenidate ($\beta = -0.0005$, 95% CI $= -0.0159$ to 0.0150, $z = -0.06$, $p = .95$) or amphetamine derivatives ($\beta = -0.0028$, 95% CI $= -0.0280$ to 0.0224, $z = -0.22$, $p = .83$).
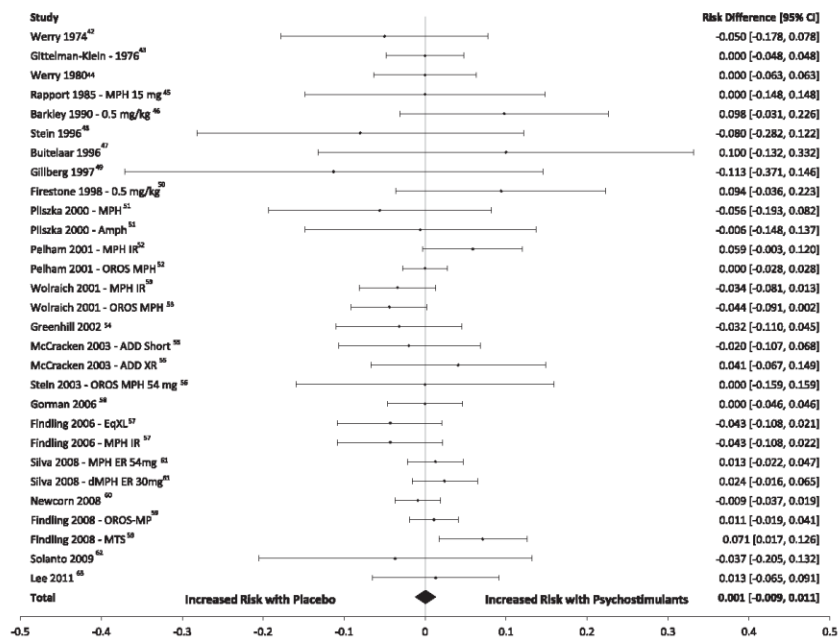
Duration of Active Treatment
Meta-regression demonstrated no significant association between duration of active treatment and the risk of new onset or worsening of tics associated with psychostimulant medication ($\beta = -0.010$, 95% CI $= -0.022$ to 0.002, $z = -1.69$, $p = .09$).

Recorder of Side Effect Data
Stratified subgroup analysis demonstrated no significant difference in risk of new onset or worsening of tics based on whether clinicians or nonclinical informants (i.e., parents and/or teachers) were rating tic outcomes (test for subgroup differences $\chi^2 = 1.49$, $p = .22$). The relative risk of tics was nonsignificantly lower when using clinician recorders of tics (RR $= 0.72$, 95% CI $= 0.41$–1.29, $z = -1.10$, $p = .28$) rather

FIGURE 3 Absolute risk difference of tics between psychostimulants and placebo. Note: Forest plot depicting the absolute risk difference of tics in participants treated with psychostimulants compared to placebo in short-term, randomized-controlled trials. Meta-analysis demonstrated no significant difference in the risk of tics with stimulants compared to placebo (absolute risk difference = 0.001, 95% confidence interval = −0.009 to 0.011, $z = 0.18$, $p = .86$).

Study		Risk Difference [95% CI]
Werry 1974[42]		-0.050 [-0.178, 0.078]
Gittelman-Klein - 1976[43]		0.000 [-0.048, 0.048]
Werry 1980[44]		0.000 [-0.063, 0.063]
Rapport 1985 - MPH 15 mg[45]		0.000 [-0.148, 0.148]
Barkley 1990 - 0.5 mg/kg[46]		0.098 [-0.031, 0.226]
Stein 1996[48]		-0.080 [-0.282, 0.122]
Buitelaar 1996[47]		0.100 [-0.132, 0.332]
Gillberg 1997[49]		-0.113 [-0.371, 0.146]
Firestone 1998 - 0.5 mg/kg[50]		0.094 [-0.036, 0.223]
Pliszka 2000 - MPH[51]		-0.056 [-0.193, 0.082]
Pliszka 2000 - Amph[51]		-0.006 [-0.148, 0.137]
Pelham 2001 - MPH IR[52]		0.059 [-0.003, 0.120]
Pelham 2001 - OROS MPH[52]		0.000 [-0.028, 0.028]
Wolraich 2001 - MPH IR[53]		-0.034 [-0.081, 0.013]
Wolraich 2001 - OROS MPH[53]		-0.044 [-0.091, 0.002]
Greenhill 2002[54]		-0.032 [-0.110, 0.045]
McCracken 2003 - ADD Short[55]		-0.020 [-0.107, 0.068]
McCracken 2003 - ADD XR[55]		0.041 [-0.067, 0.149]
Stein 2003 - OROS MPH 54 mg[56]		0.000 [-0.159, 0.159]
Gorman 2006[58]		0.000 [-0.046, 0.046]
Findling 2006 - EqXL[57]		-0.043 [-0.108, 0.021]
Findling 2006 - MPH IR[57]		-0.043 [-0.108, 0.022]
Silva 2008 - MPH ER 54mg[61]		0.013 [-0.022, 0.047]
Silva 2008 - dMPH ER 30mg[61]		0.024 [-0.016, 0.065]
Newcorn 2008[60]		-0.009 [-0.037, 0.019]
Findling 2008 - OROS-MP[59]		0.011 [-0.019, 0.041]
Findling 2008 - MTS[59]		0.071 [0.017, 0.126]
Solanto 2009[63]		-0.037 [-0.205, 0.132]
Lee 2011[65]		0.013 [-0.065, 0.091]
Total	Increased Risk with Placebo ◆ Increased Risk with Psychostimulants	0.001 [-0.009, 0.011]

than nonclinical report (RR = 1.08, 95% CI = 0.82–1.42, $z = 0.53$, $p = .59$).

Trial Design
Crossover studies reported a significantly greater association of new onset or worsening of tics with psychostimulants compared to parallel-group studies (test for subgroup differences $\chi^2 = 5.3$, $p = .02$). However, neither crossover trials (RR = 1.23, 95% CI = 0.90–1.68, $z = 1.3$, $p = .19$) nor parallel-group studies (RR = 0.67, 95% CI = 0.44–1.02, $z = -1.88$, $p = .06$) reported a significant association of tics with psychostimulant use.

Participant Age
Meta-regression demonstrated no significant association between participants' mean age and measured risk of new onset or worsening of tics with psychostimulant medications ($\beta = -0.39$, 95% CI = −0.83 to 0.05, $z = -1.75$, $p = .08$).

DISCUSSION
Meta-analysis demonstrated no statistically significant relationship between psychostimulant use and new onset or worsening of tics in children with ADHD. Specifically, the relative risk of new onset or worsening of tics was 0.99 (95% CI = 0.78–1.27), indicating no evidence of an association between psychostimulants and tics. Furthermore, we found no association between risk of new onset or worsening of tics and type of psychostimulant, dose, type or duration of treatment, recorder of side effect data, or participant age. Taken together, data from this meta-analysis is most consistent with an absence of a risk of new onset or worsening of tics with psychostimulant medications, although the power of this meta-analysis is not sufficient to rule out the possibility of a small increased risk of tics with psychostimulant use. However, based on the available data, it remains equally likely that psychostimulants reduce the risk of tics as they do raise the risk of tics.

Current evidence from this meta-analysis and previous work examining the effects of psychostimulants in children with tics and ADHD does not support the clinical practice of restricting the use of psychostimulants in children with tics or at high risk for developing tics.[11,12] Previous meta-analysis examining the effects of methylphenidate in children with ADHD and comorbid tics demonstrated that psychostimulants appear to have a similar effect size in reducing ADHD

symptoms in children with comorbid tics as in children without comorbid tic disorders.[2] Furthermore, there was no evidence that psychostimulants worsened tic symptoms in children with both ADHD and tics.[2] Randomized controlled trials in children with ADHD and tics have further demonstrated that combination treatment with methylphenidate and clonidine is more effective than either medication alone.[26] Our meta-analysis extends upon these previous results by demonstrating that there is no increased risk of new onset or worsening tics with psychostimulant use compared to placebo in meta-analysis of randomized, placebo-controlled trials in children with ADHD alone.

The results of this meta-analysis also provide strong support for rechallenging children (or even continuing children on psychostimulants) who develop tics that are temporally related to the initiation of psychostimulants. Assuming the absolute risk difference of 0.001 observed in the meta-analysis, the number needed to harm for new onset or worsening tics with psychostimulants is 1,000 (95% CI = 77–∞). If we additionally assume that the baseline risk of experiencing new onset tics over short-term trials of medications is equivalent to the 6.5% observed in the placebo arms of randomized, controlled trials of psychostimulants, then in a child who develops tics shortly after initiating psychostimulants, the tics are 65-fold more likely to be the result of coincidence than caused by the medication. Even assuming the highest risk of tics (0.011, at the upper bound of the 95% confidence interval of absolute risk difference), when new onset or worsening of tics appear after the initiation of psychostimulants, the tics are 6-fold more likely to be a result of coincidence than to be caused by the medication. Given the absence of data suggesting that psychostimulants make existing tics worse,[2,26] rechallenging appears reasonable, whether or not the tics persist after discontinuation of the psychostimulant. Rechallenging appears to be particularly advisable in children whose ADHD does not respond sufficiently to other medications such as α_2 agonists and atomoxetine, which are used to help ADHD and may also help improve tics symptoms.[38,64,65]

There are several limitations to this meta-analysis that may have affected our findings. Foremost among these limitations is the fact that a limited number of randomized, placebo-controlled trials of psychostimulants for children with ADHD actually reported the frequency of tics as side effects. The selective reporting of tics in side effect data, if it existed, could lead to publication bias that would likely exaggerate the association between tics and psychostimulants. Many trials reported only side effects that were above a certain percentage threshold in the active treatment group or were statistically different between groups. This practice would also lead to an inflated estimate of the association between psychostimulants and tics, as trials with increased associations would be selectively published and included in our meta-analysis. To minimize this potential bias, we e-mailed authors of potentially eligible trials that did not include data on tics to obtain additional data to include in the meta-analysis. However, many authors were unresponsive or did not have available data from the trial, so this potential bias should not be discounted. Another potential

limitation is the inclusion of crossover trials in addition to parallel-group trials in this meta-analysis. We made the decision to include crossover trials to maximize power in our meta-analysis. Crossover trials of psychostimulants were designed using washout periods of sufficient time to eliminate any beneficial effects of psychostimulants before the start of the next phase of the trial. It remains quite possible that if tics occurred as an adverse event in crossover trials, they might still carry over to the next trial phase and thus dampen our ability to detect tics as an adverse effect of treatment. However, stratified analysis demonstrated an increased measured risk of tics with psychostimulants in crossover studies compared to parallel-group studies, arguing against this phenomenon occurring. An additional potential limitation is the heterogeneity in how tics were assessed as a side effect between trials—some trials relied on parent report, whereas others included direct observation of participants. We conducted stratified subgroup analysis based on whether a clinician was recording side effects. We did not observe any significant effect based on who was recording side effect symptoms. In addition, some trials require significant impairment for side effects to be reported, whereas others do not. Because of the manner in which tics are reported as a side effect in trials, we are unable to determine whether individual-reported adverse events in trials were due to a new onset of tics or a worsening of pre-existing tics. We therefore are able to comment only on the aggregate risk of either of these 2 events occurring but not of each event individually. It should also be emphasized that our data apply only to use of psychostimulants within the recommended therapeutic dose range. Data in animal models as well as data in children with tics has suggested that supratherapeutic doses of psychostimulant medications may worsen tics.[27,31-33] Another limitation to this meta-analysis is the fact that the studies included in our meta-analysis do not have available data on whether tics resolve or persist after medication or placebo discontinuation.

In conclusion, this meta-analysis suggests that new onset or worsening of tics appears to occur at a fairly high rate (5%–7%) in the period immediately after starting psychostimulants. However, in this study, tics were no more likely to be associated with psychostimulant treatment than with placebo. When tics occur in temporal relationship to psychostimulant use, this relationship is much more often coincidental than causative. There are several potential confounding factors that may explain the high rate of tics reported in children after starting psychostimulants. The high rate of tics observed in children with ADHD and the waxing and waning nature of tic symptoms may explain some of this phenomenon.[66] In addition, tics have been demonstrated to worsen during periods of stress, excitement, and fatigue.[66] The initiation of psychostimulants often coincides with the start of the academic year or occurs in the face of increasing academic/social difficulties—natural periods of high stress, excitement, and fatigue for children. Therefore, the temporal relationship between psychostimulant use and new onset of tics could be largely or completely attributable to confounding. Future research investigating side effects associated with medications could be greatly

enhanced by requiring pivotal trials to make side-effect data publically available. In addition, this research would benefit from a standardized method of reporting and measuring tics and other side effects in clinical trials of psychostimulants. &

CG Clinical Guidance

- New onset or worsening of tics are commonly experienced by children with ADHD in both the active and placebo groups of psychostimulant trials.

- There is no evidence of an association between psychostimulant use and risk of new onset or worsening of tics in placebo-controlled trials.

- When new onset or worsening of tics occurs after the initiation of a psychostimulant medication, it is much more likely to be a result of coincidence than caused by the medication.

- Using psychostimulant medications in children with ADHD and comorbid tics (or with a family history of tics) should be considered, especially when agents that target both ADHD and tic symptoms (e.g. α_2 agonists) have failed.

- Rechallenging children who experience new onset or worsening of tics while on psychostimulants appears to be a reasonable treatment strategy if ADHD symptoms remain impairing.

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