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An Overview of the Treatment of Tourette's Disorder and Tics

Humberto C. Párraga, M.D.,[1] Kara M. Harris, B.S.,[1] Karen L. Párraga, M.Ed.,[1]
George M. Balen Psy.D.,[1] and Cristina Cruz, M.D.[2]

Abstract

Objective: The aim of this study was to review the efficacy of various treatments for Tourette's disorder (TD) and tics.
Method: This study is a historical review of the treatment modalities prior to the advent of neuroleptics. A review of double-blind and placebo-controlled clinical trials and open studies on the use of neuroleptics and selected reports was also carried out.
Results: The literature review reveals that the treatment of TD and tics has evolved from an early history of marginally effective approaches to the advent of neuroleptics, which started a new era in TD and tic treatment, with a significantly broader range of effectiveness.
Conclusions: Although progress has been made, the literature review nevertheless reveals a great deal of confusion as related to the clinical heterogeneity of TD and tics, differences in populations, medication–dose combinations, and outcomes. However, a role for a limited number of pharmacologic agents, combined with psychosocial approaches, has been identified. There is a need for studies in larger, diagnostically homogenous samples and for the use of more sophisticated methodology, to identify intelligible models that would allow the development of more effective treatment approaches.

Introduction

Because tics are a component of multiple disorders, classically Tourette's disorder (TD), the history of the treatment of TD parallels the treatment of tics. This overview represents a substantial effort beginning with the description of a variety of early interventions (which, at present, may be deemed only of historical interest), followed by a review of clinical studies of neuroleptics and their striking implications for the treatment of TD and tics.

Historical Review

The early history of the treatment of TD and tics includes a gamut of diverse and inventive, albeit marginally effective, approaches.

An early paper (Itard 1825) offered one of the most graphic descriptions of the methods of symptom alleviation available in the early to mid-1800s, such as "the application of leeches for 2 consecutive days monthly, and cupping in a series of areas along the spine while the patient was in a prone position." The author also recommended "drinking an emulsion of ground chicken along with the simultaneous administration of two baths with a total immersion in cold water for a duration of 3 hours for 2 consecutive days." Another prescription for one of his female patients was the application "of leeches to the vulva along with the application of cupping to the thighs while the patient lay prone for 2 hours" and the application of "leeches to the thighs while soaking the patient's feet in a mildly caustic solution after the application of valeriane powder." At last, he suggested, "cold river baths and additional cooling of the body by application of refrigerant lotions and breezes of cold air" with subsequent removal of the patient to "a place of isolation."

Reeducation with the use of massages and methodical gymnastics in cases of "severe chorea" were alleged to provide rapid and excellent results (Blache 1864). Gymnastic exercises of the involved muscles to the rhythmic accompaniment of a metronome or the pendulum of a clock were also recommended (Trousseau 1873).

Gilles de la Tourette (1885) himself acknowledged the tremendous difficulties in treating this ailment. He claimed that the one course of treatment that seemed to impact the syndrome was "isolation, in combination with the use of tonics of all sorts including iron preparations and hydrotherapy." These patients equally appeared to benefit from the "prolonged use of static electricity in combination with hydrotherapy and isolation." He also emphasized that these approaches could only delay the evolution of the illness rather than cure it, clarifying that all sedatives of the central nervous systems known at that time had been tried and found to be ineffective.

An article on "convulsive tics" (Guinon 1887) devoted only a few lines to the issue of treatment, recommending hydrotherapy combined with isolation. Another (Charcot 1888) cautiously stated,

Departments of [1]Child Psychiatry and [2]Pediatrics, Fourth Street Clinic, Springfield, Illinois.

"we can not say that cure is certain but may count on longer or shorter intervals of arrest, either spontaneous or a sequel to the employment of serviceable measures such as hydrotherapy and gymnastics."

The value of motor discipline in tic control was demonstrated (Brissaud 1899) by the use of a method that was a combination "of immobilization of movements with *movements* of immobilization." The exercises were intended to teach the patient how to preserve immobility by remaining absolutely motionless as long as he could without fatigue, gradually increasing the periods of immobility, and emphasizing that "one must rest content even with the most insignificant gain." A doctoral thesis (Cruchet 1902) written in this period advocated interventions, including motor discipline, training the antagonists, respiratory drill, and gymnastics.

A very influential book *Tics and Their Treatment* (Meige and Feindel 1902, 1907) listed a number of diverse invasive methods of intervention recommended by different practitioners, available in the late 1800s and early 1900s, which included the rhythmic traction of the tongue, application of mustard plasters, thoracic compression, electric shock of the phrenic nerve, and application of an actual cautery to the vertebral column. General hygiene, diet, altering the patient's lifestyle by prescribing recreation, sea voyages, time at seaside curative resorts, and hydrotherapy were mentioned along with medicinal, surgical, and orthopedic treatments. They concluded that most of the medicinal agents used at that time had been found to be ineffective in treating tics. These drugs included caffeine, coca, cocaine, arsenic, quinine, ether, chloroform, curare, atropine, laudanum, opium, morphine, chloral hydrate, *Cannabis indica*, zinc valerianate, and bromides.

The surgical procedures, mentioned in the same book, included the elongation, ligature, and section or resection of the spinal accessory. The authors nevertheless emphasized that surgical procedures were "applicable only to a small minority of tics, principally those of the neck." They also expressed doubts about the efficacy of the orthopedic treatment, indicating that in some instances the various forms of apparatus used to intervene for temporary relief of symptoms were more harmful than beneficial. The treatment of tics by the use of psychotherapy, conscious education, hypnotic suggestion, and reeducation in combination with surgical treatment was also emphasized as a means of maintaining the general health of the patient, including proper sleep and the use of sedatives such as bromides to ensure the patient's rest (Brain 1928). In the treatment of children, the same author encouraged the whole household be united "in a conspiracy to take no notice of the child's movements" to promote reduction of symptoms. Punishment and reproof of the child for exhibiting symptoms were prohibited. If lack of improvement resulted, the child was "sent to relatives in another town for a time, or admitted to a suitable hospital."

The use of intensive psychotherapy was actively promoted (Mahler and Rangell 1943). Later, persuasion, reeducation, autogenic training, and psychoanalysis were also recommended (Mahler and Gross 1945; Mahler and Luke 1946). Bimedial frontal leucotomy (Baker 1962), carbon dioxide inhalation (McDonald 1963; Downing et al. 1964), experimental hypnotherapy (Erickson 1964), social-psychiatric management (Faux 1966), and behavior management (Clark 1966) were also reported.

Group therapy, family therapy, biofeedback, insulin coma, electroconvulsive treatment, acupuncture, and transcendental meditation were mentioned as additional treatment modalities for TD with inconsistent results (Shapiro et al. 1978).

Contemporary Review

Classic or typical antipsychotics

The advent of the neuroleptics started a new era in the treatment of TD and tics. Antipsychotics are thought to act primarily by blocking dopamine receptors, thus decreasing dopaminergic input from the substantia nigra and ventral tegmentum to the basal ganglia.

Multiple clinicians (Seignot 1961; Challas and Brauer 1963; Chapel et al. 1964; Abuzzahab and Anderson 1973; Shapiro et al. 1973) reported the efficacy of haloperidol (HAL) in the treatment of tics and TD (Table 1). HAL was approved by the FDA for the treatment of adult TD patients in 1969 and for children in 1978. However, a number of nonuniversal adverse and side effects (cognitive blunting, weight gain, lethargy, and akathisia) limited its use (Mikkelsen et al. 1981).

Pimozide was the most widely used alternative to HAL. Approved by the FDA in 1984 for the use in TD patients, it was touted as having lower potential for adverse effects. Pimozide was used with good results in multiple studies (Debray et al. 1972; Shapiro and Shapiro 1984; Regeur et al. 1986; Sallee et al. 1997), one of which showed a mean percentage decrease of symptoms at the endpoint of 71% for pimozide and 62% for HAL.

Penfluridol was used with significant symptomatic improvement and fewer adverse effects compared with HAL, but concerns about its carcinogenic potential limited its use (Parihk et al. 1979; Shapiro et al. 1983a).

Phenothiazines such as fluphenazine and trifluoperazine were compared with HAL in a double-blind, placebo-controlled study in 10 TD patients and all three active medications were better than placebo in tic suppression. None of these medications statistically proved to be better than the other (Borison et al. 1982). In another open study, 21 TD patients, considered to be resistant to HAL, were subsequently treated with fluphenazine, with decrease of tics, improvement of efficacy, and fewer adverse affects (Goetz et al. 1984).

Chlorpromazine, trifluoperazine, perphenazine, and thioridazine were also used with lesser efficacy and the limitations were a cohort of significant adverse effects including photosensitivity, dermatitis, extrapyramidal symptoms, and blood and liver dyscrasias (Shapiro et al. 1988).

In summary, the typical antipsychotics have demonstrated efficacy in the treatment of tics and TD. However, a number of nonuniversal side and adverse effects of variable degree have limited their use.

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) became the focus of significant controversy throughout the years because of contradictory reports (Table 2) of tic precipitation, exacerbation, no tic changes, and tic amelioration.

Precipitation of tics by TCAs was suggested in an incidental reference (Golden 1977) in which imipramine (IMI) was listed among the "stimulant" drugs taken by 32 patients with TD, before and after their TD became manifested. Precipitation of tics consistent with TD during IMI administration was also reported in two children with apparent genetic vulnerability (Párraga and Cochran 1992).

Exacerbation of TD by IMI (Fras and Karlavage 1977; Fras 1978) and mixed results with clomipramine (CMI) and desipramine (DMI) were reported (Caine et al. 1979a).

Table 1. Typical Antipsychotics, Butyrophenones and diphenylbutylpiperidines, Used in the Treatment of Tics and Tourette's Disorder

	Study characteristics				*Patient characteristics*			*Exposure*	
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
Tic amelioration									
Seignot (1961)	Case report	1	1960–1961	France	35	100	Motor and vocal tics decreased	HAL	1 mg once a day
Shapiro and Shapiro (1984)	Double-blind crossover	20	1983–1984	USA	Range = 11–53 Mean age = 24.65 SD = 2.71	65	Motor and vocal tics decreased	Pimozide	0.2 mg/kg/day
Sallee (1997)	Double-blind	22	1996–1997	USA	Range = 7–16 Mean age = 10.2, SD = 2.5	77	Motor and vocal tics decreased	Pimozide HAL	1–6 mg/day 1–8 mg/day
Phenothiazines: lesser efficacy									
Borison et al. (1982)	Double-blind, placebo-controlled	10	1980–1982	USA	Range = 12–43	90	Decreased tics	Fluphenazine Trifluoperazine HAL	8–24 mg/day 10–25 mg/day 5–20 mg/day
Goetz et al. (1984)	Open study	21	1984	USA	Range = 1–4	unknown	Decreased tics	Fluphenazine HAL	2–15 mg/day 1–20 mg/day

This table includes double-blind studies and only selected open trials and reports.
Abbreviation: HAL = haloperidol.

Table 2. Tricyclic Antidepressants Used in the Treatment of Tics and Tourette's Disorder

	Study characteristics				*Patient characteristics*			*Exposure*	
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
Tic precipitation									
v	Case series	32	1974–1977	USA	Under 14	Unk	Tic worsening, precipitation (53%) cases	IMI 2 cases. Stimulants, 30 cases	Unk doses
Tic exacerbation									
Caine (1979a)	Double-blind	6	1977–1978	USA	Range = 13–31	Unk	CMI exacerbated symptoms in 1 patient. No change in the other 5 on CMI or DMI.	CMI DMI	50 mg three times a day 50 mg three times a day
Tic amelioration									
Messiha and Knopp (1976)	Longitudinal blind	1	1975	USA	44	100	Tic suppression	IMI	75 mg/day
Singer et al. (1995)	Double-blind, placebo-controlled	34	1994	USA	Range = 7.2–13.6	91	Beneficial effects in TD and ADHD	DMI	25 mg four times a day
Yaryura-Tobias and Neziroglu (1977)	Double-blind	20	1976	USA	Mean age = 10.6 Range = 5–52 Mean age = 23	65	Good control of TD symptoms	CMI	25–350 mg/day; mean = 113.33

This table includes double-blind studies and only selected open trials and reports.
Abbreviations: ADHD = attention deficit hyperactivity disorder; CTD = chronic tic disorder; TD = Tourette's disorder; CMI = clomipramine; DMI = desipramine; IMI = imipramine.

No tic worsening by IMI in a boy with TD and attention deficit hyperactivity disorder (ADHD), with significant improvement of ADHD symptoms (Dillon et al. 1985), and control of panic attacks in another boy with TD and panic disorder (Sverd 1988) were reported.

Beneficial effects of IMI on TD with tic amelioration were reported (Messiha and Knopp 1976; Sandyk and Bamford 1988). DMI was found to be effective for the treatment of boys with ADHD and tics (Riddle et al. 1988; Spencer et al. 1993a). A double-blind, placebo-controlled protocol (Singer et al. 1995) was used in children with TD and ADHD to examine the ability of clonidine and DMI to modify ADHD behaviors. The results of this study suggested that DMI was superior to clonidine and may be a useful alternative for the treatment of symptoms of ADHD in children with TD.

CMI was reported to have beneficial effects in two TD patients who had failed to respond to various treatments, prompting remission of motor symptoms and amelioration of obsessive-compulsive disorder (OCD) (Yaryura-Tobias 1975). Another study (Yaryura-Tobias and Neziroglu 1977) also suggested beneficial effects of CMI on TD patients. CMI was later used to treat a boy with TD and comorbid OCD with excellent response (Ratzoni et al. 1990), shown by an almost complete remission of OCD and cessation of motor tics around his eyes and nose.

Finally, nortriptyline was used with beneficial effects in children with chronic ADHD and chronic tic disorder (Spencer et al. 1993b).

In summary, TCAs have shown efficacy in the treatment of TD and tics, but their use has significantly decreased through the years because of risks of cardiovascular toxicity, EEG changes, seizures, and incoordination among others.

Psychostimulants

Psychostimulants (Table 3) have also been reported to cause tic precipitation, exacerbation, no tic changes, and amelioration of tics and TD symptoms.

Precipitation of TD and tics by amphetamines, methylphenidate (MPH) (Golden 1974; Pollak et al. 1977), pemoline (Mitchell and Mattews 1980; Lowe et al. 1982), and dexmethylphenidate hydrochloride (Silva et al. 2008) have been reported.

Exacerbation of tics and TD by amphetamines (Singer 1963; Cohen et al. 1978; Feinberg and Carroll 1979), MPH (Fras and Karlavage 1977), and MPH, pemoline, and dextroamphetamines (DEX) (Price et al. 1986) were also reported.

Some researchers (Denckla et al. 1976; Shapiro and Shapiro 1981) found no evidence of tic changes or worsening by psychostimulants, if properly dosed, in patients with preexisting tics or TD. Similarly, in a double-blind, placebo-controlled study of children with TD and ADHD, MPH improved ADHD symptoms without exacerbating tics in 9 of the 11 patients; of the other 2, 1 showed no change and the other showed behavioral deterioration (Konkol et al. 1990). In another double-blind, placebo-controlled study of children with ADHD and tic disorder, MPH effectively suppressed hyperactive, disruptive, and aggressive behaviors without increasing tic severity (Gadow et al. 1995). Still other placebo-controlled, double-blind studies (Law and Schachar 1999; Gadow et al. 1999) of ADHD children treated with MPH, at doses based on the typical titration procedure, during long-term treatment, did not produce significantly more tics than the placebo in children with or without preexisting tics.

Some literature also suggests that stimulants might have a beneficial effect on TD or reduce the long-term severity of TD and tics by desensitizing catecholamine receptor sites (Comings and Comings 1987; Gadow et al. 1992). In a review of TD patients treated with stimulants, about 10% to 20% showed a decrease in tics as well as hyperactive/disruptive behaviors (Gadow and Sverd 1990).

Another placebo-controlled, double-blind crossover treatment trial using a wide range of doses of MPH and DEX in subjects with ADHD comorbid with TD showed the majority experienced improvement in ADHD symptoms, with acceptable effects in tics. MPH was better tolerated than DEX. Adverse effects, including tic exacerbation, were reversible in all cases (Castellanos et al. 1997).

Dexmethylphenidate hydrochloride has not been studied in children with preexisting tics or TD. However, in a multicenter, double-blind crossover study of 82 children, 6–12 years of age (which specifically excluded children with tic disorder or TD), tics were reported as an adverse event in two patients (2.4%) at a dose of 30 mg/day (Silva et al. 2008).

Methylphenidate transdermal patches have been available since 2006, with only a premarketing caution about its use in children with tics (Palumbo et al. 2004), but they have not been well studied.

Lisdexamfetamine dimesylate, in a randomized, double-blind, forced-dose, parallel-group study, was shown to be effective in treating ADHD symptoms with the potential to precipitate tics only in a small percentage of patients (Biederman et al. 2007).

In summary, the literature indicates there is no evidence that properly dosed stimulants can cause or exacerbate tics and that tic exacerbations, if they occur, are reversible. Some literature also suggests that psychostimulants might have beneficial effects on TD and tics in patients with comorbid ADHD. However, caution should be exercised in dosing the stimulants, because certain individuals may be more predisposed to tics.

Nonstimulants

Nonstimulants, such as atomoxetine, have been introduced as an alternative to stimulants, and initial data (McCracken et al. 2003) indicated that this medication did not induce tic activity. This study randomly assigned patients to a double-blind treatment with placebo or atomoxetine (0.5–1.5 kg/day) for ~18 weeks. The atomoxetine group showed a significantly greater numeric reduction of tic severity (group data) on the Yale Global Tic Severity Scale (YGTSS). However, there are more recent reports of tic exacerbation and precipitation during atomoxetine treatment (Lee et al. 2005).

α-Adrenergic medications

α-Adrenergic drugs primarily activate presynaptic autoreceptors in the locus ceruleus, reducing norepinephrine release and turnover in the cerebral cortex. Decreased norepinephrine levels in the thalamus may be responsible for the sedation reported during the use of clonidine and guanfacine.

Clonidine has been used since the early 1970s as an antihypertensive agent and since 1980 to treat TD and tics (Table 4) with contradictory reports of its efficacy. After the initial descriptions of clonidine treatment in children with TD with favorable response (Cohen et al. 1980; Bruun 1982), other studies failed to show any significant benefits from its use (Shapiro et al. 1983b; Goetz et al. 1987). Another long-term (60 weeks), single-blind, placebo-controlled study of 13 patients with TD found that 6 had a beneficial response, whereas an equal number had a poor to marginal response

TABLE 3. PSYCHOSTIMULANTS USED IN THE TREATMENT OF TICS AND TOURETTE'S DISORDER

	Study characteristics				*Patient characteristics*			*Exposure*	
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
Tic precipitation									
Silva et al. (2008)	Randomized, double-blind, placebo-controlled	67	2007–2008	USA	Mean age = 9.5	66	Tic onset in 3 ADHD patients without previous history of TD or tics	Dexmethylphenidate hydrochloride	20 mg/day 30 mg/day 54 mg/day
Tic exacerbation									
Feinberg and Carroll (1979)	Controlled blind	2	1978	USA	Range = 9–18	50	Increased tic severity	Dextroam phetamine Levfetamine	30 mg/day 50 mg/day
No tic changes									
Denckla et al. (1976)	Review of charts	20	1975	USA	Range = 7–14 Mean age = 10	90	Only 14 patients developed tics; 13 got remission	MPH	10–60 mg/day
Konkol et al. (1990)	Double-blind, placebo-controlled	11	1989	USA	Unk	Unk	Benefited ADHD without tic exacerbation	MPH	0.2–0.4 mg/kg two times a day
Gadow et al. (1995)	Double-blind, placebo-controlled	34	1993–1994	USA	Mean age = 8.10 SD = 1.11	91	Did not affect severity of tics	MPH	5–20 mg/day
Law and Schachar (1999)	Double-blind, random-crossover	91	1997–1998	USA	Mean age = 8.4 SD = 1.6	81	No significant tic worsening	MPH	10–15 mg two times a day
Gadow et al. (1999)	Double-blind, placebo-controlled	34	1997–1999	USA	Range = 6.1–11.9 Mean age = 8.8 SD = 1.9	91	No change in severity of motor or vocal tics	MPH	0.1–0.5 mg/kg
Tic amelioration									
Gadow et al. (1992)	Double-blind	11	1991	USA	Mean age = 8.3 SD = 1.96	100	Reduced vocal tics, suppressed ADHD	MPH	0.1, 0.3, 0.5 mg/kg/day
Castellanos et al. (1997)	Double-blind, placebo-controlled	20	1994–1997	USA	Mean age = 9.4 ± 2.0	60	Tics improved in a majority of patients	MPH	20–70 mg/day
Nonstimulants									
McCracken (2003)	Double-blind treatment with placebo	76	2002	USA	Mean age = 10.9 SD = 2.5	92	Beneficial in ADHD and tics. May reduce tic severity	Atomoxetine	0.5–1.5 mg/kg/day

This table includes double-blind studies and only selected open trials and reports.
Abbreviation: MPH = methylphenidate.

TABLE 4. α-ADRENERGIC MEDICATIONS FOR THE TREATMENT OF TICS AND TOURETTE'S DISORDER

	Study characteristics				*Patient characteristics*		*Exposure*		
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
Tic amelioration (clonidine)									
Bruun (1982)	Open study	20	1980–1982	USA	Range = 9–38	80	Improved TD symptoms	Clonidine	0.1–0.4 mg/day
No significant tic changes									
Goetz et al. (1987)	Double-blind, placebo-controlled	30	1986	USA	Unk	Unk	Did not significantly reduce TD symptoms	Clonidine	0.015 mg/kg/day
Shapiro et al. (1983b)	Open clinical study	68	1982	USA	Mean age = 22.3 ± 1.5	74	Low percentage of decrease of tics	Clonidine	0.40 ± 0.05 mg/day (mean dosage)
Tic amelioration (guanfacine)									
Scahill (2001)	Double-blind, placebo-controlled	34	2000	USA	Range = 7–15 Mean age = 10.4 SD = 2.0	91	Beneficial for children with ADHD and tics	Guanfacine	1.5–3 mg/day
Chappell (1995)	Double-blind	10	1994	USA	Range = 8–16	90	Decreased severity of motor and vocal tics	Guanfacine	1.5 mg/day

This table includes double-blind studies and only selected open trials and reports.

(Leckman et al. 1985). Clonidine can be started at a dose of 0.05 mg/day with gradual titration up to a dose of 0.2–0.3 mg/day.

Guanfacine differs from clonidine in that it appears to be less sedating and less hypotensive. The plasma half-life of guanfacine is about 17 hours (range: 10–30 hours), compared with 12.7 hours (range: 4–10 hours) for clonidine. The efficacy of guanfacine in the treatment of ADHD children with comorbid TD has been evaluated in double-blind, placebo-controlled studies (Chappell et al. 1995; Scahill et al. 2001), with group mean decreases in severity of motor and phonic tics as determined by both clinician and self ratings. Guanfacine can be started at a dose of 0.5 mg/day, with gradual titration up to a dose of 1.5–4 mg/day.

In summary, even when α-adrenergic medications may be effective in treating ADHD children with comorbid TD and tics, it should be kept in mind that there are more effective treatment approaches. Some practitioners still use α-adrenergic medications as first-line therapy for TD and tics. This appears acceptable on a trial basis before a decision to move to or add a neuroleptic is made.

Selective serotonin reuptake inhibitors

The role of selective serotonin reuptake inhibitors (SSRIs) in the treatment of tics and TD has not been, to the date, adequately documented. Tic amelioration (and decrease in obsessive thoughts) was reported with sertraline (Table 5) in a TD patient concomitantly receiving pimozide therapy (Buckingham and Gaffney 1993).

Paroxetine was also found to suppress motor tics in a child with TD, congenital albinism, dysthymia, and ADHD concomitantly receiving pimozide (Horrigan and Barhill 1994). However, this patient developed an occulogyric crisis, which subsided when paroxetine was discontinued, pointing to the presence of paroxetine–pimozide interactions.

Fluoxetine was found to be well tolerated by TD patients with OCD in preliminary and open-label trials, significantly reducing tics and OCS (Silvestri et al. 1994). These findings indicate that fluoxetine may be an effective agent for the treatment of OCD in TD patients.

Citalopram and fluvoxamine were used in an open trial in patients with TD (Bajo et al. 1999). The group receiving citalopram was the only one to show significant improvement in motor and vocal tics, approaching statistical significance. No other studies on the use of citalopram for the treatment of TD were found in the literature.

No tic exacerbation was observed in an open-label trial of fluoxetine (20–40 mg/day) in 32 TD patients with OCD (Como and Kurlan 1991). There was a significant reduction in scores on the obsessional inventory, with reports of subjective improvement in obsessions and compulsions without tic exacerbation. Similarly, no tic exacerbation and a dramatic decrease in temper outbursts and distractibility were reported upon the addition of sertraline in a patient with treatment-resistant ADHD and TD, receiving concomitantly pimozide, clonazepam, and diphenhydramine (Frandenburg and Kando 1994).

Fluvoxamine was used in a study (McDougle et al. 1993) to determine the effects of this medication in a group of OCD patients with comorbid chronic tic disorder compared with another age- and sex-matched group of OCD patients without chronic tic disorder. Clinical improvement occurred in 21% of OCD patients with chronic tic disorder, compared with a 52% response rate in OCD patients without tic disorder. Although the clinical improvement in both groups was significant in terms of reduction of OCS,

TABLE 5. SELECTIVE SEROTONIN REUPTAKE INHIBITORS USED IN THE TREATMENT OF TICS AND TOURETTE'S DISORDER

	Study characteristics				Patient characteristics		Exposure		
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
Tic amelioration									
Silvestri (1994)	Preliminary trial	2	1993	USA	Range = 21–32	100	Significant reduction of tics and OCS	Fluoxetine (also received CMI)	20 mg, case 1 40 mg, case 2
Bajo (1999)	Pilot study	6	1998	Italy	Range = 6–14 Mean age = 10.7 ± 4.31	Unk	Improvement in vocal and motor tics	Citalopram	10–30 mg/day
No tic changes									
Como and Kurlan (1991)	Open-label trial	26	1990	USA	Adults: Range = 22–42; Mean age = 30 ± 6.5 Children: Range = 6–17; Mean age = 12 ± 3.2	77	Marked reduction of OCD without tic improvement or worsening	Fluoxetine	20–40 mg/day
McDougle et al. (1993)	Case-controlled analysis	33	1992	USA	Mean age = 30.1 ± 8.2	93	Improved OCD without affecting tic frequency or severity	Fluvoxamine	50–300 mg/day

This table includes double-blind studies and only selected open trials and reports.
Abbreviation: OCD = obsessive-compulsive disorder.

depression, and anxiety symptoms, the results suggested that fluvoxamine may be less effective for patients with tics than without.

Tic emergence (echolalia) was reported fairly recently as an unusual occurrence in a patient with TD taking sertraline (Ghanizadeh 2008).

A literature search failed to identify data regarding the use of trazodone hydrochloride and duloxetine hydrochloride in the treatment of TD or tics.

Among the serotonergic noradrenergic reuptake inhibitors (SNRI), venlafaxine hydrochloride and nefazodone hydrochloride have not been investigated in TD or tics.

In summary, SSRIs have not been individually studied in the treatment of TD or tics. However, the current literature supports a role for SSRIs in the treatment of TD and comorbid disorders, such as OCD, depression, anxiety, and ADHD, with good symptomatic response on comorbid disorders but only mild to moderate beneficial effects on tics.

Atypical and newer antipsychotics

The atypical antipsychotics block both serotonin and dopamine receptors, potentially having fewer extrapyramidal effects than typical antipsychotics, even when variations in receptor affinity for dopamine, serotonin, and adrenergic receptors have been identified.

Clozapine, although synthesized in the 1960s, was released in this country in the early 1990s (Table 6). In a double-blind, placebo-controlled trial (Caine et al. 1979b), clozapine was used to treat patients with TD, Huntington's disease, and atypical persistent dyskinesia (drug induced). Two subjects with Huntington's disease showed a marked decrease in movements; the other individuals (TD patients included) obtained no therapeutic benefits.

Another researcher (Pfeiffer and Wagner 1994) reviewed the role of clozapine in the treatment of Parkinson's disease and other movement disorders. In this study, some patients with Parkinson's disease showed improvement in tremor and other abnormal movements when given clozapine. A few patients with Huntington's disease responded to clozapine, but no conclusions could be drawn.

Tic amelioration of significant degree has been reported by the use of the following atypical antipsychotics: Risperidone was used in two open-trial studies (Lombroso et al. 1995; Bruun and Budman 1996) in patients with TD and chronic tic disorders who had not responded to conventional treatments. In one of the studies, the patients were assessed with the YGTSS before and after a month of treatment. At the end, 58% were reported to have improved, and 18% did not show appreciable change.

In another study, risperidone was used in children and adolescents, three of which had comorbid OCD. The patients were assessed by the YGTSS and the children's version of the Yale-Brown Obsessive Compulsive Scale (YBOCS). Statistically significant improvement in tic scores (18%–66%) was observed in these patients. Subsequent controlled trials (Dion et al. 2002; Scahill et al. 2003) have demonstrated the superiority of risperidone over placebo for the treatment of TD or tics.

Risperidone is started at a dose of 0.5 mg/day and increased at weekly intervals up to a maximum of 3 mg/day in divided doses. The most common adverse effects are weight gain, sedation, sleep disturbances, and rarely extrapyramidal problems.

Olanzapine appears to be useful in the treatment of patients with TD but has not been adequately investigated. There are a few small studies of TD patients (Stephens et al. 2004; McCracken et al. 2008) receiving olanzapine with improvement of tics. The patients

Table 6. Atypical Antipsychotics Used in the Treatment of Tics and Tourette's Disorder

	Study characteristics				*Patient characteristics*			*Exposure*	
Author (year)	*Study design*	*Sample size*	*Monitoring period*	*Location*	*Age (years)*	*Gender (% male)*	*Outcome*	*Treatment*	*Dose/frequency*
No significant tic changes									
Caine et al. (1979b)	Double-blind, placebo-controlled	7	1978	USA	Range = 12–19	57	Tic control in 1, mild decrease in 1, no change in 5	Clozapine	8–10 mg/kg/day
Pfeiffer and Wagner (1994)	Double-blind, placebo-controlled	7	1993	USA	Unk	Unk	Did not decrease tics	Clozapine	150–500 mg/day
Tic amelioration									
Dion (2000)	Double-blind, placebo-controlled	46	1999	USA	Range = 17–49	78	Decreased TD symptoms	Risperidone	0.5–6 mg/day
Scahill (2003)	Double-blind, placebo-controlled	34	2002	USA	Range = 6–62 Mean age = 19.7 ± 17.0	88	Reduced motor and phonic tics	Risperidone	Max 3 mg/day (children) Max 4 mg/day (adults)
Stephens (2004)	Single-blind study	10	2003	Canada	Range = 7–13 Mean age = 9.9 ± 1.7	90	Reduced aggression and tic severity	Olanzapine	2.5–20 mg/day
McCracken et al. (2008)	Open-label flexible dose	12	2003–2005	USA	Range = 7–14 Mean age = 11.3 ± 2.4	91	Decrease in total tic severity, ADHD, and aggression	Olanzapine	5–20 mg/day
Sallee (1999)	Double-blind, placebo-controlled pilot study	28	1998	USA	Range = 7–17 Mean age = 11.3	78	Effective antitic medication in TD or CTD	Ziprasidone	5–40 mg/day

This table includes double-blind studies and only selected open trials and reports.

who had not previously used neuroleptics achieved a measurable reduction in symptoms. The patients who previously were refractory or did not tolerate neuroleptic drugs achieved only a partial response. Olanzapine is usually started at a dose of 2.5 mg/day. The side effects include sedation and weight gain.

Ziprazidone was used in a placebo-controlled trial, with encouraging results in children and adolescents with TD (Sallee et al. 2004). This study showed ziprazidone to be similar to risperidone in terms of tic reduction. However, concerns about QTc prolongation and cardiac conduction alterations persist.

Quetiapine has not been formally studied for the treatment of TD. However, there are few case reports indicating a positive response (Párraga et al. 2001).

Aripiprazole has been investigated (Murphy et al. 2005; Bubl et al. 2006) in a few case series of TD patients with favorable results.

In summary, the atypical antipsychotics, with the exception of clozapine, have demonstrated efficacy in the treatment of TD and tics and should be considered an essential component of any treatment plan. They are all explained by the pharmacological feature of combined serotonin-2/dopamine-(5-HT2/D2) antagonism.

Other pharmacologic agents and modalities of treatment

Anticonvulsants such as carbamazepine, phenytoin, phenobarbital, ethosuximide, primidone, and valproic acid have been used with mixed observations of tic amelioration, exacerbation, and precipitation (Zawadski 1972; Burd et al. 1986).

Newer anticonvulsants such as topiramate and lamotrigine have not been fully investigated. Preliminary studies (Nelson et al. 2007; Jankovic et al. 2010) conducted in children with TD and tics show that topiramate may reduce tic severity by 50% in add-on therapy patients and by 51% in monotherapy patients.

Lamotrigine is not indicated for children with tics or TD. Lamotrigine-induced tics, tourettism, and other movement disorders secondary to its use have been reported (Sotero de Menezez et al. 2000; Vance et al. 2004).

Benzodiazepines such as clonazepam, diazepam, chlordiazepoxide, fluorazepam, and clorazepate were used without clear evidence of clinical efficacy (Voulter et al. 1985) and need to be studied. Corticosteroids such as prednisone were used with good response; however, the long-term adverse effects have limited their possible use in TD (Popielarska and Werry 1972).

Beta adrenergic blocking agents (e.g., propranolol) (Sverd et al. 1983), calcium channel blockers (e.g., verapamil) (Walsh et al. 1986), as well as lecithin (Moldofsky and Sandor 1983), naloxone (Berecz et al. 1979), and lithium (Hamra et al. 1983) elicited contradictory findings or were not useful.

Other alternative pharmacologic agents are still under investigation: Baclofen, a gamma-aminobutyric acid (GABA) analog (Singer et al. 2001), selegiline (L-deprenyl), a phenethylamine derivative (Feigin et al. 1996), and tetrabenazine, a monoamine depleting agent (Jankovic and Beach 1997), have shown favorable preliminary results.

Nicotine (Silver et al. 1999) in the form of polacrilex gum or transdermal nicotine patch (TNP) has been used in open-label studies to obtund motor and vocal tics in children and adults. Reduction of tics occurred during chewing of nicotine gum. However, the improvement lasted no longer than 1 hour after chewing. When a TNP was given to subjects who were not responding to dopamine blockers (with some also receiving clonidine), or to SSRIs, motor and vocal tics were decreased 45% over baseline in 85% of 35 subjects, within 30 minutes to 3 hours after TNP application.

Botulinum toxin (Salloway et al. 1996), in injection, appears to have a limited role in the treatment of TD. It has been used for localized facial tics and vocal tics (because it appears to decrease the loudness). It was also used (Jankovic 1994) for dystonic motor tics because of its capacity to decrease the actual contraction and the premonitory sensory component.

Although the autoimmune hypothesis for tics and/or OCD is not established, it is viable, and immunomodulatory treatments (Perlmutter et al. 1999) certainly harken back to medieval approaches (plasmapheresis as exchange of ''bad blood'' for ''good blood''). Keeping in mind that these were highly selected treatment-resistant cases, and adding the possibility of placebo effects, it is unlikely to have a solitary explanation for the reported observations.

Transcranial stimulation is a technology in which a brief, powerful magnetic field is generated by a small coil positioned over the skull. Such brain stimulation may affect long-term changes in cortical excitability (George et al. 2001). Deep brain stimulation is a new approach for intractable TD (Vanderwalle et al. 2001). Bilateral stimulation of the postventral internal segment global pallitus (GPi) was performed in a patient with refractory TD (Van der Linden et al. 2002).

Functional imaging studies have evaluated several implicated neurotransmitter systems and focused predominantly on the frequency or severity of tics. The results have been inconclusive and frequently contradictory with little light shed on pathogenetic mechanisms (Adams et al. 2004).

Behavioral interventions, although promising, have not been evaluated in large-scale controlled trials. A recent comprehensive behavioral intervention, compared with supportive therapy and education (Piacentini et al. 2010), resulted in greater improvement in symptom severity among children with TD and chronic tic disorder. Treatment gains were durable, with 87% of available responders to behavior therapy exhibiting continued benefit for 6 months following treatment.

Conclusions

An extensive review of double-blind, placebo-controlled clinical trials, open studies, and selected reports on the pharmacological treatment of TD reveals a great deal of confusion. Our initial intention of conducting a meta-analysis did not crystallize because of the difficulties posed by the differences in populations, differences in medication–dose combinations, and differences in outcomes, all capable of influencing the accuracy of the analysis, producing results that would go beyond the objectives of this article. However, baseline pharmacotherapeutic approaches clearly emerge from this review.

The atypical antipsychotics should be the main component of any treatment plan for tics and TD, in combination with SSRIs, as needed, to aid in the treatment of comorbid disorders such as depression, anxiety, OCD, and ADHD. α-Adrenergic medications, even when effective for the treatment of ADHD with comorbid tics and TD, should be used only on a trial basis and before a decision is made to move to or add a neuroleptic. TCAs and typical antipsychotics have shown efficacy in the treatment of TD and tics, but their use has been significantly limited by a cohort of side or adverse effects and the current availability of better alternatives.

Medications should be used judiciously, only if strictly needed, and as part of an individualized treatment plan, because each medication has a cohort of potentially adverse and side effects. All

treatment modalities for TD or tics are still symptomatic, and thus most patients receive more than one medication in addition to psychological treatment.

The variable responses to the multiple approaches mentioned in this historical review should alert us about placebo effects as well as the possible spontaneous fluctuations in tic severity, which are well described in the literature. The fact that many patients are able to suppress their tics voluntarily, for variable periods of time, can also confound evaluation and treatment planning.

The field of TD and tics continues to be an active area of investigation. Thus, the need for studies in larger sample sizes and narrower age ranges of diagnostically homogenous patients as well as an increased awareness of changing perspectives is imperative. For example, metabolic derangements have been demonstrated within regions of the basal ganglia, limbic system, and sensorimotor cortex and are in keeping with the concept of TD as both a motor and behavioral disorder (Adams et al. 2004). Even when TD has long been regarded an involuntary movement disorder, many patients have stated that without the premonitory sensation, there would be no tics. For this reason, it has been suggested that the premonitory urge to tics (Yaryura-Tobias and Neziroglu 1977) places TD within the group of OCD. Thus, the urge may be considered the involuntary component of TD and the performance of the tic merely a voluntary response.

TD symptoms may also markedly improve during adolescence for the vast majority. However, for a minority of patients, the symptoms appear chronic and incurable (Leckman et al. 1998).

Awareness of this natural history forms a crucial framework within which to consider the relatively meager research database and the options that we offer to patients and parents. Because TD does not shorten the life span or lead to physical or intellectual deterioration, improvement in quality of life becomes the main goal of the treatment. The decision to use medications as a component of the treatment should include the patient and the parents and should be made when the symptoms are severe enough to interfere with success at school or work, or compromise normal social development.

Disclosure

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Address correspondence to:
Humberto C. Párraga, M.D.
Department of Child Psychiatry
Fourth Street Clinic
922 South Fourth Street
Springfield, IL 627003

E-mail: parragahc@aol.com