PSYCHOLOGICAL, PHARMACEUTICAL OR NEUROSURGICAL:

A META-ANALYSIS OF TREATMENTS FOR TOURETTE'S SYNDROME

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Introduction

George Gilles de la Tourette, a neurobiologist who worked with Sigmund Freud, was the first to describe the condition now known as Tourette's syndrome (TS) (Olson, 2004). While working in France in 1885, George Gilles de la Tourette discovered similar symptoms among his patients including motor tics, coprolalia, and echolalia. These observations led to his discovery of the most widely known and most severe of disorders within the DSM classification of “Tic Disorders” (Sadock & Sadock, 2003).

TS is generally believed to occur in about 1 in every 2000 people (Cohen, Leckman & Shaywitz, 1984), with consistent symptomatology across cultural boundaries (Robertson, 2000). Tic disorders occur in a continuum with less problematic tic disorders such as transient tic disorder on one end and more severe types such as Tourette’s Syndrome on the other (Peterson, Campise, & Azrin, 1994).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Tourette's Syndrome or “Tourette's Disorder” is classified by multiple motor and vocal tics that occur numerous times a day within a period of one year (Diagnostic, 2000). The DSM-IV-TR defines tics as “A sudden, rapid, recurrent, non-rhythmic, stereotyped motor movement or vocalization” (Diagnostic, 2000). The motor and vocal tics involved in TS come in two forms, simple and complex. Simple vocal tics include features like coughing, snorting, and repetition of short noises (Sadock & Sadock, 2003). Similarly, simple motor tics include behaviors such as eye rolling, blinking, or neck jerking (Sadock & Sadock, 2003). In contrast, complex vocal and motor tics are much more noticeable than the simple repetition of sounds or small physical movement. Often ritualistic, complex motor tics include characteristics often seen in those with Obsessive Compulsive Disorder such as
grooming, touching, or echopraxia (the repetition and imitation of behavior) (Sadock & Sadock, 2003). Many misperceptions exist about TS, as the media often portrays complex verbal tics such as coprolalia (the use of vulgar language), echolalia (repetition of the most recently heard word) and palilalia (repetition of one's own words) as the defining symptoms of TS (Sadock & Sadock, 2003). However, the occurrence of these behaviors is not as common as the media portrays them to be; coprolalia, echolalia, and palilalia occur in less than 30% of all sufferers of TS (Thoence, 1995).

**Etiology**

*Genetic evidence*

While considering causes of this disorder, it is not surprising that research shows a genetic aspect to the disease. Research indicates that Tourette's syndrome is passed down through generations from parent to child (Olson, 2004). It has been shown that up to 70 percent of all cases appear to have a genetic link (Thoence, 1995). The use of twin studies has confirmed the genetic nature of TS (Hoekstra et al., 2004). Further study on TS shows that it is an autosomal dominant gene trait and is more common in males than females (Beers and Berkow, 1999). Research shows that in comparison to the 70% chance that women have of exhibiting symptoms of TS after inheriting the gene, males have a 99% chance that those who have inherited Tourette's syndrome genes will show at least minimal symptoms of the disorder (Blachford, 2002). As a dominant gene disorder, there is approximately a 50% chance that TS will be passed down genetically from a parent to child (Blachford, 2002).

*Neurological*

Tourette’s syndrome is believed to be a neurodevelopmental disorder linked to abnormal circuitry of the brain, especially in the basal ganglia (Channon et al., 2006).
Studies focusing on the basal ganglia have found abnormal asymmetries among TS sufferers (Peterson & Klein, 1997). MRI studies have shown that the basal ganglia of TS and non-TS individuals have significantly different volumes on average (Hoekstra, 2004). Other brain structures implicated in the etiology of TS are the cortico-striato-thalamo-cortical circuits (CSTC) (Leckman, et al., 1997), caudate nucleus (Peterson et al., 2003), and prefrontal cortex (Peterson et al., 1998). Relative volume of the regional orbito-frontal, midtemporal, and parieto-occipital areas of the brain are related to the severity of TS symptoms (Hoekstra et al, 2004).

Other research suggests that an increased amount of the neurotransmitter dopamine is involved in the symptoms of TS (Blachford, 2002). Other neurotransmitter systems including the noradrenergic, serotonergic system, and glutamatergic system, as well as endogenous opioid peptides are associated with TS (Hoekstra, et al, 2004).

Psychosocial

There is a strong correlation between stress and the symptoms of TS. In a study of 33 subjects with Tourette's syndrome it was found that there is a correlation between psychological stress, including stress from social interactions, and the increased experience of TS and OCD symptoms (Findley et al., 2003). However, it has not yet been clearly determined whether this is directly caused by TS itself or the fact that having to deal with Tourette's can be stressful and cause anxiety. Psychosocial treatments do attempt to address the issue of psychosocial factors by increasing the knowledge, understanding, and acceptance of TS in their children. After the education of the parents and a more appropriate home setting for the child was established there was an apparent decrease in tic frequency. Furthermore, once parents began to revert to their less-accepting attitudes, tic frequency
increased (Funakoshi & Yuji, 2002). This seems to address the issue that various social factors such as understanding and comfort in one’s environment play important roles in the prognosis of TS.

**Diagnosis**

The first symptoms of TS often present themselves in children around 6 or 7 years old, with motor tics appearing first, followed by vocal tics at around 8 or 9 years of age (Piacentini & Chang, 2005). However, onset of TS may occur as early as 2 years old in some children (Diagnostic, 2000). While statistical documentation has not been adequately acquired, it is approximated that close to 1% of children report having symptoms of TS (Piacentini & Chang, 2005). Tourette's syndrome is often considered a chronic disease, however periods in which the patient is symptomatic may sporadically occur (Diagnostic, 2000). The frequency and severity of symptoms often decrease as time passes, while some disappear completely by adulthood (Diagnostic, 2000). Despite this information, predictors of the course of Tourette's are still unknown (Diagnostic, 2000).

Unlike many medical diseases Tourette's syndrome is a disorder that can only be diagnosed through observation or interviews (Blachford, 2002). However, this is not always possible, and diagnosing TS is often complicated and obstructed in many ways. For instance, some behaviors exhibited by those with TS are not always outside the realm of normal behavior. Also, tics that involve using obscene words or mimicry may be seen as “psychotic” or inappropriate behavior instead of a characteristic of a mental disorder (Blachford, 2002). As TS falls under the broad category of “tic disorders”, there is also sometimes confusion concerning which diagnosis to make. However, in order to make correct diagnosis easier, the DSM-IV-TR has set forth specific requirements to classify one
as having Tourette's syndrome. As specified by the DSM-IV TR, the criteria for Tourette's syndrome are:

A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.

B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.

C. The onset is before age 18 years.

D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or post-viral encephalitis) (Diagnostic, 2000).

Using these specified criteria makes diagnosing Tourette's syndrome easier, however, there are still a number of factors of concern in the diagnosis of TS. For example, social factors play a very important role in TS. Social anxieties tend to flourish around both the person afflicted by TS and their families (Irons-Georges, 2005). As stated, many people, children especially, hide their tics from others so they may go unnoticed until later (Blachford, 2002). Also, social stigmatization can play an important role in the life of a child with TS. The media often portrays and generalizes those who have TS as always exhibiting coprolalia, while the majority of those with TS experience tics of a different and more socially acceptable nature. Children with TS often experience social problems among peers and may isolate themselves from others so not to embarrass themselves (Blachford, 2002). Also, there is a waxing and waning period of symptoms of tics which makes diagnosis as well as treatment difficult due to the nature of patients seeking relief only when the tics occur at a greater rate than usual (Swerdlow & Sutherland, 2005). This can lead to an over-diagnosis or a false positive result in treatment.
When considering a diagnosis of TS, it is also important to consider the factors that separate it from other disorders within the tic spectrum. For example, transient tic disorder consists of motor and/or phonic tics that occur nearly every day for at least four weeks but no longer than a year consecutively. Chronic motor or vocal tic disorder is also separated from TS and transient tic disorder with its diagnostic criteria of either motor or vocal tics, but not both that occur almost every day for longer than a year without a tic free period of 3 months. Finally, tic disorder NOS is the diagnosis given to those whose disorder is characterized by tics but does not meet the specific criteria for any of the aforementioned tic disorders. The relative similarities between each of the diagnoses illustrate how important it is for a clinician to carefully examine the data they have before them in order to provide a correct diagnosis, prognosis, and eventually treatment.

Comorbidity

As with many psychopathological disorders Tourette's syndrome shares links with other illnesses. TS appears to be associated with disorders such as attention deficit disorder, anxiety, depression, self-injurious behaviors, learning disabilities, and personality disorders (Blachford, 2002). While its nature is ambiguous, there is a significant relationship between TS, obsessive compulsive disorder, and attention deficit hyperactivity disorder (American, 2003). ADHD is perceived to be the most common comorbid condition found with TS with a range of 21 to 90% of all clinical TS populations having comorbid ADHD (Robertson, 2000). As such there are numerous explanations about their relationship such as the idea that they may be genetically related or that there may be various types of TS which include ADHD symptoms while another form of TS may occur separately.
Obsessive compulsive disorder is also commonly found among those with TS, with comorbidity rates ranging for 11% to 80% (Robertson, 2000). Currently there appears to be some agreement that certain types obsessive compulsive behaviors are genetically related to TS as seen through familial studies. (Robertson, 2000). While less common than ADHD or OCD, self injurious behavior has been shown to be reported in over one-third of TS patients seen in clinics and that rates of SIB were positively correlated to the severity of TS (Robertson et al., 1989). While TS is considered an Axis I disorder by the DSM, it has been shown that Axis II personality disorders can be highly comorbid with TS. In a study of 34 patients with TS, 65% of these patients met criterion for a personality disorder compared with only 16% of the control group meeting these criterion (Robertson 2000). Finally, other behaviors such as aggression and inappropriate sexual behavior have been found to be correlated with TS and are the focus of many studies on the comorbidity and social factors of Tourette’s syndrome.

**Treatments**

**Pharmacological**

While not being able to determine a definite cause hampers the ability to cure TS, there are numerous treatments to suppress and control Tourette's Syndrome. Pharmacological treatments of TS can be divided into roughly two categories, antipsychotics (neuroleptics) and non-antipsychotics (Scahill et al, 2006). The most traditional treatment has been antipsychotic drugs that block postsynaptic dopamine on various receptors, such as haloperidol (Scahill et al, 2006). Pimozide, another typical neuroleptic, acts on the D1 dopamine receptor while benzamides are selective to D2 receptors (Roberton, 2000).
While the aforementioned antipsychotics are typical dopamine antagonists, there also exists another classification entitled atypical dopamine antagonists. The definition of an atypical neuroleptic is variously defined, but usually includes a decreased risk of extrapyramidal side effects, such as movement disorders, as well as the utilization of different binding mechanisms than the typical neuroleptics (Robertson, 2000). These include drugs such as Clozapine, a D1-4 receptor antagonist and Olanzapine.

Although neuroleptics have been the TS treatment of choice for many years, research is accumulating on the negative side effects of these drugs (Scahill et al, 2006). These side effects include serious neurological complications such as tardive dyskinesia, motor restlessness, cognitive effects such as impaired concentration, dysphoria and depression, fog states, symptoms resembling Parkinson’s disease, as well as metabolic abnormalities such as weight gain (Robertson, 2000).

The second general class of pharmacological treatments, the non-antipsychotics, has less evidence supporting their effectiveness, but also less evidence of side-effects (Scahill, 2006). Included within this category are sub-categories of dopamine agonists, noradrenergic-modulating drugs such as clonidine, stimulants such as methylphenidate, antidepressants such as desipramine and clomipramine, selective serotonin reuptake inhibitors like fluoxetine, benzodiazepines and GABA modulating agents such as baclofen, and diazepam, and other “alternative” forms of medication including botulinum toxin, nicotine, and THC, the active chemical in marijuana (Roberts, 2000; Scahill, 2006; Howson et al., 2004). Dopamine agonists such as pergolide have the exact opposite reaction as dopamine antagonists. While antagonists bind to postsynaptic receptors to block dopamine activity, dopamine agonists bind to these sites in effort to increase the activity of dopamine within the
brain. Most noradrenergic-modulating drugs act to inhibit the release of norepinephrine, also known as noradrenaline which is believed to lead to a decrease in the frequency of tics. Stimulants such as methylphenidate act to increase activity of various systems in the body including, most importantly for TS, the central nervous system. Research on methylphenidate has shown some decrease in vocal tics, however, other studies indicate that stimulants may increase the number of tics a person experiences (Robertson, 2000). SSRI’s, or selective serotonin reuptake inhibitors, most often used as an antidepressant, act to increase the amount and activity of serotonin present in the neuronal synapse by inhibiting the reuptake of the neurotransmitter, forcing them to remain active for longer periods than usual, increasing their effects.

While the neuroleptic haloperidol has previously been the clinician’s standard, many now choose to administer one of the non-antipsychotics for patients with moderate symptoms (Scahill, 2006). Various “alternative” treatments are now being studied in efforts to treat TS. For example, patients experiencing only a single physical tic can be given botulinum injections at the tic site to locally relax the muscles (Scahill, 2006). Also, many case studies report reductions in tics following the smoking of marijuana for periods of up to 7 hours although the mechanisms which lead to this reduction are largely unknown (Muller-Vahl, 1999). Finally, nicotine has been experimented with using a transdermal delivery which has been reported as moderately effective in tic reduction (Dursun & Reveley 1996).

**Psychological**

Along with pharmacological interventions, psychological treatments have also been examined for the treatment of TS. Current studies have shown that strictly psychological...
treatments have been effective in the treating of TS, and may be a better alternative to pharmacological treatments in moderate cases.

It is believed that one of the most promising behavioral treatments of TS is massed negative practice, which involves performing the offending tics repeatedly at specific times & intervals (Piacentini & Chang, 321). For example, one may be asked to purposefully repeat a tic for long periods of time which will supposedly lead to fatigue and lack of ability to perform the tic afterwards. This procedure is generally repeated for three sessions followed by break periods in between each practice session (Tuprin, 1983). This method has been investigated in a number of settings, and while it has moderate effectiveness in the short term, there is the least evidence for its long term effectiveness (Peterson, Campise, & Azrin, 1994). During the technique known as self monitoring, the patient keeps a journal of tics and triggers in order to become more aware of the environmental and biological precursors to their tics, in an effort to decrease their frequency. Many studies support that the monitoring of these tics alone can reduce their prevalence (Turpin, 1983), however, effectiveness seems to decrease over time (Peterson et al., 1994). Similarly, relaxation and anxiety relief techniques also have high rates of relapse (Peterson & Azrin, 1992).

Relaxation training and anxiety management are often used to combat situations which may arouse anxiety leading to the exacerbation of tics. Relaxation training for TS may include biofeedback methods focusing on muscle relaxation as well as the use of breathing exercises and imagery techniques such as guided imagery. Often, these techniques are used in combination with other psychological methods (Turpin, 1983). However, it is believed that while relaxation and anxiety management techniques are beneficial in short-term intervals,
there is some difficulty in finding appropriate relaxation techniques and being able to generalize them beyond specific treatment situations (Turpin, 1983).

Habit reversal training is a newer behavioral treatment for TS that has received much interest. In this technique, the patient first describes their tics thoroughly, then marks the occurrence of each tic, then begins noting the onset of triggers, and finally works to identify and predict the situations in which the tics occur (Piancentini & Chang, 2005). Once the factors associated with tics are more fully understood, the focus shifts to developing competing muscular responses in an effort to develop a competitive behavior which may lead to the decrease of tic behavior. The final stage involves testing this new competitive muscle behavior against a specific tic to reduce tic frequency (Turpin, 1983). Some studies have documented up to 92% reduction in tics at 12 month follow up (Peterson, Campise, & Azrin, 1994). However, although habit reversal therapy is successful, the implementation of the technique varies across the studies, making it difficult to quantify what specific techniques work best.

Exposure and response prevention is a similar technique to habit reversal therapy in that both focus on sensory experiences and identifying premonitory feelings. However, exposure and response prevention focuses less on creating a competitive muscle behavior and more on attempting to gain a certain level of self-control over the tics through suppression by one’s will, eventually culminating in the elimination of symptoms (Hoogduin, Verdellen, & Cath, 1997). For example, a clinician would first have the patient undergo training sessions in which the patient identifies their key premonitory urges. Then exposure and response prevention sessions occur in which the patient is asked to suppress their urges and refuse to
express their tics for increasing periods of time up to two hours or as long as possible (Hoogduin, Verdellen, & Cath, 1997).

Operant conditioning, in which periods of time where the person does not exhibit tics are reinforced, theoretically leads to decreased tic behaviors. Also some studies have focused on decreasing tics through the use of punishment such as shock treatments with limited results (Turpin, 1983). Studies have shown that operant conditioning has had some effectiveness in treating TS but it is often used along with other forms of treatments leaving it hard to determine if operant conditioning was the main mechanism of change (Piancentini & Chang, 2001).

Other clinical techniques have also been effective in the treatment of TS. For example, allowing the patient to verbalize feelings towards their families helped create a more understanding environment for the patient and decreased the amount of symptoms exhibited (Funakoshi & Fuse, 2003). Also, it has been shown that many patients with TS have a broad range of behavioral problems which are positively related to the amount of symptoms expressed with Tourette's syndrome (Zhu et al., 2006). Combating these behavioral problems may help reduce the incidence of tics. Finally, psychotherapeutic methods centered around psychoanalytic frameworks focused on parental management training have been used to facilitated an adjustment to a more understanding environment to help redirect the parents attitudes towards tics and reduce situations in which tics are influenced. Less commonly used within this framework is the use of hypnosis or carbon dioxide abreaction. The efficacy of these treatments can be difficult to establish however due to the physiological changes that occur during the treatment process (Turpin, 1983).
Treatments are also being considered that attempt to remedy TS at its source, the brain. While neurosurgery has been used in an attempt to treat this disorder, there has been no clear evidence that it is superior to other methods, even though it coincides with extreme cost and risk.

Anterior cingulotomies and infrathalamic lesions are among the most common neurosurgical treatments for TS. Cingulotomies are surgical techniques for various forms of psychopathology focusing on the cingulate gyrus and associated bundles. Alternatively, infrathalamic and thalamic lesions are also used to treat TS. These treatments focus on delivering lesions to very specific areas of the brain such as the lamella medialis thalamus or the ventrolateral nuclei in an effort to reduce symptoms. Various reports have offered some therapeutic benefits of these procedures but many have not resulted in significant improvements and have been associated with severe side effects (Temel & Visser-Vandewalle, 2004). For example, in a study conducted by Leckman et al, a gentleman with TS received infrathalamic lesions to reduce TS symptoms. A four month follow up showed a decline in tics, however he also presented characteristics of labored movement, restricted motion of facial areas such as the lips, tongue, and jaw and reduced intelligibility of speech. Also, his ability to initiate speech was greatly reduced and lead to increased exhaustion. Further, he had difficulty with swallowing both solids and liquids as well as difficulty chewing. Later, he developed micrographia, bradykinesia, and diminished motor function along with an overactive gag reflex. Finally, his balance was decreased drastically and resembled patients of “severe progressive supranuclear palsy” (Leckman et al, 1993). This example illustrates the obvious dangers of neurosurgery; it is only conducted in severe cases when other treatments have provided no relief.
More commonly, recent studies have focused on topics such as stimulation of the brain. It has been shown that “deep brain stimulation,” using electrodes to send impulses to specific areas of the brain such as the thalamus and the globus pallidus internus, has resulted in substantial reduction of the symptoms associated with Tourette's syndrome (Ackermans et al., 2000). For example, in studies focusing on repetitive transcranial magnetic stimulation to treat TS, the motor cortex, basal ganglia and reticular activating system are the areas of focus. Electrodes are used to deliver a frequency of electricity to these areas which is believed to decrease corticospinal excitability leading to decreased tic behaviors (Chae et al, 2004). The frequency and intensity of stimulus varies from patient to patient, and must be adjusted to provide the optimal results. Alternatively, electroconvulsive therapy, often used with those who experience severe depression or mania has been used in attempts to decrease symptoms of TS. In this method, invasive surgery is not necessary, instead, electrodes are either placed on each side of the head (bilateral ECT) or on one side of the head (unilateral ECT) and shocks are delivered concurrently with anesthetics at varying degrees of amplitude (Rudofer, Henry, & Sackeim, 2003).

Meta-analysis

A meta-analysis is a comprehensive quantitative synthesis of multiple research studies on a particular topic. Meta-analyses begin with a literature review, in which relevant studies are assembled and qualitatively assessed, then move a step beyond reviews by coding the data from each study into a common format that can be compared between studies. Meta-analysis is a relatively new technique. The first systematic meta-analysis was conducted by Gene Glass and Mary Lee Smith in 1977 on the topic of the general effectiveness of psychotherapy (Rosenthal & DiMatteo, 2001).
in the field of Psychology, and medical research is relying increasingly on the technique as well (Berman & Parker, 2002).

In research, individual trials often produce conflicting data that only reveals clear trends after numerous replications. In the same way, studies on a particular phenomena often generate conflicting results. A meta-analysis allows these studies to be systematically and quantitatively integrated, with the expectation that the underlying trend (or lack thereof) behind the data will reveal itself. Meta-analysis is particularly useful in the field of clinical psychology, where a large number of studies are published with small sample sizes. While each study individually proves little, a proper meta-analysis allows the data to be combined and considered in the same way as a much larger clinical trial. A meta-analysis can also provide a great deal of statistical power, allowing one to analyze moderator variables that contribute to specific sub-effects within the data set. When comparing psychological and pharmaceutical treatments, as in the case of TS, it might be easy to conclude that medication is the best choice because of the clinical trials with big sample sizes. The evidence for psychological treatments appears less compelling, because it is spread out over many studies. In this format, it is difficult for the clinician to assess which treatment is best. Although literature reviews provide some guidance, the subjective narrative format cannot take the place of a systematic quantitative analysis.

One point of controversy in the field of meta-analysis is the inclusion of case studies. In the early years of meta-analysis following Glass & Smith, case studies were excluded because adequate statistical techniques were not available for calculating their effect sizes. New mathematical techniques have developed since then (Allison & Gorman, 1993), although many meta-analyses still refuse to take advantage of them (Abramowitz, Whiteside,
& Deacon, 2005). In the present study, excluding case studies would unfairly tip the scales in favor of large pharmaceutical trials. In the cases of invasive surgical treatments of TS and experimental treatments like deep-brain stimulation, the vast majority of studies are naturally case studies.

The common metric of meta-analyses is known as the effect size. The effect size for each study is calculated based on the level of statistical significance of the treatment being analyzed as well as the size of the subject pools (Rosenthal & DiMatteo, 2001). Studies conducted on a larger subject pool are given more weight than studies using small numbers of subjects in the final weighted-average comparison of effect sizes (Lipsey & Wilson, 2001).

Cohen’s $d$ and Hedge’s $g$ are the effect sizes most commonly reported in meta-analyses. These effect sizes measure the standardized mean difference between control group and treatment group mean improvements, using the following formulas:

\[
\text{Cohen’s } d = \frac{(M_1 - M_2)}{\sigma_{\text{pooled}}} \quad \text{Hedge’s } g = \frac{(M_1 - M_2)}{S_{\text{pooled}}}
\]

where $M_1$ and $M_2$ represent the mean post-treatment score of the treatment and control (placebo) groups, respectively, $\sigma_{\text{pooled}}$ is the square root of the average of the squared sample deviations for both measures, and $S_{\text{pooled}}$ is the square root of the squared population deviations for both measures (Rosenthal & DiMatteo, 2001). Cohen’s $d$ is perhaps the most common effect size because it can easily be converted to other effect sizes (including Hedge’s $g$ and $r$ values), percentile rankings, percent of nonoverlap scores, and standardized qualitative descriptions (large, medium, and small effect) (Lipsey & Wilson, 2001).

A third effect size in the $d$ family, known as Glass’s $\Delta$, is particularly useful in cases where pre-test post-test measures are being made. The formula is
\[ \Delta = \frac{(M_1 - M_2)}{S_{\text{control}}} \]

where \( S_{\text{control}} \) is the standard deviation of the control group only. Utilizing only the control group standard deviation provides a more accurate measure of the variation that exists naturally in the study population (i.e., individuals with Tourette’s Syndrome), whereas including the experimental group standard deviation introduces variation that may result from treatment effects (Rosenthal, 1994, 232).

Although Cohen’s \( d \), Hedge’s \( g \), and Glass’s \( \Delta \) are ubiquitous in meta-analysis, they are not useful in every circumstance. Cohen’s and Hedge’s formula requires that each study have independent treatment and control (placebo) groups. Cohen and Hedge, like Glass before them, believed that case studies and repeated measure designs should be excluded from meta-analyses. Since that time, new statistical techniques have developed that allow for the calculation of effect sizes in these study types. This is particularly useful in the field of clinical psychology, where researchers are usually interested in how some measure changes in an individual following treatment, and often only have access to small treatment groups.

The recommended effect size measurement is \( \Delta_{\text{RM}} \) (\( \text{RM} = \text{repeated measures} \)) (Morris & DeShon, 2002; Rosenthal, 1994). The calculation for \( \Delta_{\text{RM}} \) is essentially the same as Glass’s \( \Delta \),

\[ \Delta_{\text{RM}} = \frac{(M_{\text{pre-test}} - M_{\text{post-test}})}{S_{\text{pre-test}}} \]

thus it remains in the “\( d \)” family of effect sizes. However, the RM subscript is used to distinguish this formulation from the classic Glass’s \( \Delta \), and to remind the reader that effect sizes calculated in this manner cannot necessarily be converted to other effect sizes using the formulas that accompany Glass’s \( \Delta \). The standard deviation of the pre-test measure is used rather than the control group standard deviation at the recommendation of Morris & DeShon,
2000 (108) because it is more representative of the variation that exists in the population of individuals with TS, and should reveal homogeneity between studies, in the same way as using only the control group standard deviation in Glass’s $\Delta$.

Although analyses of controlled studies using Cohen’s $d$ are often perceived as the gold standard of meta-analysis, rejecting case studies and repeated measure designs eliminates a large pool of available literature, especially in the case of clinical psychology. Using $\Delta_{RM}$ allows these alternative study types to be included. As this study includes a large number of repeat-measure designs in which no placebo group is available, this was a necessary choice. Although they are very similar, Glass’s $\Delta$ values cannot be directly compared to $\Delta_{RM}$ values, nor can they be averaged together during analysis. This presents a problem for meta-analyses that wish to compare and combine these different study types. The basic goals and theoretical constructs of the study types are different; controlled independent group designs examine comparison scores between groups, while repeated measure designs examine scores of change. The formulas for comparing Glass’s $\Delta$ and $\Delta_{RM}$ are complex, and their validity is debated (Morris & DeShon, 2002). For these reasons, this study recorded both pre-test and post-test data for studies with independent measure designs, and calculated $\Delta_{RM}$ values as if control groups were not included, allowing independent measure studies to be compared equally with repeat measure studies.

Raw effect sizes are calculated as described previously, and denoted as $\Delta_{RM}$ in this study. However, $\Delta_{RM}$ does not take into account the number of subjects included in each study. Study A and B may have an identical $\Delta_{RM}$, but if Study A included 30 participants, and Study B only included 2, the results of Study A are statistically more meaningful than those of Study B. Using a weighted effect size measure allows one to differentiate between
Study A and B. It is common practice to weight effect sizes by the inverse of the effect size variance (Rosenthal & DiMatteo, 2001). For $\Delta_{RM}$, the variance is given by the formula

$$v = \frac{n_1 + n_2}{n_1 n_2} + \frac{(\Delta_{RM}^2)}{2(n_2)}$$

where $n_1$ and $n_2$ are the number of subjects in the pre and post test groups, respectively. The formula for calculating weighted effect sizes is

$$W\Delta_{RM} = \Delta_{RM} \times \frac{1}{v}$$

where $W\Delta_{RM}$ denotes the weighted effect size. Both weighted and unweighted effect sizes were calculated.

**Methods**

The basis of every meta-analysis is a thorough search and review of the literature. Articles included in this study were located using searches of the online databases PsycINFO, the Psychology and Behavioral Sciences Collection, and the Electronic Journal Center. Dissertations were identified using ProQuest and UMI Dissertation Express. All searches utilized combinations of the following keywords: Tourette, Tourette’s, Gilles de la Tourette, tic, syndrome, disorder, tourettism, TS, GTS, treatment, review. Articles available online were downloaded and stored as Adobe PDF files; other articles were obtained as paper files through Inter-library loan (ILL). The reference list of each article was also examined, and any article with a potentially relevant title was also obtained, either through additional online searches, or via ILL. Although non-experimental review articles were not analyzed in this study, particular care was taken to locate reviews of TS treatments, as these sources often reference many experimental works of interest. The results of these searches produced an
initial pool of 259 studies, which was narrowed to 134 studies using the exclusion/inclusion criteria detailed below.

**Inclusion and Exclusion Criteria**

This study includes published research and dissertations on the topic of Tourette’s Syndrome treatments released between 1950 and March 2008 in the English language. For studies dating after the publication of DSM-III in 1980, only studies in which the subjects were diagnosed with TS according to DSM specifications are included. For studies of TS conducted before DSM criteria were established, the symptoms described must be consistent with accepted definitions of TS, including multiple motor and vocal tics occurring throughout the day, with the age of onset sometime before adulthood. Although many of the subjects experienced comorbid disorders, TS must be the primary diagnosis, and the primary purpose of the study must be to treat the symptoms of TS, not any comorbid disorder. Both case studies and controlled studies are included. Studies that reported only observational results rather than quantitative data were excluded. Similarly, studies that did not include both baseline and post-treatment data in the same reporting measure (i.e. using the same scale) were excluded. A manual review of the data was performed to ensure that no data set was repeated, as in the case of multiple publications.

Although each study usually included multiple measures of treatment efficacy, only one measure was included from each study to prevent sampling the same data twice. When reported, total tic scores from the Yale Global Tic Severity Scale (YGTSS) were used because it is the most commonly used measure of tic frequency and severity, and has high reliability (Leckman et al., 1989). In cases where YGTSS data was not available, recordings of tic frequency by the clinician were preferentially used rather than self-report measures.
Clinician measurements were used as these reports are usually based from videorecordings of the subjects, and tics are counted independently by multiple researchers. Self-report measures suffer from subjectivity on that part of the patient, and may vary with the patient’s mood or perceptiveness. Other studies have suggested that the number of tics may vary, either positively or negatively, when the patient tries to focus attention on them (Woods, Miltenberger, & Flach, 1996).

When data for multiple post-treatment evaluations or follow-ups was available, data from the follow-up most distant from the treatment was used. This method was chosen to ensure that the subjects in each study had received the full course of treatment. This is also important for pharmaceutical treatments especially to allow the body enough time to adjust to the drug properly. Finally, symptoms of TS are known to wax and wane over time. Although there is no simple way to control for these natural fluctuations in symptoms, choosing data from the most distant follow-up date should eliminate some of the symptom fluctuation associated with the experience of being treated, but not the treatment itself. For example, patients may experience periods of nervousness or anxiety when presented with a new clinician or treatment, and these feelings could exacerbate their symptoms. In the most distant follow-up date, patients are presumably more adjusted to the treatment situation, and less prone to symptom fluctuations caused by these extraneous factors.

For each study, pre-treatment and post-treatment test values, treatment method, sample size and % male, mean sample age, and control information, if available, were recorded. Treatment type was recorded explicitly (i.e. haloperidol, habit reversal therapy) and abstracted into one of each of the following categories for comparative purposes: pharmaceutical, psychological, and neurosurgical.
Effect size

Effect sizes were calculated as $\Delta_{RM}$ values using the formula

$$\Delta_{RM} = (M_{pre-test} - M_{post-test}) / S_{pre-test}$$

as described above (Morris & DeShon, 2002). Given this formulation, treatments that decreased symptoms have positive effect sizes; those that worsened symptoms have negative effect sizes. While calculating effect sizes, the researcher was blinded to treatment type to eliminate potential bias. Effect size measures are also reported as weighted effect sizes, with each measure weighted by the inverse variance using the formulas

$$W\Delta_{RM} = (\Sigma (\Delta_{RM} * (1 / v))) / (\Sigma (1 / v))$$

$$v = (n_1 + n_2) / (n_1 * n_2) + (\Delta_{RM}^2) / (2(n_2))$$

as described in Rosenthal, 1994. The standard error of the $W\Delta_{RM}$ was calculated as

$$SE = \sqrt(1 / \Sigma (1 / v))$$

and the $Z$-test for the mean $W\Delta_{RM}$ was calculated as

$$Z = W\Delta_{RM} / SE$$

and converted to $p$ values using a standard normal distribution chart (Lipsey & Wilson, 2000).

Results

Using the search methods described above, an initial pool of 259 articles was obtained. Thirty-three of these articles were review papers containing no experimental data. Eight additional articles were removed from analysis because Tourette’s syndrome was not the primary diagnosis, or was not explicitly diagnosed. Fifty-one studies were removed because they did not contain quantitative outcome data, or reported only the outcome of a
variable irrelevant to this study (ie change in ADHD or depression measures). Twelve articles were theoretical analyses of TS or studies of rodent models of TS. Twenty-one studies that otherwise met the inclusion criteria were excluded because the data was not presented in a usable format, or the outcome data was incomplete. This resulted in a final pool of 134 studies.

Table 1 presents the average effect size, weighted and unweighted, for the three classes of TS treatments: psychological, pharmaceutical, and neurosurgical. P values are presented as calculated from Z scores of the weighted average effect sizes.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (studies)</th>
<th>M ΔRM (±SD)</th>
<th>M WΔRM (±SE)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>33</td>
<td>2.945 (4.22)</td>
<td>0.627 (0.12)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>86</td>
<td>1.529 (5.02)</td>
<td>0.948 (0.05)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>15</td>
<td>12.891 (28.94)</td>
<td>1.664 (0.31)</td>
<td>&lt; 0.00001</td>
</tr>
</tbody>
</table>

Neurosurgical treatments were found to be the most effective using unweighted measures, followed by psychological then pharmaceutical treatments. However, after weighting the effect sizes using a combination of subject number and sample variation using the inverse variance formula, neurosurgical treatments proved to have the greatest effect, followed by pharmaceutical, then psychological treatments (Table 1). The information is also presented in Figure 1.
FIGURE 1. Unweighted and Weighted Effect Sizes for each Treatment Category. Error bars for $\Delta_{RM}$ values represent standard deviation; error bars for $W\Delta_{RM}$ values represent 95% CI.

Descriptive characteristics of the studies analyzed and subjects within those studies are listed in Table 2. Studies of pharmaceuticals typically used twice as many subjects ($M = 10.74$) as studies of psychological treatments ($M = 5.33$), and three times as many subjects as neurosurgical trials ($M = 3.47$). All three treatment categories used a similar percentage of male subjects, which is consistent with the overall incidence characteristics of TS, although the neurosurgical treatments were conducted on a larger percentage of females than the other two treatment types. The psychological and pharmaceutical treatment categories also worked with a similar age group of patients ($M = 18.45, 21.07$ respectively). Patients used in neurosurgical treatments were generally older ($M = 35.54$), presumably as neurosurgery is typically only conducted on adults after many other attempted treatments are unsuccessful.
To examine the overall distribution of effect sizes, a funnel plot was constructed comparing unweighted effect size ($\Delta_{RM}$) and sample size, as shown in Figure 2. The unweighted effect size is used, as the weighted effect size would merely exhibit strong correlation with the sample size (since sample size is a significant portion of the weight). Funnel plots are used to visually examine for publication bias in meta-analysis, whereby studies with null or negative results are not published (Greenhouse & Iyengar, 1994). If no bias exists, the plot should resemble an upside-down funnel, with at least some studies revealing negative or null effects (Greenhouse & Iyengar, 1994).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n (studies)</th>
<th>n (participants)</th>
<th>M participants per study</th>
<th>M % male</th>
<th>M age (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>33</td>
<td>176</td>
<td>5.33</td>
<td>83.70</td>
<td>18.45</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>86</td>
<td>924</td>
<td>10.74</td>
<td>83.73</td>
<td>21.07</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>15</td>
<td>52</td>
<td>3.47</td>
<td>77.92</td>
<td>35.54</td>
</tr>
</tbody>
</table>

TABLE 2. Study and Participant Characteristics
Although it is difficult to definitively state that no publication bias exists, Figure 2 resembles the classic shape of a meta-analysis not affected by publication bias (Greenhouse & Iyengar, 1994, 394). The general shape is that of an upside-down funnel, and a number of studies with negative results exist at smaller sample sizes.

In addition to analyzing the effect sizes of the three categories of treatment, the average effect size, weighted and unweighted, for specific treatments was examined. The categories of pharmaceutical treatments are those suggested in a review by Robertson (2000). Results are presented in Table 3 and Figures 3 and 4. Z scores of the $W\Delta_{RM}$ were calculated for each treatment type and converted to p values using a standard normal table.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>WΔRM (±SE)</th>
<th>95% CI</th>
<th>p value</th>
<th>ΔRM (±SD)</th>
<th>n (studies)</th>
<th>n (participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical neuroleptics***</td>
<td>1.082 (0.11)</td>
<td>0.87, 1.29</td>
<td>&lt; 0.0001</td>
<td>1.570 (1.39)</td>
<td>15</td>
<td>258</td>
</tr>
<tr>
<td>Atypical neuroleptics***</td>
<td>1.260 (0.14)</td>
<td>0.99, 1.53</td>
<td>&lt; 0.0001</td>
<td>4.237 (6.26)</td>
<td>15</td>
<td>164</td>
</tr>
<tr>
<td>Other dopamine antagonists</td>
<td>1.005 (0.71)</td>
<td>-0.38, 2.39</td>
<td>0.079</td>
<td>1.005</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Dopamine agonists &amp; L-Dopa***</td>
<td>1.017 (0.16)</td>
<td>0.70, 1.33</td>
<td>&lt; 0.0001</td>
<td>1.119 (0.71)</td>
<td>8</td>
<td>107</td>
</tr>
<tr>
<td>Noradrenergic modulators***</td>
<td>1.061 (0.24)</td>
<td>0.60, 1.52</td>
<td>&lt; 0.0001</td>
<td>1.233 (0.54)</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>Stimulants*</td>
<td>-1.739 (0.94)</td>
<td>-3.58, 0.10</td>
<td>0.032</td>
<td>-1.739</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>-0.377 (0.48)</td>
<td>-1.33, 0.57</td>
<td>0.218</td>
<td>0.316 (2.81)</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>SSRIs</td>
<td>1.177 (0.58)</td>
<td>-0.96, 1.31</td>
<td>0.380</td>
<td>0.177</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>GABA modulators*</td>
<td>1.086 (0.51)</td>
<td>0.09, 2.08</td>
<td>0.016</td>
<td>1.086</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Other***</td>
<td>0.619 (0.11)</td>
<td>0.41, 0.83</td>
<td>&lt; 0.0001</td>
<td>2.773 (5.91)</td>
<td>15</td>
<td>208</td>
</tr>
<tr>
<td>Serotonin antagonists*</td>
<td>0.718 (0.27)</td>
<td>0.19, 1.25</td>
<td>0.004</td>
<td>1.444 (0.75)</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>Opioid agonists</td>
<td>0.446 (0.36)</td>
<td>-0.26, 1.15</td>
<td>0.107</td>
<td>-5.332 (8.95)</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>All dopamine antagonists***</td>
<td>1.146 (0.08)</td>
<td>0.98, 1.31</td>
<td>&lt; 0.0001</td>
<td>2.842 (4.66)</td>
<td>31</td>
<td>427</td>
</tr>
<tr>
<td>HRT***</td>
<td>0.824 (0.18)</td>
<td>0.47, 1.17</td>
<td>&lt; 0.0001</td>
<td>3.892 (5.08)</td>
<td>17</td>
<td>80</td>
</tr>
<tr>
<td>ERP***</td>
<td>1.235 (0.34)</td>
<td>0.57, 1.90</td>
<td>0.0001</td>
<td>2.036 (1.23)</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Relaxation training</td>
<td>0.382 (0.55)</td>
<td>-0.69, 1.45</td>
<td>0.242</td>
<td>0.593 (0.28)</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Self-monitoring</td>
<td>0.511 (0.53)</td>
<td>-0.54, 1.56</td>
<td>0.170</td>
<td>1.303 (0.85)</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Parent ed. / SP</td>
<td>0.208 (0.20)</td>
<td>-0.18, 0.60</td>
<td>0.146</td>
<td>0.225 (0.17)</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>Reinforcement / BT</td>
<td>2.851 (1.91)</td>
<td>-0.89, 6.60</td>
<td>0.068</td>
<td>4.309 (2.14)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>MNP</td>
<td>0.361 (1.39)</td>
<td>-2.36, 3.08</td>
<td>0.398</td>
<td>5.156 (5.16)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>DBS*</td>
<td>1.189 (0.34)</td>
<td>0.52, 1.86</td>
<td>0.002</td>
<td>5.621 (4.70)</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>Surgery***</td>
<td>3.631 (0.70)</td>
<td>2.27, 5.00</td>
<td>&lt; 0.0001</td>
<td>41.970 (55.18)</td>
<td>3</td>
<td>19</td>
</tr>
</tbody>
</table>

**TABLE 3. Average Effect Sizes for Treatment Subcategories.**

SSRI = selective serotonin reuptake inhibitor; HRT = habit reversal therapy; ERP = exposure and response prevention; SP = supportive psychotherapy; BT = behavioral therapy; MNP = massed negative practice; DBS = deep brain stimulation. * p < 0.05; ** p < 0.01; *** p < 0.001
FIGURE 2: Weighted Effect Sizes for Pharmaceutical Treatments Sub-categories.

FIGURE 3: Weighted Effect Sizes for Psychological and Neurosurgical Treatments.
The most effective treatment was found to be surgical ($W_{\Delta_{RM}} = 3.631, p < 0.0001$). The most effective pharmaceutical treatment was the atypical neuroleptics ($W_{\Delta_{RM}} = 1.260, p < 0.0001$). The least effective were stimulants ($W_{\Delta_{RM}} = -1.739, p = 0.032$) and antidepressants ($W_{\Delta_{RM}} = -0.377$). The most effective psychological treatment was habit reversal therapy ($W_{\Delta_{RM}} = 0.824, p < 0.0001$), followed closely by exposure and response prevention ($W_{\Delta_{RM}} = 1.235, p = 0.0001$). The least effective was parent education / supportive psychotherapy ($W_{\Delta_{RM}} = 0.208, p = 0.146$).

The pharmaceutical treatments typical neuroleptics, atypical neuroleptics, dopamine agonists & L-dopa, noradrenergic modulators, GABA modulators, other pharmaceuticals, including nicotine and THC, and serotonin antagonists produced a significant reduction of symptoms. The overall $p$ value for all pharmaceutical treatments was $< 0.00001$. Among the psychological treatments, habit reversal therapy and exposure and response prevention were effective. The overall $p$ value for psychological treatments was $< 0.00001$. Among the neurosurgical treatments, both surgery and deep brain stimulation produced significant effects, with an overall $p$ value for both types of neurosurgical treatment $< 0.00001$.

The number of unpublished studies showing a null effect, otherwise known as the file drawer problem, was also examined. Figures were calculated as shown in Table 4, using the equation

$$X = (k / 2.706) * [k * Z_k^2 - 2.706]$$

where $X$ is the number of studies showing zero effect that would be required to reduce the effect size of this study below the 0.05 significance level, $k$ is the number of studies included in the meta-analysis, and $Z_k$ is average Z score for those studies (Rosenthal, 1979).


Discussion

The present study represents the first meta-analysis of the three major categories of treatments for Tourette’s syndrome. While previous studies have examined the efficacy of specific treatments or compared the efficacy of more than one specific treatment, this study compiles data from 134 studies spanning all three major categories of Tourette’s syndrome treatments, examining over 45 specific treatments. In addition, previous analyses have excluded the results of case studies and repeated-measures designs. By choosing a method that includes these types of studies, this meta-analysis presents a more comprehensive view of the current status of Tourette’s research.

One criticism of meta-analyses is that it is difficult to prove that one has obtained all of the possible data available on the given subject. Further, many studies with insignificant results go unpublished, remaining tucked away in the ‘file drawers’ of researchers scattered about the world. If there are a large number of these unpublished null studies, then the published results analyzed are not representative of the true effect of the treatment. The method used to assess the effect these unpublished data would have on the meta-analysis is known as the file-drawer statistic. Analysis indicates that over 837,000 unpublished studies showing an effect size of zero would have to exist to bring the effect size of this study out of

<table>
<thead>
<tr>
<th>Treatment Category</th>
<th>$Z_k$</th>
<th>$X$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological</td>
<td>5.358</td>
<td>11,522</td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td>17.360</td>
<td>823,580</td>
</tr>
<tr>
<td>Neurosurgical</td>
<td>5.420</td>
<td>2,427</td>
</tr>
</tbody>
</table>

TABLE 4: File-drawer Problem Statistics
the 0.05 significance level. It is highly unlikely that this many unpublished null studies are in existence. This result, along with the funnel plot presented in Figure 2 indicate that it is unlikely that the present meta-analysis suffers from publication bias, or the file-drawer problem.

One other issue of concern in meta-analyses is that of heterogeneity among the studies included, commonly called the ‘apples and oranges’ problem. If the studies considered are too different, then some argue that it makes little sense to consolidate their data. This problem is partially addressed by the use of effect sizes in meta-analyses, which allows diverse outcome measurements to be translated to a common metric. Even though the treatments vary, and the way those treatments are assessed vary, converting the data to a common effect size allows them to be compared. Of concern for TS, however, is that various definitions of TS have existed over time. Before the implementation of DSM-III, there was no clear diagnosis criteria for TS. Therefore, studies conducted before this time labeled their subjects as having “Tourette’s Syndrome” without having a consistent definition of what TS is. Even after the introduction of DSM-III, the definition of TS has changed with each subsequent revision (see Appendix 1). Although these changes exist, they have been largely superficial, and have not made significant changes to the population designated as having TS.

Similarly, before DSM-III, clinicians maintained a relatively consistent idea of what TS was, based on Gilles de la Tourette’s original description of the phenomena.

The results of this study indicate that neurosurgical treatments are the most efficacious treatment for TS, followed by pharmaceutical treatments, then psychological treatments. While each of these categories exhibited different levels of efficacy, each category was significant at the p < 0.00001 level. This is an important point to consider.
when weighing the costs and benefits of a particular treatment method. Similarly, each treatment category contains specific treatments that are more efficacious than others. In addition to dividing the treatments into categories, the treatments were also divided into twenty-one specific methodological subtypes (See Table 3). Of these subtypes, “surgery” was the most effective ($W_{\Delta RM} = 3.631, p < 0.0001$), including lesioning of the brain such as bilateral cingulotomy. Although surgery was revealed to be the most efficacious treatment, it is obviously not a preferable treatment course for all patients. Neurosurgery can be associated with extreme risks that must be taken into consideration when making a decision on a course of treatment.

While the surgery subcategory was the most efficacious treatment overall, each of the categories contained specific treatment types that were extremely efficacious in their own right. The second most efficacious treatment was the subcategory of atypical neuroleptics such as clozapine and olanzapine, followed by typical neuroleptics which include the clinician’s preferred treatment haloperidol. The fourth most efficacious treatment was the noradrenergic modulators including clonidine and guanfacine. The next most efficacious treatment were the dopamine agonists, including L-Dopa. The sixth most efficacious treatment was habit reversal therapy, followed by the “other” subcategory of pharmaceutical treatments which includes nicotine, THC, and botulinum-toxin. Exposure and response therapy was the next most efficacious and the second most efficacious behavioral treatment for TS. Deep brain stimulation, serotonin antagonists, and GABA modulators were also found to be effective ($p < 0.05$).

One treatment subcategory, stimulants, produced a significant negative effect ($W_{\Delta RM} = -1.739, p = 0.032$), meaning that this treatment worsened symptoms of the patients.
Although the effect was significant, further study of stimulants may still be warranted, as this treatment subcategory is represented by only one study, with four subjects. The antidepressants also produced a negative effect ($W_{∆RM} = -0.377$), although the effect was not significant ($p = 0.218$).

Treatments that were not found to produce a significant effect were the other dopamine antagonists, antidepressants, SSRIs, opioid agonists, relaxation training, self-monitoring, parent education and supportive therapy, reinforcement and behavioral therapy, and massed negative practice. Care should be taken before dismissing these treatments as ineffective, however, as many of these treatments were represented by small numbers of studies or subjects; further research may have revealed a stronger effect.

Perhaps the first point that should be noted is that when considering TS, the clinician has a variety of efficacious treatment choices; twelve of the twenty-one treatment subcategories considered were effective at the 0.05 level, ten at the 0.0001 level. The choice of which treatment to initially pursue must be carefully balanced against the needs of the patient. Because TS is a complex disorder with complex causes, different treatments may be effective for some individuals more so than others, depending on the specific etiology of the individual’s TS. However, because the etiology of TS cannot be identified in most cases, an examination of the moderator variables for treatment success is difficult. Thus, it falls on the clinician to choose a treatment with significant evidence for success and a low risk of side effects.

Based on the results of this study, neurosurgery is the most efficacious treatment for TS, however it would be impractical to choose neurosurgery as the first treatment for an individual with TS. The risks of this technique are high, and unlike with pharmaceuticals or
psychological treatments, the side effects of neurosurgery, should any occur, are usually permanent. In the past, clinicians have typically turned to the typical neuroleptic haloperidol or the atypical neuroleptic risperidone as the first treatment of choice in TS. However, neither haloperidol or risperidone are recommended as first-choice treatments, as each produce undesirable side effects in the majority of patients. While most patients see great improvement in their symptoms, most do not take the drugs long-term due to the side effects.

Following the neuroleptics, the noradrenergic modulators were shown to be the next most effective, including clonidine and guanfacine. Both drugs have low rates of side effects, and are particularly effective in children and adolescents with comorbid ADHD. For these reasons, clonidine and guanfacine are good candidates as a first-choice pharmaceutical for TS.

Although pharmaceutical treatments were more effective than psychological treatments, clinicians trained in these methods may do well to attempt these treatments first in moderate cases of TS, as side effects are much less of a concern than with pharmaceuticals. Habit reversal therapy in particular may be a good first-choice given its efficacy, although exposure and response therapy should be considered as well. Finally, a note should be made concerning massed negative practice (MNP). While other reviews have recommended MNP, the effect size was low in this study. However, MNP is represented here by only two studies and two subjects, thus further testing is obviously warranted.

Tourette’s syndrome is a multifaceted disorder affecting a range of individuals. Because of the numerous treatments available for TS, choosing the best course of action is often difficult. The results of this study indicate that neuroleptics are highly effective pharmaceuticals, but the noradrenergic modulators clonidine and guanfacine may prove
better first-choice drugs due to their decreased incidence of side effects. The psychological treatments habit reversal therapy and exposure and response prevention are also particularly promising, and good first-choice options for clinicians skilled in their use, although other methods may be effective as well. Finally, neurosurgery and deep-brain stimulation are very effective options for individuals with severe TS that is irresponsive to other techniques.
References

(* indicates studies included in meta-analysis)


*Black, K., & Mink, J. (2000). Oral levodopa seems to be effective in reducing the severity of chronic tics. *Inpharma*, 1271, 16.


Appendix 1. DSM criteria for Tourette’s Syndrome diagnosis.

**DSM – III (1980):**
A. Age at onset between 2 and 15 years.
B. Presence of recurrent, involuntary, repetitive, rapid, purposeless motor movements affecting multiple muscle groups.
C. Multiple vocal tics.
D. Ability to suppress movements voluntarily for minutes to hours.
E. Variations in the intensity of the symptoms over weeks or months.
F. Duration of more than one year.

**DSM – III-R (1987):**
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than one year.
C. The anatomic location, number, frequency, complexity, and severity of the tics change over time.
D. Onset before age 21.
E. Occurrence not exclusively during Psychoactive Substance Intoxication or known central nervous system disease, such as Huntington’s chorea and postviral encephalitis.

**DSM – IV (1994):**
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.)
B. The tics occur many times a day (usually in bouts), nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.
C. The disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning.
D. The onset is before 18 years of age.
E. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington’s disease or post-viral encephalitis).

**DSM – IVTR (2000):**
A. Both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently.
B. The tics occur many times a day (usually in bouts) nearly every day or intermittently throughout a period of more than 1 year, and during this period there was never a tic-free period of more than 3 consecutive months.
C. The onset is before age 18 years.
D. The disturbance is not due to the direct physiological effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington’s disease or post-viral encephalitis).