Treatment strategies for tics in Tourette syndrome

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***Abstract*:** Tourette syndrome (TS) is a chronic neurodevelopmental disorder characterized by tics: repetitive, involuntary movements and vocalizations. These symptoms can have a significant impact on patients' daily functioning across many domains. Tics tend to be most severe in child and adolescent sufferers, so their presence has the potential to impact a period of life that is both critical for learning and is often associated with the experience of greater social tension and self-consciousness than adulthood. Furthermore, control over tics that lead to physical impairment or self-injurious behaviour is of vital importance in maintaining health and quality of life. There are numerous complicating factors in the prescription of treatment for tics, due to both the side effects associated with alleviating agents and patient characteristics, such as age and comorbid conditions. This review summarizes literature pertaining to the efficacy and safety of both traditionally prescribed and more modern medications. We also discuss the merits of behavioural and surgical techniques and highlight newer emerging treatments. Although treatment response is to some extent variable, there are a number of agents that are clearly useful as first-line treatments for TS. Other interventions may be of most benefit to patients exhibiting refractory tics or more specific symptom profiles.

***Keywords*:** antipsychotics, botulinum toxin, deep brain stimulation, medication, neuroleptics, tics, Tourette syndrome, treatment

Introduction

Recent epidemiological studies show that tic disorders are far from rare and Tourette syndrome (TS) may be seen in up to 1% of children [Robertson *et al.* 2009]. TS is diagnosed according to the presence of multiple motor and one or more phonic tics, which do not have to be present simultaneously. Other tic-related symptoms that may be present include coprophenomena (such as coprolalia: the uttering of obscene language), echophenomena (copying behaviours) and paliphenomena (repetitive behaviours).

The majority of individuals with TS exhibit comorbid conditions, the most common of which are obsessive–compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) [Cavanna *et al.* 2009]. Other behavioural difficulties can include impulse discontrol (e.g. explosive outbursts or conduct disorder), affective dysregulation and sleep disturbances. Moreover, at least a third of patients with TS exhibit tic-related self-injurious behaviours [Robertson *et al.* 1989] such as head banging and/or self-directed hitting, punching or scratching. Self-injurious behaviours may be integral to TS as they are sometimes even present in mild cases [Robertson and Stern, 2000], and control of these symptoms is clearly of great importance in maintaining physical health. In addition, a significant proportion (perhaps up to 30%) of patients with TS exhibit nonobscene socially inappropriate symptoms (NOSIS). These socially inappropriate symptoms include uncontrollable urges to insult others or behave aggressively, and can sometimes lead to physical confrontation and trouble with the law [Kurlan *et al.* 1996].

As well as leading to social difficulties, tics and tic-related behavioural symptoms can have a major impact on performance at school and work. Cutler and colleagues investigated quality of life (QoL) in a UK sample of 57 young people with TS (age range 8–17 years) using focus groups and questionnaires. The QoL of young people with TS was significantly worse than the normative sample across all domains, but was

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particularly poor within emotional and school domains. Tic severity was a significant independent predictor of QoL, although features of ADHD and OCD were also found to be related. Packer and colleagues studied QoL in a similar TS sample (age range 6–17 years) [Packer, 2005]. In relation to academic performance, 50% of respondents reported that tics had moderate to significant impact, whereas 24% reported a mild impact. Tic-related difficulties included eye, head, neck and arm tics which interfered with reading, and the avoidance of reading aloud or speaking out in class due to vocal tics. Other possible impacts on academic performance include distraction and inattention due to premonitory urges and symptom exacerbation due to time-related pressure. The time of life when tics tend to be most severe comprises a critical period of continuous growth and adjustment. These periods of social and educational development may themselves prompt a greater need for treatment, as tics are often at their worst during times of heightened emotional stress, such as during exams. Thus, the treatment of tics and tic-related symptoms in TS is vital in maintaining patients' current QoL and could even have an impact on their future wellbeing.

The treatment of TS is complicated by the range of symptoms associated with this condition and the variability across individual symptom profiles. In relation to efficacy, studies clearly indicate that no pharmacological agent has yet been identified that will reliably ameliorate tics in all sufferers. Judgments of treatment efficacy are further complicated by the waxing and waning nature of tics. A trial and error approach is likely to be necessary in order to identify the most appropriate combinations of treatments for patients with a more complex array of symptoms, such as those exhibiting features of OCD or ADHD. In such complex cases, there are clear safety issues pertaining to drug interactions and contraindications, in addition to concerns related to the use of medication in children.

The majority of treatment options for tics are pharmacological. The most commonly prescribed drugs are primarily dopamine antagonists, such as neuroleptics (e.g. haloperidol), benzamides (e.g. sulpiride) or atypical antipsychotics (e.g. risperidone). Other agents that may be efficacious include drugs which modulate noradrenaline (e.g. clonidine), GABA (e.g. benzodiazepines) and acetylcholine (e.g. nicotine). Nonpharmacological interventions include behavioural approaches such as habit reversal training and exposure response prevention therapy. Surgical techniques involving deep brain stimulation (DBS) of the thalamus or globus pallidus may also be considered for severe, treatment refractory patients. Some of the more recent treatments that have been trialled include electroconvulsive therapy and repetitive transcranial magnetic stimulation.

This review focuses primarily on the efficacy and safety of interventions designed to treat tics, although for some patients other behavioural symptoms may lead to considerable distress or functional impairment [Cavanna *et al.* 2008]. We identified relevant studies by searching Web of Knowledge and Health Information Resources (including CINAHL, EMBASE, MEDLINE, Health Business Elite and PSYCInfo) using the key terms 'Tourette', 'tics', 'therapy' and 'treatment', and focusing on the literature spanning the last decade (2000–2009). Other relevant articles were initially identified through consultation of the reference list of earlier reviews discussing similar subject matter [Bloch, 2008; Himle *et al.* 2006; Scahill *et al.* 2006; Robertson and Stern, 2000].

The majority of studies reviewed involve a wide array of pharmacological investigations. However, we also address the potential merits of behavioural and surgical options and highlight some more recent interventions. Thirty years of research have established a number of pharmacological agents as promising first-line treatments for TS despite methodological limitations. New, well-controlled studies are crucial in order to determine the most appropriate interventions for patients exhibiting specific constellations of behavioural symptoms.

Pharmacological treatments for tics

Neuroleptics

Some of the medications proven to be most effective in treating tics are neuroleptics, such as haloperidol and pimozide. Key studies investigating the treatment of neuroleptics are shown in Table 1, along with a brief summary of identified treatment advantages and disadvantages. Neuroleptics act to antagonize dopamine, through the blockade of type 2 dopamine receptors. In general, the higher the potency of dopamine blockade, the more effective a drug is in

Table 1. Studies investigating the efficacy of neuroleptics in treating tics and identified treatment advantages and disadvantages.

Medication		Efficacy for tics	Key advantages (A) and disadvantages (D)
Haloperidol	+	Shapiro *et al.* [1988]	A: May be most effective in treating severe cases
	+	Shapiro *et al.* [1989]	
	+	Sallee *et al.* [1997]	D: Toxicity and increased likelihood of EPSEs e.g. dyskinesia and dystonia
	+	Sandor *et al.* [1990]	Higher discontinuation rate
	−	Sallee *et al.* [1996]	
Pimozide	+	Sallee *et al.* [1997, 1996]	A: Less sedation and lethargy than haloperidol
	+	Shapiro and Shapiro [1984]	
	+	Bruggeman *et al.* [2001]	D: Regular ECG needed as it may prolong QTc interval
	+	Gilbert *et al.* [2004]	
	+	Shapiro *et al.* [1989]	
	+	Ross and Moldofsky [1978]	
Fluphenazine	+	Borison *et al.* [1983]	A: Less sedation and EPSEs than haloperidol
	+	Borison *et al.* [1982]	D: Lack of studies comparing with newer medications (e.g. atypical antipsychotics)
	+	Goetz *et al.* [1984]	
	+	Singer *et al.* [1985]	
	+	Silay *et al.* [2004]	

+ = generally positive results; − = evidence of poor treatment response.
EPSEs, extrapyramidal side effects.

ameliorating tics [Scahill *et al.* 2006]. However, these agents are also known to alter cholinergic, serotonergic, histaminergic and alpha-adrenergic transmission, thus leading to side effects. The most common side effects associated with these drugs are relatively mild and include weight gain and drowsiness, although some patients may experience excessive sedation leading to difficulty in performing cognitive tasks. The greatest concern relating to the use of neuroleptics is the potential for them to lead to hyperprolactinaemia (which is associated with amenorrhoea, galactorrhoea and gynaecomastia) and extrapyramidal symptoms, such as dystonia, parkinsonism, akathisia and tardive dyskinesia. Although hyperprolactinaemia is reversible, abnormal movements may persist after the cessation of treatment.

Many studies have investigated the efficacy of haloperidol, which can provide an estimated 78–91% reduction in tics [Shapiro *et al.* 1988]. However, this agent may be associated with more side effects than other neuroleptics and may have detrimental effects on cognitive function. Among reported side effects there is the risk of neuroleptic malignant syndrome [Robertson and Stern, 2000]. Some studies suggest that other similar agents such as pimozide [Sallee *et al.* 1997] and fluphenazine [Borison *et al.* 1983] may be as efficacious as haloperidol and lead to fewer side effects.

Pimozide blocks dopamine D1 receptors and exhibits less noradrenaline antagonism than haloperidol. It is less sedating than haloperidol, but can be associated with arrhythmia, so ECG is necessary before and annually during treatment. Many studies report that pimozide is effective in treating tics [e.g. Gilbert *et al.* 2004; Bruggeman *et al.* 2001] although some argue that it is not as effective as haloperidol. For example, Shapiro and colleagues tested 57 patients in a double-blind study using haloperidol, pimozide and placebo [Shapiro *et al.* 1989]. Both agents were better than placebo, but haloperidol was most effective. Moreover this study reported than haloperidol was not associated with more side effects than pimozide.

In a placebo-controlled, double-blind study, Ross and Moldofsky reported that six of seven patients (aged 8-28 years) taking pimozide and one of two taking haloperidol showed 75% improvement in symptoms [Ross and Moldofsky, 1978]. While both agents significantly reduced tic frequency, pimozide led to less lethargy. Regeur and colleagues showed that pimozide was popularly prescribed and led to few side effects and a good response in 81% of patients (although some patients were also taking clonidine or tetrabenazine) [Regeur *et al.* 1986]. Reported side effects included weight gain, depression, Parkinsonism, akathisia and acute dystonia.

Table 2. Studies investigating the efficacy of atypical antipsychotics in treating tics and identified treatment advantages and disadvantages.

Medication		Efficacy for tics	Key advantages (A) and disadvantages (D)
Risperidone	+	Bruun and Budman [1996]	A: As effective as haloperidol and may be good for OCSs and aggressive symptoms
	+	Lombroso *et al.* [1995]	
	+	Shulman *et al.* [1995]	
	+	Lim and Shin [2006]	D: Rare reports of EPSEs, high discontinuation rates which may be due to common side effects including fatigue, somnolence, weight gain etc.
	+	Bruggeman *et al.* [2001]	
	+	Zhao and Zhu [2003]	
	+/–	Robertson *et al.* [1996]	
Clozapine	+	Jaffe *et al.* [1995]	A: Fewer EPSEs than neuroleptics
	+	Kalian *et al.* [1993]	D: More serious potential side effect of agranulocytosis; more likely to cause weight gain
	–	Caine *et al.* [1979]	
Olanzapine	+	Budman *et al.* [2001]	A: Fewer side effects than haloperidol, and can help with symptoms of ADHD and aggression
	+	Stamenkovic *et al.* [2000]	
	+	Ji *et al.* [2005]	
	+	McCracken *et al.* [2008]	D: Milder side effects such as drowsiness and weight gain
	+	Stephens *et al.* [2004]	
Quetiapine	+	Mukkedes *et al.* [2003]	A: Fewer EPSEs than neuroleptics
	+	Parraga and Parraga [2001]	D: Weight gain may be fairly common
	+	Copur *et al.* [2007]	

+ = generally positive results; – = evidence of poor treatment response.
OCSs, obsessive–compulsive symptoms; EPSEs, extrapyramidal side effects; ADHD, attention deficit hyperactivity disorder.

In another placebo-controlled, double-blind study, Sallee and colleagues investigated the use of pimozide for tics in 22 children (aged 7–16) over 24 weeks [Sallee *et al.* 1997, 1996]. Pimozide led to a greater improvement in tics than placebo. Haloperidol did not lead to a significant improvement in symptoms, but was associated with three times more side effects than pimozide. They also found evidence that increases in prolactin constituted a marker for treatment response [Sallee *et al.* 1996]. A long-term follow-up study (1–15 years) assessed 33 patients [Sandor *et al.* 1990] who were taking haloperidol, pimozide or no treatment. More discontinuations, acute dyskinesias and dystonias were associated with haloperidol. Eight percent of patients discontinued pimozide, while 47% discontinued haloperidol. This study reported no ECG abnormalities with the use of pimozide. However, an early randomized, controlled trial by Shapiro and Shapiro (1984) showed that pimozide was the agent most related to prolongation of the QTc interval. Findings are mixed, as a later study suggested that although QTc interval can be prolonged with use, it is not generally in the abnormal range [Shapiro *et al.* 1989].

Fluphenazine may also be better tolerated than haloperidol, and lead to less sedation and extrapyramidal side effects [Borison *et al.* 1982]. An open-label study reported that this drug was effective for tics in 17 out of 21 patients tested [Goetz *et al.* 1984], while another study reported efficacy in 24 out of 31 patients [Singer *et al.* 1985]. A naturalistic follow-up study of patients treated for a year indicated that fluphenazine is safe overall and is unlikely to lead to tardive dyskinesia [Silay *et al.* 2004]. This agent was also shown to have good efficacy in a placebo-controlled, double-blind trial, in which fluphenazine and trifluoperazine were shown to be as effective as haloperidol and lead to fewer side effects [Borison *et al.* 1983].

Atypical antipsychotics

Atypical antipsychotics are more selective dopamine receptor D2 blockers, although they can also affect serotonin. These drugs include risperidone, clozapine, olanzapine, quetiapine and the partial agonist aripiprazole. Atypical antipsychotics may be considered a safer treatment for tics due to the reduced risk of developing acute or subacute side effects. Table 2 lists studies which assessed the efficacy of atypical antipsychotics in treating tics.

The effectiveness of risperidone in the treatment of tics has been investigated extensively. Many studies report a positive response [Bruun and Budman, 1996; Lombroso *et al.* 1995; Shulman *et al.* 1995], with a similar efficacy to haloperidol. Lim and Shin conducted a 16-week study in

which 74 patients with a diagnosis of either TS or chronic tic disorder were randomly assigned to risperidone or haloperidol [Lim and Shin, 2006]. Symptoms were assessed at baseline and then 4, 8 and 16 weeks later. According to tic severity scores, risperidone led to a mean tic reduction of 28% and haloperidol to a mean reduction of 21%, however there was no significant difference in efficacy between the two drugs.

Bruggeman and colleagues suggest that risperidone may improve tic symptoms in 30–62% of patients, although some studies have reported even greater success rates [Bruggeman *et al.* 2001]. Zhao and Zhu studied the effectiveness of risperidone in treating tics in 14 children aged 8–13 years [Zhao and Zhu, 2003]. Doses were titrated from 0.5 mg a day up to a maximum of 3.5 mg/day. Tic severity ratings were recorded at baseline then after the first, second, fourth and eighth week of treatment. Three cases improved by end of first week and by week eight the total effective rate was 85.7%. Three patients suffered side effects, which were mainly extrapyramidal symptoms, and mild somnolence was reported in two cases. The authors suggested that low doses of risperidone (1–3.5 mg/day) should still be considered a more favourable alternative to haloperidol.

A double blind trial carried out by Dion and colleagues investigated the effect of risperidone in 24 patients with TS (taking 0.5–6 mg/day) in comparison with 24 patients taking placebo [Dion *et al.* 2002]. Medication was increased initially in fixed increments and then flexibly according to patient response. A median dose of 2.5 mg/day was found to be significantly better at improving tics than placebo, based on global tic severity rating scores. In the active treatment group, 60.8% of patients improved by at least 1 point compared with 26.1% in the placebo group. There was some indication that hypokinesia and tremor scores increased for those taking risperidone, although the latter effect was mainly observed in patients with a higher baseline tremor score.

Robertson and colleagues investigated risperidone in 19 patients with TS, who took a mean daily dose of 1.5 mg [Robertson *et al.* 1996]. Forty-one percent were found to respond positively, 35% reported that there was no difference in their symptoms and 24% felt it made them worse (although this finding is likely to be explained by the characteristic waxing and waning nature of tics). Fifty-three percent of patients from this sample experienced side effects, but these did not include extrapyramidal symptoms. However, on follow up 8–11 months later it was found that only two patients were still taking risperidone.

Other studies agree that one major drawback with the use of risperidone is a high discontinuation rate. Chappell and colleagues suggest that only 20–30% of patients can tolerate the use of this medication in the long term, due to associated side effects [Chappell *et al.* 1995a]. While extrapyramidal side effects are rare, studies have reported that common adverse effects include fatigue and somnolence [Dion *et al.* 2002], emotional lability, nausea, vomiting, sleep problems, dizziness [Sandor and Stephens, 2000] and weight gain [Hernandez and Fernandez, 2005; Sandor and Stephens, 2000]. Hyperprolactinaemia and galactorrhoea can occur at higher doses [Robertson and Stern, 2000]. Finally, Scahill and colleagues reported social phobia as a side effect for risperidone use [Scahill *et al.* 2003].

One possible advantage for risperidone is that it could have a favourable effect on some of the behavioural symptoms associated with frequently comorbid conditions. In a retrospective review of seven TS patients, Hernandez and Fernandez reported that tics improved in four patients and comorbidities improved in two [Hernandez and Fernandez, 2005]. Such findings could reflect the relatively greater affinity of risperidone (e.g. *versus* haloperidol) for 5HT-2A receptors. Since serotonin appears to be implicated in obsessive–compulsive symptoms (OCSs), risperidone may augment the effect of selective serotonin reuptake inhibitors (SSRIs). Perhaps similar effects could help explain the finding that risperidone could also be useful in ameliorating aggressive behaviour [Sandor and Stephens, 2000]. These authors compared aggressive symptoms (which included excessive screaming, hitting, kicking and breaking things) in 28 patients aged 5–18 years at baseline and 2–4 months after starting treatment. The vast majority (78.5%) showed reduced aggression scores based on parent, teacher and clinical observations. This effect was actually found to be more robust than decreases in tics, which were exhibited by 61.7% of patients.

Clozapine is another atypical antipsychotic that has been used to treat tics. Some studies report

successful reductions in tics following use in monotherapy [e.g. Jaffe *et al.* 1995] or in combination with propanolol or tetrabenazine [Kalian *et al.* 1993]. However, clozapine is a weaker dopamine D2 blocker than other drugs, and therefore may be less effective in treating tics. For example, Caine and colleagues studied the effect of clozapine on tics in five patients with TS, who took this medication for 4–5 weeks [Caine *et al.* 1979]. This study reported evidence of a transient increase in tics. Further factors which make the use of clozapine a less attractive treatment option are the possibility of agranulocytosis (which makes regular blood tests necessary) and the finding that this agent may be worse than other atypical antipsychotics (particularly risperidone) in leading to weight gain [Allison and Casey, 2001].

An alternative antipsychotic for the treatment of tics is olanzapine. A number of studies have shown this agent to be effective [Budman *et al.* 2001; Stamenkovic *et al.* 2000]. Ji and colleagues investigated the use of olanzapine for tics in 60 children [Ji *et al.* 2005]. After 4 weeks' treatment with either olanzapine or haloperidol, effectiveness in terms of tic severity reduction and global clinical impression was found to be 74% for both groups, but olanzapine was associated with fewer side effects than haloperidol. Stephens and colleagues conducted a study involving 10 children aged 7–13, which began with a 2-week single-blind placebo run before treatment commencement [Stephens *et al.* 2004]. An 8-week trial indicated that olanzapine led to significant reductions in tic severity and aggression, the only identified drawback being weight gain. A 6-week prospective, open-label, flexible-dose study of 12 patients (aged 7–14 years) also showed that olanzapine can result in significant reductions in tic severity [McCracken *et al.* 2008]. Specifically, tic severity scores were reported to have reduced by 30% after 6 weeks of treatment. Of note, ADHD and aggressive symptoms also appeared to improve. Side effects included drowsiness and weight gain.

Although it is associated with a low D2 receptor occupancy ratio and has low affinity for 5-HT2A and alpha-1 and alpha-2 adrenergic receptors, quetiapine may be another viable agent for treating tics [Mukkedes and Abali, 2003]. Significant changes in ratings for motor and vocal tics were apparent in a study of two children initially treated with 25 mg of quetiapine [Parraga and Parraga, 2001], which was increased up to 100 or 150 mg 3 weeks later. Tic severity scores fell significantly in both patients, and the main side effects were drowsiness and decreased appetite. The latter finding may well have been related to previous medications, as other studies report increased appetite and weight gain. Copur and colleagues reported weight gain in 12 patients (aged 8–18 years) who were taking a mean dose of 114 mg of quetiapine a day by the fourth week of investigation [Copur *et al.* 2007]. By this time, tic severity scores had reduced by over 60%.

Aripiprazole

The newer antipsychotic aripiprazole has a unique mechanism of action, being a partial agonist, rather than an antagonist, of the D2 dopamine receptor. Aripiprazole is also characterized by specific action on other receptor systems: it acts as antagonist of 5-HT2A, partial agonist of 5-HT2C, and has some affinity for alpha adrenergic receptors and 5-HT transporter [Wood and Reavill, 2007]. This medication has been approved by the FDA in the USA for the treatment of schizophrenia in 2002 and in the European Union in 2004. A total of 133 patients with tic disorders who are taking aripiprazole have been reported in the scientific literature over the last 5 years (Table 3). All studies have suggested good efficacy in terms of tic reduction and improvement of behavioural symptoms and excellent tolerability in this patient population.

Aripiprazole is generally well tolerated and side effects are usually mild to moderate and transient. The most common side effects include insomnia, fatigue, drowsiness, nausea, headache, tremor and agitation [Pae, 2009]. Moreover, aripiprazole has been reported to have fewer side effects with respect to weight gain, QT interval alterations, extrapyramidal symptoms and hyperprolactinaemia [Pae, 2009] when compared with other antipsychotics (both neuroleptics and atypicals). No routine or regular blood monitoring is required with aripiprazole [Travis *et al.* 2005].

When considering a potentially useful treatment for patients with TS, it is not only efficacy in treating tics that must be considered, but also the effects of the drug on comorbid disorders. With regards to this, aripiprazole has been reported as an effective augmentation strategy for improving therapeutic response to SSRIs in patients with major depressive disorders or

Table 3. Aripiprazole in the treatment of patients with tic disorders.

Study	*n* patients	Age range (years)	Significant response	Length of Follow up	Dose/range	Side effects
Kawohl *et al.* [2009a]	10	21–36	10/10	4–26 months	5–30 mg (mean = 15 mg)	3/10 = akathisia
Kawohl *et al.* [2009b]	2	23, 25	2/2	8 months 12 months	15 mg 10 mg	1/2 = attentional disturbances
Winter *et al.* [2008]	1	N/S	1/1	6 months	7.5 mg	Nil
Budman *et al.* [2008]	37	8–18	29/37	12 weeks	2.5–40 mg (mean = 11.7 mg)	13/37 = weight gain 6/37 = akathisia 3/37 = agitation 3/37 = mood lability/anxiety 1/37 = EPSEs
Seo *et al.* [2008]	15	7–19	15/15	12 weeks	8.17 mg	7/15 = nausea 5/15 = sedation
Ben Djebara *et al.* [2008]	1	28	1/1	14 months	15 mg	Nil
Miranda and Castiglioni [2007]	10	10–35	9/10	8 months	5–25 mg (mean = 10 mg)	1/10 = EPSEs transient nausea
Davies *et al.* [2006]	11	7–50	10/11	1–2 months = 3 3–5 months = 4 >9 months = 4	10–20 mg	None significant
Yoo *et al.* [2006]	14	7–17	10/14	8 weeks	2.5–15 mg (mean = 10.89 mg)	1/14 = nausea
Duane [2006]	15	9–25 (mean = 15)	14/15	8 weeks	2.5–15 mg	1/15 = nausea
Constant *et al.* [2006]	1	23	1/1	3 weeks	15 mg	Insomnia (transient)
Bubl *et al.* [2006]	2	19, 21	2/2	12 months 4 months	15 mg 40 mg	Nil
Fountoulakis *et al.* [2006]	1	18	1/1	3 days	10 mg	Acute dystonia
Padala *et al.* [2005]	2	39, 55	2/2	12–18 weeks	10 mg 30 mg	Nil
Murphy *et al.* [2005]	6	8–19 (mean = 12.1)	6/6	12 weeks	5–20 mg (mean = 11.7 mg)	None significant
Dehning *et al.* [2005]	1	19	1/1	2 weeks	10 mg	Nil
Kastrup *et al.* [2005]	2	33, 48	2/2	16 weeks	15 mg	Nil
Hood *et al.* [2004]	1	16	1/1	N/S	10 mg	N/S
Hounie *et al.* [2004]	1	20	1/1	N/S	15 mg	N/S

EPSEs, extrapyramidal side effects; N/S, not specified.

anxiety disorders, including OCD [Curtis and Richards, 2007; Worthington *et al.* 2005].

The published literature suggests that aripiprazole may be a useful medication for treating young patients with TS, particularly as it is well tolerated and only has mild transient side effects. The unique receptor profile of aripiprazole may well make it different from the other atypical antipsychotics in terms of efficacy in treating both tics and comorbid conditions, as well as side effects. The lack of serious side effects is an important aspect of treatment. Clearly, further studies are needed to establish the usefulness of this promising agent. Specifically, a double-blind trial against placebo or other neuroleptics is advisable to verify the efficacy of aripiprazole for the pharmacotherapy of TS.

Table 4. Studies investigating the efficacy of alternative pharmacological agents to neuroleptics and atypical antipsychotics in treating tics and identified treatment advantages and disadvantages.

Medication	Efficacy for tics		Key advantages (A) and disadvantages (D)
Benzamides: sulpiride, tiapride	+	Robertson *et al.* [1990]	A: May also help with echophenomena, aggression, subjective tension and OCSs
	+	George *et al.* [1993]	D: Possibility of hyperprolactinaemia
Tetrabenazine	+	Jankovic and Beach [1997]	A: Less associated with weight gain than neuroleptics
	+	Kenney *et al.* [2007]	D: Risk of aggravating depressive symptoms
	+	Ondo *et al.* [2008]	
	+	Porta *et al.* [2008a]	
Alpha adrenergic agonists: clonidine, guanfacine	+	Singer *et al.* [1985]	A: Safe with very few side effects; can also help with OCSs, aggression and oppositional behaviours
	+	Leckman *et al.* [1985]	
	+	Borison *et al.* [1983]	
	+	Hedderick *et al.* [2009]	
	+	Cummings *et al.* [2002]	D: Treatment response varies considerably across patients; requires blood pressure monitoring
	–	Chappell *et al.* [1995b]	
	–	Gancher *et al.* [1990]	
	–	Singer *et al.* [1995]	
	–	Goetz *et al.* [1987]	
	–	Scahill *et al.* [2001]	
Benzodiazepines: clonazepam	+	Dion and Chouinard [1987]	A: Good efficacy in the short term
	+	Goetz [1992]	D: Use is likely to be limited by potential for tolerance and addiction, and troublesome side effects such as drowsiness
	+	Drtilkova *et al.* [1994]	
	+	Gonce and Barbeau [1977]	
	+	Steingard *et al.* [1994]	
Anticonvulsants: topiramate, levetiracetam	+	Jankovic [2009]	A: Few reported side effects compared with neuroleptics
	+	Awaad *et al.* [2005]	D: Conflicting evidence of efficacy
	+	Oulis *et al.* [2008]	
	+	Awaad *et al.* [2007]	
	–	Smith-Hicks *et al.* [2007]	
	–	Hedderick *et al.* [2009]	
DA agonists: pergolide, apomorphine, buspirone, ropinirole	+	Feinberg and Carroll [1979]	A: Potentially effective at low doses compared with the treatment of Parkinson's disease
	+	Durson *et al.* [1995]	D: No obvious drawbacks reported but more research needed
	+	Cianchetti *et al.* [2005]	
	+	Gilbert *et al.* [2000]	
	+	Lipinski *et al.* [1997]	
	+	Anca *et al.* [2004]	
Anticholinergics	+	Devor and Isenberg [1989]	A: Nicotine patches are potentially useful in combination with other agents
	+	McConville *et al.* [1991]	D: May only have limited transient effectiveness; use of patches may lead to more intolerable side effects
	–	McConville *et al.* [1992]	
	–	Sanberg *et al.* [1989]	
	–	Silver *et al.* [2001]	
Cannabinoids	+	Muller-Vahl *et al.* [1998]	A: Could also help with OCSs, ADHD and self-injurious symptoms
	+	Muller-Vahl *et al.* [1999]	D: Potential negative cognitive effects
	+	Muller-Vahl *et al.* [2002]	
	+	Muller-Vahl *et al.* [2003]	

+ = generally positive results; – = evidence of poor treatment response.
OCSs, obsessive–compulsive symptoms; ADHD, attention deficit hyperactivity disorder.

Other pharmacological agents

Benzamides

Table 4 shows the efficacy and key advantages and disadvantages associated with a range of pharmacological agents which may be used as an alternative to neuroleptics or atypical antipsychotics when treating tics. There is evidence for the efficacy of substituted benzamides in the treatment of tics. In a placebo-controlled, double-blind, crossover trial, Eggers and colleagues found that tiapride improved tics in children and had no adverse effect on cognitive function [Eggers *et al.* 1988]. The main drawback associated with treatment was moderate hypoprolactinaemia. Similar side effects were reported in a study that examined the effectiveness of metoclopramide. Nicholson and colleagues conducted an 8-week placebo-controlled

trial involving 27 patients of mean age 11.9 years [Nicholson *et al.* 2005]. Metoclopramide led to a mean 39% reduction in total tic severity score, whilst placebo was associated with 13% decrease.

Perhaps the most commonly prescribed agent for tics in this category is sulpiride. Robertson and colleagues reported a beneficial effect of this medication in 59% of patients [Robertson *et al.* 1990]. This study found that sulpiride led to decreases not only in motor and vocal tics, but also in echophenomena, aggression, subjective tension and OCSs. A double-blind, placebo-controlled, crossover trial by George and colleagues also reported some evidence of decreased OCSs [George *et al.* 1993]. Sulpiride was found to significantly decrease tics, although the improvement in OCSs did not reach statistical significance. The most common side effects include drowsiness and depression [Robertson *et al.* 1990], although a case of sulpiride-related tardive dyskinesia has been reported [Eapen *et al.* 1993].

Tetrabenazine

Tetrabenazine acts as dopamine antagonist, by reducing the presynaptic storage of monoamines and blocking postsynaptic DA receptors. A recent retrospective chart review carried out by Porta and colleagues showed that 2 years' treatment with tetrabenazine led to an improvement in 80% of patients with tics, and was associated with long-term benefits [Porta *et al.* 2008a]. Jankovic and Beach reported that of 64 patients with TS treated with this drug, approximately two-thirds showed between a moderate to marked improvement in tics [Jankovic and Beach, 1997]. Tetrabenazine's efficacy is also supported by an open-label study of 77 patients treated for an average of 2 years [Kenney *et al.* 2007]. Treatment led to a moderate to marked improvement in TS symptoms and functional improvement was apparent in 83.1% of patients. Side effects included fatigue and drowsiness, nausea, depression, insomnia and, rarely, Parkinsonism. Overall, tetrabenazine was found to be safe and well tolerated. Another factor in favour of this treatment option is that it has been suggested that tetrabenazine is less associated with weight gain than other agents [Ondo *et al.* 2008].

Noradrenaline modulating agents

The alpha-2 adrenergic agonist clonidine inhibits the release of noradrenaline. Studies supporting the efficacy of this drug in ameliorating tics include a retrospective study which found clonidine was efficacious in 47% of patients treated and had few side effects [Singer *et al.* 1985]. Similar figures were reported by a single-blind, placebo-controlled trial conducted by Leckman and colleagues, where 46% of the patients treated responded well, exhibiting improved motor and phonic tics [Leckman *et al.* 1985]. Of note, no adverse effects were highlighted by this study. A later placebo controlled study [Leckman *et al.* 1991] involving 47 patients (aged 7–48 years) provided more evidence for the efficacy of this drug. A recent 15-week randomized, double-blind, crossover study reported more modest improvements [Hedderick *et al.* 2009]. In this study, 10 patients (aged 8–27 years) with moderate to severe tics were assessed using the Yale Global Tic Severity Scale (YGTSS), Clinical Global Impression (CGI) and other behavioural measures. Treatment with clonidine was associated with a decrease in the mean total tics score from 25.2 to 21.8 and minor sedation-related side effects.

Other studies argue against the effectiveness of clonidine, especially when compared with other medications [e.g. Singer *et al.* 1995; Gancher *et al.* 1990]. An open trial by Shapiro and colleagues found that neuroleptics were more efficacious [Shapiro *et al.* 1983]; although conflicting findings were reported by Borison and colleagues, who showed that clonidine could be as efficacious as haloperidol [Borison *et al.* 1983]. It has been suggested that clonidine needs to be taken for longer periods (e.g. 4–6 months) to lead to improvement [Leckman *et al.* 1982]. However, Goetz and colleagues carried out a 6-month placebo crossover study involving 30 children and adults, and reported that even at higher doses, clonidine exhibited little efficacy in treating tics [Goetz *et al.* 1987].

In patients who have been shown to respond to clonidine, positive effects have been reported on a range of behavioural symptoms in addition to tics. These include compulsions [Leckman *et al.* 1982], hyperactivity and impulsivity [Leckman *et al.* 1991]. Cohen and colleagues showed that 70% of patients showed a reduction in tics, and that additional improvement in frustration, aggression, obsessive–compulsive and oppositional behaviours were seen [Cohen *et al.* 1981, 1980]. Sandyk reported the case of a 15-year-old boy with TS and severe self-mutilatory behaviour [Sandyk, 1986]. It was found that combined administration of and clonidine and oxycodone

led to a dramatic reduction in the frequency and severity of these behaviours within 12 hours.

The side effects linked to clonidine include drowsiness, sedation, headache, dizziness, constipation, nausea, dry mouth and bradycardia. Blood pressure monitoring is advised and discontinuation may lead to blood pressure effects in addition to tic worsening [Leckman *et al.* 1986]. Although one case study reported by Kessler reported that clonidine could lead to an increase in tics and severe systemic heat sensations [Kessler, 2001], this agent is likely to lead to fewer adverse effects than haloperidol [Borison *et al.* 1983].

The similar agent guanfacine was shown to improve motor and vocal tics by 30% in two placebo-controlled studies [Cummings *et al.* 2002; Scahill *et al.* 2001]; but was not significantly better than placebo in the study by Scahill and colleagues. The possible advantages of guanfacine as an alternative to clonidine are that this drug may be less sedating and hypotensive, and has been linked to improved cognitive performance in addition to beneficial effects on motor and vocal tics [Chappell *et al.* 1995b].

GABA modulating agents

Some reports suggest that tics may be reduced through the administration of benzodiazepines. The efficacy of clonazepam [e.g. Dion and Chouinard, 1987] has been indicated by a number of studies. Goetz reported a good response in 53–71% of patients across three investigations [Goetz, 1992] and Drtilkova and colleagues argue that clonazepam is superior in treating tics when compared with clonidine, and leads to fewer side effects [Drtilkova *et al.* 1994]. However, other studies have reported modest effectiveness [Gonce and Barbeau, 1977; Steingard *et al.* 1994]. Benzodiazepines should always be prescribed with caution due to associated changes in tolerance and the potential for addiction. Despite the common side effects of drowsiness, irritability, fatigue and paradoxical aggression, benzodiazepines may prove useful in selected cases for short-term relief.

Topiramate and levetiracetam are GABA transmission enhancing anticonvulsants which have been used to treat tics in recent years. A double-blind, placebo-controlled study of 29 patients with TS was conducted by Jankovic, who concluded that topiramate was safe and effective for use in moderate to severe TS [Jankovic, 2009]. A study of 60 children with TS [Awaad *et al.* 2005] showed that levetiracetam led to a mean 20% reduction in tics, and improvement on both the YGTSS and CGI measures. Forty-three patients also improved in behaviour and school performance. Levetiracetam was generally well tolerated, with only three patients discontinuing use. In a 4-year follow-up study [Awaad *et al.* 2007], 49 of 70 patients exhibited improvement after treatment with levetiracetam, which was found to be safe and well tolerated. A highly significant effect was reported in one case study by Oulis and colleagues [Oulis *et al.* 2008]. The patient was a 23-year-old woman who had previously responded poorly to haloperidol, clozapine and pimozide. After 5 weeks of treatment with a combination of clonidine and levetiracetam, her YGTSS score had fallen from 70 to 25. Improvement was preserved at four months and no serious side effects were documented.

Two randomized, double-blind, crossover studies involving levetiracetam have provided conflicting evidence with regards to efficacy. Smith-Hicks and colleagues administered levetiracetam and placebo for 4 weeks, with a 2-week break before the second condition [Smith-Hicks *et al.* 2007]. The children tested were aged 8–16 with moderate to moderately severe tics. Mild reductions in tics were observed for both levetiracetam and placebo; the active treatment was no better. The other study [Hedderick *et al.* 2009] found that the change in mean total tics score for 10 patients aged 8–27 years who were treated with levetiracetam went from 22.7 to 23.6.

The GABA-derivative baclofen has also been investigated as a possible treatment for tics. Some authors have reported a lack of efficacy [e.g. Shapiro *et al.* 1988]. However, a randomized trial involving nine children aged 8–14 years [Singer *et al.* 2001] reported more favourable results. The study involved a 4-week cycle of baclofen (20 mg three times a day) and placebo with a 2-week washout period. Symptom measures included the CGI and YGTSS. The CGI mean score significantly improved after 4-weeks of treatment with baclofen in comparison with placebo. YGTSS ratings also improved and the mean change in total score was almost significant. However, the authors noted that improvement seemed to be related to decreases in impairment scores rather than decreases in tics *per se*. No major side effects were reported.

Dopamine agonists

A few studies have investigated the effects of dopamine agonists on tics. Although predictions of beneficial effect could be considered counter-intuitive based on the efficacy of antagonist treatment, some findings have been favourable. Both apomorphine [Feinberg and Carroll, 1979] and the partial D2 (and 5-HT1A) agonist buspirone [Durson *et al.* 1995] may effectively treat tics. Ropinirole has also been shown to improve tic frequency and severity. Anca and colleagues showed that 86% of patients taking this drug reported improvements in motor tics, and 61.5% in vocal tics, by 8 weeks of treatment [Anca *et al.* 2004]. Although effective when used in much lower doses than with patients with Parkinson's disease, pergolide may also have a positive effect. Cianchetti and colleagues reported improved symptoms in three cases taking this treatment [Cianchetti *et al.* 2005], while Gilbert and colleagues provided further support for this agent's effectiveness in a double-blind, placebo-controlled study [Gilbert *et al.* 2000]. A 6-week, open-label study [Lipinski *et al.* 1997] found that 75% of patients (from a sample of 32 7–19 year olds) had a greater than 50% drop in tic severity in comparison to baseline. Highly significant improvements were reported on all measures after 6 weeks of treatment. These authors noted that the presence of restless legs in comorbidity (59%) was associated with a positive treatment response.

Acetylcholinergic agents

A few reports suggest that nicotine could help ameliorate tics. For example, Devor and Isenberg reported that TS symptoms improved if patients smoked [Devor and Isenberg, 1989], and McConville and colleagues found that nicotine could potentiate the effects of haloperidol in reducing tics [McConville *et al.*, 1991]. Nicotine patches can lead to some improvement, but the positive effects are not durable and may be outweighed by side effects. The evidence supporting the benefits of nicotine are not convincing overall, even when this drug is given in addition to antipsychotics [e.g. Silver *et al.* 2001; McConville *et al.* 1992; Sanberg *et al.* 1989].

Cannabinoids

Muller-Vahl and colleagues have conducted a number of studies investigating the therapeutic benefit of cannabinoids in treating tics. One of these studies [Muller-Vahl *et al.* 1998] found that when interviewed, 17 of 64 patients with tics admitted using cannabis, and 14 of these said that it reduced tics, premonitory urges and OCSs. Muller-Vahl and colleagues also reported a case report of a 25-year-old man with tics, ADHD, OCD and self-injurious behaviour, who found that the use of tetrahydrocannabinoid (THC) helped with many of these symptoms [Muller-Vahl *et al.* 1999]. A single dose of THC was shown to reduce his tic score on the YGTSS from 41 to 7, 2 hours after treatment. The patient also reported reduced premonitory urges and OCSs and neuropsychological testing indicated improvements in signal detection and sustained attention. Another study has also reported that THC is no threat to cognitive performance [Hemming and Yellowlees, 1993].

A later randomized, double-blind, crossover trial [Muller-Vahl *et al.* 2002] indicated that both motor tic severity and OCSs were significantly improved by THC. Similar findings were found in a 6-week study [Muller-Vahl *et al.* 2003] in which the dose of THC was gradually titrated up to 10 mg. Small improvements in tic frequency and severity were evident according to assessment using different measures of tic severity. The side effects associated with the use of THC were reported to be mild and transient. However, there are limitations associated with these two studies. As noted by Curtis and colleagues, these include the possibility that effect sizes could be artificially inflated, as those participants who drop out may do so due to lack of treatment response [Curtis *et al.* 2009].

Drawbacks in the use of cannabinoids in treating tics include side effects such as short-term memory impairment, poor hand–eye coordination, and impairments in attention, time and space perception. Withdrawal can be associated with restlessness, anxiety, depression, tremor and insomnia. There is also some evidence that THC use can precipitate or exacerbate psychotic symptoms. Muller-Vahl and colleagues reported no deterioration in verbal or visual memory, reaction time, intelligence, sustained attention, divided attention, vigilance or mood, with the use of THC [Muller-Vahl *et al.* 2001]. However, there was some evidence for increased OCSs and a trend towards increased phobic anxiety.

Behavioural techniques

A number of nonpharmacological treatments can be used to treat patients with TS of moderate severity. One behavioural technique which

may help with tics is exposure plus response prevention therapy. Tics are suppressed for prolonged periods of time, in order for patients to learn to habituate to associated premonitory urges. Verdellen and colleagues showed that this method could reduce tics according to observation and YGTSS ratings and that this treatment was equally effective to the more widely applied technique of habit reversal training [Verdellen *et al.* 2004]. Although focusing attention on tics may increase inhibitory effort leading to exacerbation [Robertson and Stern, 2000], Verdellen and colleagues reported no evidence for a rebound effect after exposure plus response prevention therapy sessions [Verdellen *et al.* 2007].

The effectiveness of habit reversal training has been evaluated more thoroughly [for a review, see Himle *et al.* 2006]. Woods and colleagues reported improvements of between 89% and 96% in four children with motor tics [Woods *et al.* 1996]. Habit reversal training may also help with vocal tics, as shown by Woods and colleagues [Woods *et al.* 2003]. Four out of five children (aged 10–13 years) showed a reduction in vocal tic frequency of 38–96%, while untreated motor tics remained the same; these gains were maintained three months later. Studies by Azrin and colleagues have also provided favourable evidence. Ten patients were found to exhibit 93% reduction in tics at home and 93.5% reduction in clinic after treatment [Azrin and Peterson, 1990]. Beneficial effects were apparent in both children and adults, in both motor and vocal tics and in tic severity and frequency. A study of 22 adults [Azrin *et al.* 1980] found this technique more effective than another behavioural technique (massed negative practice). Self-reported tics decreased by 92% in the habit reversal group and 33% in the massed negative practice group. Habit reversal training can also be successful when combined with cognitive behavioural therapy [O'Connor *et al.* 1997]. One clear limitation associated with this behavioural technique is that tics in one part of the body may be replaced by tics in another part [Robertson and Stern, 2000]. Long-term evaluation of treatment outcome is therefore necessary.

Invasive techniques

Botulinum toxin injections

Botulinum toxin (botox) inhibits localized release of acetylcholine leading to reduced muscle activity. When used to treat tics, it is administered directly into the muscle group involved in the motor tic, or into the laryngeal muscles for vocal tics. Although some studies report a lack of efficacy [Chappell *et al.* 1997], many studies have noted improvement with the use of this treatment [e.g. Trimble *et al.* 1998]. These include cases involving patients with self-injurious symptoms [Aguirregomozacorta *et al.* 2008; Robertson *et al.* 1989]. Marras and colleagues reported that treatment with botox was associated with a 40% improvement in comparison with placebo [Marras *et al.* 2001].

In relation to vocal tics, botox has been shown to help coprolalia and accompanying premonitory sensations [Scott *et al.* 1996]. The efficacy of botox for phonic tics was also illustrated by a prospective, nonrandomized study carried out by Porta and colleagues which investigated the effectiveness of vocal cord injections of botox for phonic tics [Porta *et al.* 2008b]. Seventy patients (29 aged 10–16, 41 aged 19–55) were assessed 15 days after treatment and then a further four times over the next year following the injection of botox into the vocal cords. Assessment using the CGI indicated that phonic tics improved in 94% of patients, and that 41% appeared to be tic-free. Moreover, premonitory sensations were reduced and patients' QoL improved. There were no serious side effects, although 84% of patients reported hypophonia.

Deep brain stimulation

Candidates for surgical treatment include patients exhibiting life-threatening self-injurious symptoms or severe tics that lead to significant functional impairment. Patients who fail to respond to many other forms of intervention may also be considered. The most common invasive technique for tics is DBS of the thalamus or globus pallidus. Activation of the implanted electrode leads to a localized paradoxical decrease in neural activity in the site of implantation. Although this form of treatment is still in its infancy, studies have provided encouraging evidence for the effectiveness of this technique in ameliorating tics.

Many studies have investigated the effectiveness of DBS of the medial thalamus for tics. Visser-Vanderwalle and colleagues reported the results of DBS of the medial thalamus in three patients with TS [Visser-Vanderwalle *et al.* 2003].

Treatment led to tic reductions of 90%, 72% and 83%. Another study of five patients [Maciunas *et al.* 2007] showed that DBS of the medial thalamus region led to a 40% decrease in motor tics and a 21% decrease in vocal tics. In a larger sample of 18 patients, Servello and colleagues reported evidence of good tic reduction at 3–17 months post treatment, although on a few occasions, surgery led to complications [Servello *et al.* 2008].

DBS of the globus pallidus has also been shown to improve tics. Shahed and colleagues reported an 84% reduction in tics following treatment, and no side effects [Shahed *et al.* 2007]. Houeto and colleagues compared DBS of the globus pallidus interna (GPi) and centromedial parafascicular nucleus of the thalamus [Houeto *et al.* 2005]. Tics improved by 70% after either treatment and reductions in coprolalia and self-injurious behaviour were also noted. The centromedian parafascicular nucleus of the thalamus and ventromedial GPi were targeted in three patients who participated in a controlled, double-blind, randomized, crossover study [Welter *et al.* 2008]. DBS of the GPi resulted in a dramatic improvement in tics according to YGTSS scores. Motor tics reduced by 65%, 96% and 74%. For the thalamus, there were reductions of 64%, 30% and 40% in tic severity. No advantage was apparent when both regions were targeted together. DBS also reduced self-injurious behaviour and impulsiveness.

Not all studies report complete success. One case of DBS of the posteroventral GPi [Foltynie *et al.* 2009] involved a patient who initially scored 81/100 on the YGTSS. After treatment, at 3- and 6-month follow up there was almost complete resolution of motor and vocal tics at rest, but recurrence of vocal tics on speaking. An important finding was that the patient felt that surgery had not improved his QoL overall, although he did prefer the stimulator to be switched on. Burdick and colleagues reported one case of nucleus accumbens/capsular DBS that was not successful [Burdick *et al.* 2009]; although another study showed DBS of similar sites may lead to a 40–50% reduction in tics, without side effects [Kuhn *et al.* 2007]. The side effects that have been reported after DBS of the thalamus include drowsiness and changes in sexual behaviour [Visser-Vanderwalle *et al.* 2003], reduced energy [Servello *et al.* 2008], psychosis and spontaneous tic recurrence [Maciunas *et al.* 2007].

Other emerging treatments

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is most often applied to treat depressive disorders, but a few case reports have documented potential effectiveness in treating TS. Four single case reports to date [Karadenizli *et al.* 2005; Strassnig *et al.* 2004; Trivedi *et al.* 2003; Rapoport *et al.* 1998] have reported beneficial effects; however these cases were quite complex. Two patients had comorbid depression, one had comorbid OCD and one experienced self-injurious tics. ECT could have a less-specific therapeutic effect in TS by altering stress levels, or could indirectly reduce dopamine levels by increasing serotonin [Bloch, 2008]. However, it remains to be shown if this approach could be effective in ameliorating tics in pure TS. In addition, no data is available to support the usefulness of this approach with adolescents and it is unlikely to be appropriate for use with children. The limitations of this approach also include side effects such as short-term memory problems and benefits may not be durable. Until better-controlled studies have been conducted this approach may be best reserved for cases involving severe depression.

Repetitive transcranial magnetic stimulation

A few preliminary studies investigating the therapeutic effectiveness of repetitive transcranial magnetic stimulation (rTMS) have reported a favourable outcome [e.g. Mantovani *et al.* 2007]. For example, Mantovani and colleagues showed that rTMS over bilateral supplementary motor cortex led to an average of 67% reduction in tic severity in five patients, and complete symptom remission in two [Mantovani *et al.* 2006]. Treatment also resulted in reduced scores on scales assessing depression and OCSs and therapeutic effects were still present after 3 months. Another randomized, blinded, crossover study assessed the efficacy of rTMS (1 and 15 Hz) over prefrontal cortex or motor cortex in eight patients with TS. There were minimal side effects and no worsening of tics. Tic symptoms improved significantly overall during the week of the study. However, a single-blind, placebo-controlled, crossover repetitive trial [Munchau *et al.* 2002] involving 12 patients who received 1 Hz rTMS over the motor and premotor cortex reported no significant improvement of tics, obsessions or compulsions. Further controlled studies are needed to determine the effectiveness of rTMS, especially for more

severe tics. The advantages of this technique include fewer and milder side effects (e.g. headache) than other approaches such as DBS or ECT, and no anaesthesia is involved. Drawbacks include the likelihood of purely ephemeral benefit and the fact this approach requires multiple treatment sessions [Bloch, 2008].

Discussion

Implications in terms of efficacy and safety

The evidence we have reviewed relating to pharmacological treatments indicates that dopamine antagonists may lead to the most reliable treatment response, but also pose the greatest drawbacks in terms of side effects. There is strong evidence supporting the efficacy of neuroleptics in the successful treatment of tics. Some reports suggest that pimozide and fluphenazine can be as efficacious as haloperidol and less toxic. Overall, however, the use of these agents can lead to a greater risk of adverse effects (such as extrapyramidal symptoms) than atypical antipsychotics. One more favourable option is risperidone, which has the most supportive evidence for efficacy and is appears safer than neuroleptics. A number of studies provide evidence for efficacy for olanzapine and quetiapine. Clozapine, however, is associated with less supportive evidence and the potentially serious side effect of agranulocytosis. Benzamides can be effective and their use is rarely associated with extrapyramidal side effects. However, the risk of hyperprolactinaemia may lead to caution, and more data is crucial to enable a more thorough evaluation of the merits of these agents.

Clonidine appears to be a safe option, although a few studies dispute its efficacy. An additional benefit of this medication is that it could be useful in more complex cases of TS, as individuals who respond to this drug may also experience improvements in ADHD symptoms, aggression and OCSs. Benzodiazepines can also show good efficacy but should be prescribed with caution due to associated tolerance and potential for addiction. Associated sedation may also be a troublesome side effect.

A variety of other agents have the potential to be viable treatments and compel further investigation in order for their utility to be fully determined. These include tetrabenazine, levetiracetam, topiramate and cannabinoids. Tetrabenazine may be an effective medication and is less likely to lead to weight gain than atypical antipsychotics. Although there is conflicting evidence of efficacy, this agent may be the least problematic in terms of side effects. There is some good evidence for the efficacy of cannabinoids, but concerns about the possibility of some potentially serious side effects (e.g. precipitation of psychosis) may make this agent a less-favourable option.

In relation to nonpharmacological treatments, there is much evidence in support of the efficacy of both behavioural and surgical techniques. It is vital that behavioural options are available for younger patients and those who are sensitive to pharmacological interventions. Habit reversal training is a safe choice, but may not be of benefit in the long term in patients whose tics move to new body regions. There is also a clear issue of compliance, as patients are actively involved in home practice between sessions. There is a considerable amount of evidence in favour of botox for vocal and specific motor tics, although it is difficult to conduct controlled studies. Surgery may be appropriate for severe, treatment refractory patients. The evidence of the efficacy of DBS is encouraging, although the target of surgery is open to debate.

Recommended first-line treatments

While behavioural interventions are perhaps the safest treatment method and should be offered whenever possible, the therapeutic power of a number of pharmacological options establishes these agents as promising first-line treatments for tics.

Medication selection will partly depend on the age of the patient, as younger children may be more vulnerable to the toxicity of agents. Clonidine could therefore be the best agent to prescribe initially, based on the mild and infrequent nature of side effects, which include postural hypotension and minor anticholinergic effects. Another benefit of this drug is the evidence suggesting that it can help with other behavioural symptoms linked to ADHD [Leckman *et al.* 1991] which may be more common in younger patients with tics.

For adults, stronger medications may also be tolerated. The efficacy of risperidone is well established and may be needed for tics of moderate severity. If the patient needs to discontinue

treatment due to adverse effects, an alternative similar option is aripiprazole. These agents offer a good compromise between efficacy and toxicity. They are less toxic than neuroleptics and perhaps as effective.

Recommended treatments for specific cases

Some patients may not respond to the above agents, or exhibit severe tics that lead to greater distress and functional impairment. In such cases, haloperidol or sulpiride may be considered. Careful monitoring of treatment response and gradual titration of dose are particularly critical with the prescription of these agents, due to the possibility of more significant side effects (hyperprolactinaemia and extrapyramidal symptoms).

The use of these agents may also be well justified in cases involving self-injurious behaviour. If not well tolerated, a viable alternative is botox injection. Studies have shown this approach can be useful in treating specific tics through localized muscular action, so could be useful in patients with severe cervical tics. Botox may also be useful in cases where vocal tics or coprolalia are the primary problem.

For behavioural symptoms involving rage and aggression, studies have indicated that clonidine, sulpiride or risperidone may be beneficial. In relation to comorbid OCSs or ADHD symptoms, clonidine may reduce symptoms of both, and sulpiride has also been shown to be useful for OCSs. It may be possible to combine certain medications for tics with agents that specifically target severe OCD symptoms. Examples of safe combinations include atypical antipsychotics and SSRIs.

The treatment of TS is clearly complicated by the frequent presence of comorbid conditions such as OCD, ADHD, anxiety or depression. The presence of particular comorbidities may make certain treatment options for tics less likely to be effective. For example, patients with comorbid ADHD could find it more difficult to remember to take medication or more anxious patients could feel their tics are exacerbated due to increased focus on them during habit reversal training. In cases where comorbid conditions may cause more distress and impairment than tics, their treatment is of prime importance. However, treating comorbid conditions may also have the potential to lead to some improvement in tics. While medications such as SSRIs may be unlikely to have any direct mechanism of action that improves tics, their effective treatment of a comorbid condition will reduce stress, which characteristically exacerbates tics. For example, if significant symptoms of OCD are present, amelioration of these may help reduce anxiety levels and improve mood, leading to reductions in tic severity or frequency.

Methodological limitations and directions for future research

Despite encouraging findings, many studies documenting the investigation of treatment efficacy for tics are far from flawless in terms of their design and methodology. These limitations are likely to contribute to the conflicting reports of efficacy and tolerability of treatments. One critical difficulty is that studies vary in the approach they employ to assess efficacy. For example, effectiveness may be considered in terms of the percentage of patients whose symptoms improve, or by the mean percentage improvement in tic severity or frequency across the treatment group. Some treatments may be considered most effective if they are associated with changes in functional impairment. Another significant limitation is that studies often do not use QoL measures which may be particularly useful in indicating which treatments are most advantageous in a broader context and from the patient's perspective.

Enhanced scientific rigour is crucial for the advancement of knowledge in this area. Placebo control is clearly necessary, as some studies have shown placebo to be associated with as much improvement in tics as an active agent. Double-blind studies are well motivated but are limited by the possibility that significant treatment effects could always lead participants to work out which condition they are undertaking. Artificially inflated effect size may also occur when participants drop out of studies because they do not experience any treatment benefits.

More fundamental problems arise due to the nature of tics. Long-term studies are encouraged by the finding that tics tend to follow a waxing and waning course, which could obscure treatment effects. In relation to tic severity, some interventions may be effective only in mild cases, whereas others may only show an effect in patients with more severe tics who have the potential to exhibit improvement across a wider

scale. Other potentially interacting factors are age-related hormone changes. Interactions between neurotransmitters further complicate the determination of whether an agent's primary mechanism of action is directly responsible for its efficacy.

Future research should employ stringent tests of efficacy, and randomized, double-blind, placebo-controlled trials should be conducted whenever possible. Trials conducted over longer timescales will give further insight into the durability of treatment response. Particularly useful investigations will be those that systematically compare the effectiveness of different treatments in independent samples grouped according to variations in symptom severity, comorbidities or other pertinent behavioural problems. For example, controlled trials may determine that specific treatments are more effective for particular subgroups of patients with TS who exhibit coprophenomena, paliphenomena, echophenomena, self-injurious behaviours or emotional dysregulation. Future research should systematically examine data collected for a range of measures assessing tics and tic related symptoms, premonitory urge, self-injurious behaviours, emotional dysregulation, NOSIS and the severity of symptoms related to OCD and ADHD, before and after treatment. Patients' scores on clinical scales and symptom-related questionnaires could then be employed more effectively in order to inform treatment options.

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