Drugs 2001; 61 (15): 2207-2220
0012-6667/01/0015-2207/$27.50/0

Pharmacological Options for the Treatment of Tourette's Disorder

Félix Javier Jiménez-Jiménez[1] and *Pedro José García-Ruiz*[2]

1 Department of Medicine – Neurology, Hospital 'Príncipe de Asturias', Universidad de Alcalá, Alcalá de Henares (Madrid), and Neuro-Magister S.L. Company, Madrid, Spain
2 Service of Neurology, Fundación Jiménez Díaz, Madrid, Spain

Contents

Abstract

Tourette's disorder is a neuropsychiatric disorder characterised clinically by motor and vocal tics, which may be associated to conductual disorders such as obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD). Although the neurochemistry of Tourette's disorder is not well known, there are some effective therapies for tics, OCD and ADHD. However, these are not devoid of adverse effects.

Tics only require treatment when they interfere with the functioning of the

patient. If therapy is needed, monotherapy at the minimal effective dose is desirable, but some patients may require two or more drugs. The most frequently used drugs for tics are antipsychotics (mainly pimozide and haloperidol) and clonidine. The potential usefulness of atypical antipsychotic drugs (risperidone, olanzapine, clozapine, ziprasidone) and other dopaminergic drugs (fluphenazine, sulpiride, tiapride, metoclopramide, piquindone, tetrabenazine), clonazepam, calcium channel antagonists, botulinum toxin, dopamine agonists, selegiline, and other drugs is discussed.

The drugs of choice for OCD in patients with Tourette's disorder are the selective serotonin reuptake inhibitors (SSRIs), although the tricyclic antidepressant clomiplamine, which inhibits both serotonin and noradrenaline uptake, has also been found to be useful.

ADHD can be treated with some psychostimulants, mainly methylphenidate, although these drugs must be used with caution. Other potentially useful drugs for the treatment of ADHD in patients with Tourette's disorder are clonidine, guanfacine, selegiline, some tricyclic antidepressants, sertraline, pimozide and clonazepam.

Finally, the potential value of some nonpharmacological therapies (hypnotherapy, biofeedback, conductual therapies, electroconvulsive therapy, acupuncture and surgery) is briefly reviewed.

Although the treatment of the Tourette's disorder has evolved from case reports to blinded trials, most of the classical pharmacological therapies for tics have limited effectiveness and poor adverse effect profiles. In recent years some new effective and better-tolerated drugs have been developed. As well as treatment of tic symptoms, comorbid illnesses must be treated when they cause functional impairment. In this article, we attempt to discuss both established and potential future drug treatments for patients with Tourette's disorder, both for tics and for associated behavioural problems.

1. Clinical Features, Genetics and Neurochemistry

Tourette's disorder is a neuropsychiatric disorder of genetic origin, which is characterised clinically by the presence of motor and vocal tics. It is frequently associated with conductual disorders, mainly obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD).[1-5] Diagnostic criteria for tic disorders have been well defined by the Tourette Syndrome Classification Study Group[6] and in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[7] Tics are present in all patients with Tourette's syndrome, and are the initial symptom of the disease in 71% of patients.[8] Both motor and vocal tics have a typical waxing and waning course. The reported frequencies of OCD and ADHD in patients with Tourette disorder range from 32 to 50% and 32 to 63%, respectively.[5,9]

Some studies have shown that Tourette's disorder is inherited by autosomal dominant transmission, with a penetrance of 0.88 to 1.00 in males and 0.45 to 0.98 in females,[10-15] and variable expression that includes the presence of complete Tourette disorder, chronic and transient tics, OCD and ADHD.[16,17] Bilineal transmission, suggesting a role for homozygosity or polygenic influences,[18-21] and a mixed model of inheritance with a major locus of genetic susceptibility and a multifactorial base have also been suggested.[22] However, the results of linkage analyses of some candidate genes have been unsuccessful in finding the genetic defect.

Although the neurochemistry of Tourette's disorder not well known, the therapeutic effect of antidopaminergic agents and clonidine on tics imply the involvement dopaminergic (dopamine hyperactivity) and noradrenergic mechanisms (nor-

Table I. Neurochemical findings in Tourettes syndrome (original table elaborated with data from the text of reference[5])

Neurotransmitter	Examination	Findings
Dopamine	Brain (postmortem)	Increased dopamine uptake sites in the striatum (^{3}H-mazindol) Normal levels of dopamine, DOPAC and HVA in some subcortical regions and of dopamine in the basal ganglia
	CSF	HVA levels decreased, normal or increased
	Brain (PET/SPECT)	Presynaptic dopamine uptake sites in the striatum increased (^{123}I-beta-CIT SPECT) Postsynaptic D_2 dopamine receptors increased (^{11}C-N-methyl-spiperone) or normal (^{11}C-raclopride) Dopamine presynaptic terminals normal (^{11}F-Dopa)
	Platelets	Decreased dopamine uptake into platelet storage granules
Noradrenaline	Brain (postmortem)	Normal NA levels and β-adrenergic receptors densities in some cortical regions and basal ganglia
	CSF	Normal MHPG levels
	Plasma	Decreased or normal plasma MHPG levels
	Urine	Decreased urine excretion of MHPG and normethanephrine.
Serotonin	Brain (postmortem)	Normal 5-HIAA levels in some cortical areas and decreased 5-HIAA levels in some subcortical areas
	CSF	Normal or decreased CSF 5-HIAA levels
	Plasma	Normal or decreased 5-HT and tryptophan levels
	Urine	Urine excretion of 5-HT and 5-HIAA decreased or normal (but increased in patients with associated OCD)
	Platelets	Decreased 5-HT receptors (^{3}H-imiprimine and ^{3}H-paroxetine)
Acetylcholine	Brain (postmortem)	Normal choline-acetyl-transferase activity and muscarinic receptors in some cortical areas
	CSF	Normal acetyl-cholinesterase and butyryl-cholinesterase activities
	Lymphocytes	Decreased density of muscarinic receptors
	Erythrocytes	Increased choline levels in patients and first-degree relatives
GABA	Brain (postmortem)	Normal GAD activity
	CSF	Normal
	Plasma	Normal
Other	Brain (postmortem)	Decreased dynorphine A[1-17] in the striatum and globus pallidus
	CSF	Increased dynorphine A[1-8] and CRF levels, normal arginine-vasopressin and oxytocin
	Brain (PET)	Normal density of opioid receptors (^{11}C-diprenorphyne)

5-HIAA = 5-hydroxyindolacetic acid; **5-HT** = 5-hydroxytryptamine (serotonin); **DOPAC** = dihydroxyphenylacetic acid; **CRF** = corticotropin releasing factor; **CSF** = cerebrospinal fluid; **GABA** = γ-aminobutyric acid; **GAD** = glutamic acid decarboxylase; **HVA** = homovanillic acid; **MHPG** = 3-methoxy-4-hydroxyphenylenglicol; **NA** = noradrenaline; **OCD** = obsessive-compulsive disorder; **PET** = positron emission tomography; **SPECT** = single photon emission computed tomography.

adrenergic hyperactivity). On the basis of the response of patients with tics to other drugs, it is likely that other neurotransmitters such as serotonin (5-hydroxytriptamine; 5-HT), acetylcholine, γ-aminobutyric acid (GABA), and opioids are also implicated. The main neurochemical findings in patients with Tourette's disorder are summarised in table I.[5]

2. Principles of Pharmacological Treatment

The main objective of the therapy of Tourette's disorder is to obtain adequate control of symptoms, both the motor and/or vocal tics and the associated conductual disorders.

Tics only require treatment when they cause interference with psychosocial, educational and occupational functioning of the patient. Because of the waxing and waning course of tics, it is possible to taper the treatment in individual patients. At present, standard medication for tics includes antipsychotics (and other antidopaminergic drugs) and clonidine. Although these drugs have been proved to be effective, frequent adverse effects, especially sedation and learning problems (not to mention extrapyramidal adverse effects) stimulated the search

for new drugs, with inconsistent results. At present many other drugs have been investigated for the control of tics. The list includes various anticonvulsants, antidepressants, calcium channel antagonists, cholinergic agents, lithium and opiate antagonists among other drugs.[23,24] If therapy is needed, monotherapy at the minimal effective dose is desirable, but some patients may require two or more drugs.

The drugs of choice for OCD are the selective serotonin reuptake inhibitors (SSRIs). Psychostimulants are useful for the treatment of ADHD but their generalised use is not recommended. Table II summarises the most important drugs (in-

Table II. Drugs used for the therapy of Tourette's syndrome

Drug	Recommended dosages (mg/day)	Main adverse effects
Antidopaminergic agents		
Haloperidol	0.25-8	Dystonic reactions, parkinsonism, akathisia, tardive dyskinesia, sedation, intellectual impairment, dysphoria, depression, social and school phobias, bulimia and bodyweight gain
Pimozide	0.5-10	Possible prolongation of QT-interval on ECG, other similar to those of haloperidol (but much less frequent)
Risperidone	0.5-3	Anxiety, insomnia, headache. Less frequently sedation, gynaecomastia, hyperprolactinaemia-amenorrhoea-galactorrhoea and extrapyramidal symptoms
Olanzapine	2.5-10	Somnolence, weight gain, dizziness, orthostatic hypotension, oedema. Less frequently extrapyramidal symptoms, gynaecomastia, hyperprolactinaemia, gastrointestinal complaints, hypotension, tachycardia
Fluphenazine	0.5-15	Similar to those of haloperidol, but lower frequency of sedative effect, bodyweight gain and school phobia
Sulpiride	100-400	Extrapyramidal symptoms much less frequently than haloperidol, bodyweight gain, hyperprolactinaemia-amenorrhoea-galactorrhoea
Tiapride	50-300	Sedation, other similar to those of sulpiride
Tetrabenazine	12.5-100	Parkinsonism, depression, anxiety, sedation, insomnia, akathisia
Clonidine	0.075-0.30	Sedation, hypotension, irritability, dizziness, headache, insomnia, dry mouth, cutaneous exanthema (transdermic patches)
Benzodiazepines		
Clonazepam	0.25-5	Sedation, dizziness, ataxia
Calcium channel antagonists		
Nicardipine	40-100	Dizziness, nausea, constipation, facial flushing, oedema, headache
Flunarizine	10-20	Similar to those of nicardipine, drowsiness, bodyweight gain, parkinsonism, tardive dyskinesia, depression
Dopamine agonists		
Pergolide	0-125-0.25	Nausea, vomiting
Selegiline	5-10	Hypotension, nausea, vomiting, insomnia, confusion
Clomipramine	25-250	Anticholinergic adverse effects (dry mouth, constipation, blurred vision, sedation, etc), cardiotoxicity, tremor
SSRIs		
Fluoxetine	10-100	Gastrointestinal symptoms, anxiety, insomnia, tremor, dizziness, headache
Fluvoxamine	25-300	
Citalopram	10-40	
Sertraline	25-200	
Paroxetine	10-60	
Psychostimulants		
Methylphenidate	2.5-30	Insomnia, dry mouth, nausea and other gastrointestinal complaints, anxiety, exanthema, hyper- or hypotension, palpitations
Dextroamphetamine	5-30	

ECG = electrocardiogram; **SSRIs** = selective serotonin reuptake inhibitors.

cluding recommended dosages and adverse effects) used in the treatment of patients with Tourette's disorder.

3. Antidopaminergic Therapy

3.1 Haloperidol

Haloperidol is a butyrophenone antipsychotic drug that binds more specifically to postsynaptic dopamine D_2 than to D_1 receptors. It also has some α_1-adrenergic antagonistic activity.[25] This drug was first used for Tourette's syndrome in 1961, and was the drug of choice during the 1960s and 1970s, with an efficacy of 60 to 90%.[26-36] Some patients with refractory disease benefit from the use of haloperidol decanoate.[37] However, the high frequency of adverse effects in many instances led to the discontinuation of therapy.[38-40] The main adverse effects that lead to haloperidol discontinuation include dysphoric reactions, akathisia, nervousness, sedation, dystonic reactions, and cognitive dulling/feeling drugged.[40] Taking these considerations into account, haloperidol should not currently be considered the first-line agent in children as other agents have superior adverse-effect profiles.[41]

3.2 Pimozide

Pimozide is a diphenylpiperidine. Like haloperidol it preferentially binds to D_2 receptors, but has little effect on adrenergic receptors.[25] Pimozide was introduced for the treatment of Tourette's syndrome in 1978.[42] Its efficacy in controlling tics is comparable to that of haloperidol, but in most studies pimozide has a significantly lower incidence of adverse effects.[43-49]

In some patients, long-term use of pimozide can induce sedation, bodyweight gain, depression, pseudoparkinsonism and akathisia. Because prolongation of the QT-interval has been reported in some studies, it is recommended to avoid the use of this drug if the QT-interval is abnormal on the initial electrocardiogram.[50] When compared with haloperidol, pimozide has better effects on cognition.[51] A recent study showed that long-term treatment with pimozide was more effective in controlling the course of tics than using the drug to treat acute exacerbations.[52]

3.3 Atypical Antipsychotic Drugs

Although the current experience with atypical antipsychotic drugs is limited to case reports or short-term studies, they are considered as promising agents for the control of tics because they have better adverse effect profiles than haloperidol. Risperidone, a potent 5-HT_{2A}, D_2 and α_1-adrenergic receptor antagonist, has shown efficacy in short-term studies in controlling tics and OCD disorders.[53-58] Olanzapine is another atypical antipsychotic drug with high antagonistic affinity to the D_2, D_4, 5-HT_{2A}, 5-HT_{2c} and α_1-adrenergic receptors. Olanzapine has shown efficacy in the control of tics.[59-61] The experience with clozapine has been limited but unsatisfactory.[62,63] Recently, Sallee et al.[64] reported efficacy with ziprasidone in controlling tics.

3.4 Other Antidopaminergic Drugs

Two studies have shown that the piperazine phenothiazine fluphenazine has a similar efficacy to haloperidol in controlling tics but with fewer adverse effects.[65,66] The efficacy of the orthopramides or substituted benzamides sulpiride,[67-69] tiapride,[70] and metoclopramide,[71] and piquindone has been reported.[72] These drugs are selective D_2 receptor antagonists.

Tetrabenazine is a benzoquinoline derivative that depletes presynaptic storage of dopamine and has a mild blocking effect on D_2 receptors. Some studies involving a small number of patients have shown efficacy with tetrabenazine on tics.[73-76] Adverse effects include drowsiness, depression and parkinsonism.

4. Clonidine

Clonidine is an imidazole derivative that acts as α_2-adrenergic agonist, inhibiting the release of noradrenaline. This drug was introduced for the treatment of Tourette's disorder in 1979.[77] It has

a gradual onset of action, and ameloriates motor and vocal tics, compulsive behaviour and attentional problems. Clonidine has been shown to be useful both by oral[39,65,77-83] and transdermal routes of administration.[84] Although a double-blind study failed to show improvement of tics with clonidine,[85] the abrupt withdrawal of this drug can induce a rebound phenomenon with marked worsening of tics.[86]

It has been recently reported that another α_2-adrenergic agonist, guanfacine, may be useful in the treatment of motor and vocal tics and ADHD.[87]

5. Alternative Agents for the Therapy of Tics

5.1 Benzodiazepines

Clonazepam is, at present, the only benzodiazepine commonly used to treat tics. It is surprising, since the use of clonazepam in tics is supported only by a few reports, none of which were carried out with double-blind design.[39,88-90] In spite of these caveats, some experts recommend clonazepam as a second-line treatment after antipsychotics and clonidine.[91] Interestingly enough, clonazepam may induce Tourette's like disorder in exceptional cases.[92]

The putative mechanism of action clonazepam on tics is complex. Apart from the well-known effect on the $GABA_A$ receptor complex,[93] this drug also interacts with serotonin neurotransmission.[93-95] In addition, clonazepam exhibits antidopaminergic properties in experimental models.[96,97] Several of these mechanisms could explain the antidyskinetic action of clonazepam.

5.2 Calcium Channel Antagonists

In 1984, Goldstein reported the anecdotal use of nifedipine in a patient with Tourette's syndrome.[98] It is of note that in this first report, nifedipine was chosen on the assumption that decreasing calcium current would result in decreased neurotransmitter release. Since then, several reports suggested that calcium channel antagonists might be useful as therapy for tics;[99-101] however, most of these reports included anecdotal cases or short series.

The most convincing study in support of the use of calcium channel antagonists was performed by Micheli et al.[102] These researchers carried out a placebo-controlled study in seven patients with Tourette's syndrome. Flunarizine was used at a starting dose of 5mg which was increased until response was achieved or adverse effects appeared. There was a statistical response in terms of reduction in motor and phonic tics; however, adverse effects included bradykinesia in two patients. Calcium channel antagonists appear to be promising drugs for use in patients with tics, but the efficacy of these drugs still awaits confirmation by properly design trials.

The mechanism of action of calcium channel antagonists in controlling tics is not well known. Clinical and experimental studies have demonstrated that they exhibit antidopaminergic properties,[103-109] but the exact mechanism of this antidopaminergic activity is not fully understood because these drugs exhibit a complex action on dopaminergic system. Calcium channel antagonists, mainly flunarizine and cinnarizine, act at postsynaptic level by blocking D_2 receptors.[110] In addition, they can act at presynaptic level, decreasing the synthesis and release of catecholamines in experimental models.[111,112] Current information suggest that phenylalkylamines and diphenylalkylamines have a predominant postsynaptic neuroleptic-like action, whereas dihydropyridines have a predominant presynaptic effect on dopamine neurotransmission. This mechanism might explain the antidyskinetic effect of calcium channel antagonists.[109,112]

5.3 Botulinum Toxin

Botulinum toxin has been used with increasing frequency over the last decade to treat disorders characterised by inappropriate muscle contraction including focal dystonia and spasticity.[113-117] Therefore, it was only a matter of time before the effectiveness of botulinum toxin on tics was explored in patients with Tourette's syndrome.

Jankovic reported a pilot study involving ten patients,[118] his results were encouraging and were followed by two larger nonblind studies.[119,120] However double-blind, placebo-controlled studies are needed to confirm these findings. If the results of Jankovic are confirmed, botulinum toxin may be a very reasonable option for the treatment of tics. Interestingly, botulinum toxin seems to improve not only the pure motor tic, but also the sensory manifestation[118] that often accompanies the motor phenomena (premonitory sensory component). The effectiveness of injections of botulinum toxin into vocal cord for the treatment of severe vocal tics has also been reported.[121-123]

5.4 Dopamine Agonists

Since dopamine antagonists are, at present, the gold standard for the treatment of tics, the use of dopamine agonists seems to be an oddity. However, apomorphine[124] and pergolide[125] have been employed in the treatment of tics with positive results. The initial nonblind study with pergolide has been followed up with a double-blind, placebo-controlled study[126] that confirmed the efficacy of pergolide. In contrast, a double-blind trial with talipexole failed to show any efficacy.[127] The mechanism of action of pergolide in controlling tics is partially unknown, although it is likely to be related to modulation of presynaptic dopamine receptors; therefore, the net effect should be an inhibitory dopaminergic effect.[127] Of note, is the very low dose of pergolide used in the treatment of tics (<300μg), which contrasts with much larger doses used in Parkinson's disease (3mg). Dopamine agonists at low doses represent a new, interesting approach for the treatment of tics. An improvement in tics in a patient treated with the partial D_2 agonist and 5-HT_{1A} agonist buspirone has been also described.[128]

5.5 Selegiline

Selegiline has been used in patients with Tourette's syndrome and ADHD.[129] Unexpectedly, selegiline not only improved ADHD, but also had a beneficial effect on tics.[130] Because of its generally good tolerance and lack of serious adverse effects, further investigation of selegiline for this use is warranted.

5.6 Other Drugs

Awaad[119] conducted a nonblind study involving 264 patients with the GABA agonist baclofen 10 to 80 mg/day, and reported significant improvement of motor and vocal tics.

The use of some serotonin antagonists, such as the selective 5-HT_3 antagonist ondansetron[131] and the 5-HT_2 antagonist ketanserin (this drug is also a potent α_1-adrenergic agonist and a weak dopamine receptor antagonist)[132] has been reported as beneficial in controlling tics in nonblind studies involving a small number of patients. The selective 5-HT_{2C} agonist chlorophenylpiperazine (mCPP) did not show any effect on tics in a double-blind placebo-controlled study.[133]

Nicotine, used by both oral (chewing gum)[134-136] or transdermal routes of administration[137-140] has been shown to improve tics, especially by potentiation of the action of antipsychotics such as haloperidol. Interestingly, the nicotine antagonist mecamylamine also improved tics in a nonblind study involving 13 patients.[141] The author speculated with the possibility that nicotine could induce a prolonged inactivation of one or more acetylcholinergic nicotinic-receptor subtypes producing an antagonist effect. The clinical response to cholinergic agents (precursors of acetylcholine such as choline or lecithin or acetylcholinesterase inhibitors such as physostigmine) are controversial,[142-147] and their clinical usefulness should be limited.

Some case studies suggested that the modulation of the opioid system could improve tics. In support of this hypothesis, improvement of tics with the opioid antagonists naloxone[148] and naltrexone,[149,150] and with the opioid partial agonists methadone[151] and tramadol, has been described .[152] On the other hand, some authors reported worsening of tics with naloxone.[153]

On the basis of previous reports of improvement of tics with marihuana,[154,155] Müller-Vahl et al.[156,157] suggested the possible role of can-

nabinoids in the pathophysiology and therapy of Tourette's syndrome. These authors, using an structured interview, questioned a large group of patients with Tourette's syndrome about the use of nicotine, alcohol and marihuana, and their subjective experiences with these substances. Among patients drinking alcohol, 69% reported improvement of tics after alcohol consumption, and from those patients using marihuana, 85% noted marked improvement of tics. Thereafter, they report improvement in a single patient with delta-9-tetrahydrocannabinol 10mg.[158]

Preliminary experiences suggested the possible usefulness of antiandrogen or estrogenic therapy in Tourette's syndrome.[159-161] In addition, a worsening of tics with androgen therapy has been reported.[162] More recently, Peterson et al.[163] reported improvement in motor, but not in vocal tics, in a double-blind, placebo-controlled study using flutamide involving 13 patients with Tourette's syndrome. In addition, a modest effect on OCD symptoms was noted. These findings suggest a promising role of antiandrogen therapy in the treatment of tics.

Anecdotal reports suggest a beneficial effect of vigabatrine,[25] lamotrigine[25] and lithium.[164,165] On the other hand, induction of tics or tourettism by lamotrigine has also been reported.[166,167] Some authors have suggested the possibility of a good therapeutic effect of some corticotropin releasing factor antagonists under development.[168]

Muller et al.[169] reported a good response with intravenous immunoglobulins in patients with Tourette's disorder. Perlmutter et al.[170] conducted a randomised, controlled trial with intravenous immunoglobulins and plasma exchange in 30 patients with infection-triggered exacerbations of OCD or tic disorders, and found improvement of OCD symptoms with both therapeutic approaches and also of tics with plasma exchange.

6. Treatment of Conductual Disorders

The behavioural disorders associated with Tourette's syndrome, mainly OCD and ADHD, are not usually improved to the same degree as tics by antipsychotics or clonidine alone or in combination. The development of SSRIs has been very useful in the treatment of OCD, whereas ADHD is usually treated with psychostimulants.

6.1. Obsessive-Compulsive Disorder (OCD)

6.1.1. Clomipramine

Clomipramine is a tricyclic antidepressant that inhibits both serotonin and noradrenaline reuptake. This drug has been found to be useful in the treatment of patients with OCD.[171] Although some reports suggested improvement of OCD and tics in patients with Tourette's syndrome,[172] others have reported no improvement.[173] Moreover, the induction of tics related to clomipramine has been reported.[174] As with other tricyclic antidepressants, clomipramine may induce sedation, dry mouth, constipation and cardiotoxic effects.

6.1.2 Selective Serotonin-Reuptake Inhibitors

Nowadays, SSRIs are the therapy of choice for patients with OCD. A beneficial effect on OCD associated with Tourette's syndrome has been reported with fluoxetine,[175-180] fluvoxamine[181,182] and citalopram.[182] Interestingly, fluvoxamine seems to be less effective in improving OCD symptoms in patients without tics than in those with tics.[181] Although worsening of tics has been reported in some patients receiving SSRIs such as paroxetine,[183] sertraline[184] or fluvoxamine,[185] there was no worsening of tics in patients receiving fluoxetine in a double-blind study.[180]

Finally, in some patients with Tourette's syndrome and OCD refractory to fluvoxamine treatment, the addition of pimozide or haloperidol was useful in reducing OCD symptoms.[186,187]

6.1.3 Other Drugs

Some degree of improvement of OCD has been reported with the use of risperidone,[55]clonidine,[82] naloxone,[188] and naltrexone.[189]

6.2 Attention-Deficit Hyperactivity Disorder (ADHD)

6.2.1 Psychostimulants

Psychostimulants such as dextroamphetamine, methylphenidate or pemoline are likely the most

effective drugs for ADHD associated with Tourette's syndrome. Although initial reports suggested that psychostimulants might induce or exacerbate tics,[190-198] some single- or double-blind, placebo-controlled studies have shown that low doses of stimulants can improve ADHD symptoms without significant exacerbation of tics.[199-205] However, 25 to 30% of patients do not improve with these drugs and their long-term adverse effects are not well known.[206] For these reasons, long-term use of psychostimulants is not recommended, and their use in patients with Tourette's disorder should be undertaken with caution.

6.2.2 Other Drugs

An improvement of ADHD in patients with Tourette's syndrome has been reported with clonidine,[78,83,207,208] guanfacine,[87] selegiline (deprenyl),[129,130] desipramine,[208,209] imipramine,[210] nortriptyline,[211] sertraline,[212] pimozide,[51] and clonazepam.[90]

7. Nonpharmacological Therapies

Nonpharmacological therapies use in the treatment of patients with Tourette's syndrome, which have reported to produce an improvement include hypnotherapy,[213] biofeedback,[214] conductual therapies[215,216] including relaxation therapy,[217,218,219] sequential application of major habit-reversal components,[215,219] self-monitoring,[215] differential reinforcement,[220] competing responses,[221] and electroconvulsive therapy.[222,223] Wu et al.[224] reported a 92.3% of effective rate in patients who received acupuncture treatment, with higher cure rates in children aged 11 to 15 years than in children aged 6 to 10 years.

Surgery for Tourette's disorder must be considered as experimental, because the experience is limited and the possible risk/benefit ratio is not well-known.[225] The possibility of severe sequelae must be kept in mind.[226] Prefrontal leucotomy or cingulotomy could be indicated in patients with severe OCD,[227,228] although the initial improvement is not maintained in some patients.[229] Recently, Vandewalle et al.[230] have shown a marked improvement of tics in a patient with high frequency stimulation of nucleus ventral oralis of the thalamus internus. Indeed, this could be an interesting approach for patients with severe Tourette's syndrome refractory to medical therapy.

8. Conclusion

Current pharmacotherapy for Tourette's disorder is not completely satisfactory, because the efficacy is limited and adverse effects are not infrequent, especially in children. When therapy is needed because there is functional impairment, it seems reasonable to use those drugs with the least adverse effects at the lowest doses possible. Among antipsychotics, the best established and tolerated is pimozide. Clonidine is also useful both for the treatment of tics and ADHD. Although the experience with atypical antipsychotics is limited, some recent studies suggested a good effect in the control of tics and better tolerability than that of classical antipsychotics. SSRIs are the treatment of choice of OCD and, although methylphenidate and other psychostimulants can improve ADHD, these drugs are not generally recommended. The potential usefulness of other promising drugs for the treatment of Tourette's syndrome awaits confirmation.

References

1. Robertson MM. The Gilles de la Tourette syndrome: the current status. Br J Psychiatry 1989; 154: 147-69
2. Singer HS, Walkup JT. Tourette syndrome and other tic disorders. Diagnosis, pathophysiology, and treatment. Medicine (Baltimore) 1991; 70: 15-32
3. Suchowerski O. Gilles de la Tourette syndrome. Can J Neurol Sci 1994; 21: 48-52
4. Lajonchere C, Nortz M, Finger S. Gilles de la Tourette and the discovery of Tourette syndrome. Arch Neurol 1996; 53: 567-74
5. Jiménez-Jiménez FJ, García-Ruiz PJ, Zurdo M. Síndrome de Tourette. In: Jiménez-Jiménez FJ, Luquin MR, Molina JA, editors. Tratado de los trastornos del movimiento. Madrid: IM&C 1998: 931-64
6. The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. Arch Neurol 1993; 50: 1013-6
7. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington DC: American Psychiatry Press, 1994
8. Cardoso F, Veado CC, de Oliveira JT. A Brazilian cohort of patients with Tourette's syndrome. J Neurol Neurosurg Psychiatry 1996; 60: 209-12
9. Tanner CM, Goldman SM. Epidemiology or Tourette's syndrome. Neurol Clin 1997; 15: 395-402

10. Pauls DL, Leckman JF. The inheritance of Gilles de la Tourette's syndrome and associated behaviors: evidence for autosomal dominant transmission. N Engl J Med 1986; 315: 993-7
11. Price RA, Pauls DL, Kruger SD, et al. Family data support a dominant major gene for Tourette syndrome. Psychiatry Res 1988; 24: 251-61
12. Pauls DL, Pakstis AJ, Kurlan R, et al. Segregation and linkage analyses of Tourette's syndrome and related disorders. J Am Acad Child Adolec Psychiatry 1990; 29: 195-203
13. Robertson MM, Gourdie A. Tourette syndrome in a large British pedigree. Associated psychopathology, severity, and potential for linkage analysis. Br J Psychiatry 1990; 156: 515-21
14. Curtis D, Robertson MM, Gurling HM. Autosomal dominant gene transmission in a large kindred with Gilles de la Tourette syndrome. Br J Psychiatry 1992; 160: 845-9
15. Eapen V, Pauls DL, Robertson MM. Evidence for autosomal dominant transmission in Tourette's syndrome. United Kingdom cohort study. Evidence for autosomal dominant transmission in Tourette's syndrome. United Kingdom cohort study. Br J Psychiatry 1993; 162: 593-6
16. Kurlan R, Behr J, Medved L, et al. Transient tic disorder and the spectrum of Tourette's syndrome. Arch Neurol 1988; 45: 1200-1
17. Van de Wetering BJM, Heutink P. The genetics of the Gilles de la Tourette syndrome. A review. J Lab Clin Med 1993; 121: 638-45
18. Kurlan R, Bher J, Medved L, et al. Familial Tourette's syndrome: report of a large pedigree and potential for linkage analysis. Neurology 1986; 36: 772-6
19. Kurlan R, Eapen V, Stern J, et al. Bilinear transmission in Tourette's syndrome families. Neurology 1994; 44: 2336-42
20. McMahon WM, van der Wetering BJ, Filloux F, et al. Bilineal transmission and phenotypic variation of Tourette's disorder in a large population. J Am Acad Child Adolesc Psychiatry 1996; 35: 672-80
21. Comings ED, Comings BG, Knell E. Hypothesis: homozygosity in Tourette syndrome. Am J Med Genet 1989; 34: 413-21
22. Walkup JT, LaBuda MC, Singer HS, et al. Family study and segregation analysis of Tourette syndrome: evidence for a mixed model of inheritance. Am J Hum Genet 1996; 59: 684-93
23. Bressman S, Greene P. Treatment of hyperkinetic movement disorders. Neurol Clin 1990; 8: 51-75
24. Scahill L, Chappel PB, King RA, et al. Pharmacologic treatment of tic disorders. Child Adolesc Psychiatry Clin N Am 2000; 9: 99-117
25. Regeur L, Werdelin L, Pakkenberg H, et al. Pharmacological treatment of Gilles de la Tourette's syndrome. CNS Drugs 1994; 2: 191-8
26. Seignot MJN. Un cas de maladie des tics de Gilles de la Tourette gueri par le R-1625. Ann Med Psychol 1961; 119: 578-9
27. Caprini G, Melotti V. Un grave syndrome ticcosa guerita con haloperidol. Riv Sper Freniatr Med Leg Ailen Ment 1961; 85: 191-6
28. Lucas AR. Gilles de la Tourette's disease in children: treatment with haloperidol. Am J Psychiatry 1967; 124: 243-5
29. Shapiro AK, Shapiro E. Treatment of Gilles de la Tourette's syndrome with haloperidol. Br J Psychiatry 1968; 114: 345-50
30. Boris M. Gilles de la Tourette's syndrome: remission with haloperidol [letter]. JAMA 1968; 205: 648-9
31. Ford CV, Gottlieb F. An objective evaluation of haloperidol in Gilles de la Tourette's syndrome. Dis Nerv Syst 1969; 30: 328-32
32. Craven EM. Gilles de la Tourette syndrome treated with haloperidol [letter]. JAMA 1969; 210: 134
33. Bixby Jr EW. Haloperidol for the Gilles de la tourette syndrome [letter]. JAMA 1970; 211: 663
34. Shapiro AK, Shapiro E, Bruun RD, et al. Treatment of Tourette's syndrome with haloperidol. Review of 34 cases. Am J Psychiatry 1973; 28: 92-7
35. Perera HV. Two cases of Gilles de la Tourette's syndrome treated with haloperidol. Br J Psychiatry 1975; 127: 324-6
36. Bruun RD, Shapiro AK, Shapiro E, et al. A follow-up of 78 patients with Gilles de la Tourette's syndrome. Am J Psychiatry 1976; 133: 944-7
37. Clarke DJ, Ford R. Treatment of refractory Tourette syndrome with haloperidol decanoate. Acta Psychiatr Scand 1988; 77: 495-6
38. Mikkelsen EJ, Detlor J, Cohen DJ. School avoidance and social phobia triggered by haloperidol in patients with Tourette's disorder. Am J Psychiatry 1981; 138: 1572-6
39. Troung DD, Bressman S, Shale H, et al. Clonazepam, haloperidol, and clonidine in tic disorders. South Med J 1988; 81: 1103-5
40. Silva RR, Muñoz DM, Daniel W, et al. Causes of haloperidol discontinuation in patients with Tourette's disorder: management and alternatives. J Clin Psychiatry 1996; 57: 129-35
41. Robertson MM, Stern JS. Gilles de la Tourette syndrome: symptomatic treatment based on evidence. Eur Child Adolesc Psychiatry 2000; 9 Suppl. 1: I 60-75
42. Ross MS, Moldofsky H. A comparison of pimozide and haloperidol in the treatment of Gilles de la Tourette's syndrome. Am J Psychiatry 1978; 135: 585-7
43. Shapiro AK, Shapiro E, Einsenkarft GJ. Treatment of Gilles de la Tourette syndrome with pimozide. Am J Psychiatry 1983; 140: 1183-6
44. Shapiro AK, Shapiro E. Controlled study of pimozide vs. placebo in Tourette's syndrome. J Am Acad Child Psychiatry 1984; 23: 161-73
45. Regeur L, Pakkenberg B, Fog R, et al. Clinical features and long-term treatment with pimozide in 65 patients with Gilles de la Tourette's syndrome. J Neurol Neurosurg Psychiatry 1986; 49: 791-5
46. Shapiro AK, Shapiro E, Fulop G. Pimozide treatment of tic and Tourette disorders. Pediatrics 1987; 79: 1032-9
47. Shapiro E, Shapiro AK, Fulop G, et al. Controlled study of haloperidol, pimozide and placebo for the treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1989; 46: 722-30
48. Sandor P, Musisi S, Moldofsky H, et al. Tourette syndrome: a follow-up study. J Clin Psychopharmacol 1990; 10: 197-9
49. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. Am J Psychiatry 1997; 154: 1057-62
50. Fulop G, Phillips RA, Shapiro AK, et al. ECG changes during haloperidol and pimozide treatment of Tourette's disorder. Am J Psychiatry 1987; 144: 673-5
51. Sallee FR, Sethuraman G, Rock CM. Effects of pimozide on cognition in children with Tourette's syndrome: interaction with comorbid attention deficit hyperactivity disorder. Acta Psychiatr Scand 1994; 90: 4-9
52. Tourette Syndrome Study Group. Short-term versus longer term pimozide therapy in Tourette's syndrome: a preliminary study. Neurology 1999; 52: 874-7
53. Van der Linden C, Bruggeman R, van Woerkom TC. Serotonin-dopamine antagonist and Gilles de la Tourette's syndrome: an open pilot dose-titration study with risperidone. Mov Disord 1994; 9: 687-8
54. Stamenkovic M, Aschauer H, Kasper S. Risperidone for Tourette's syndrome [letter]. Lancet 1994; 344: 1577-8

55. Giakas WJ. Risperidone treatment for Tourette's disorder patient with comorbid obsessive-compulsive disorder [letter]. Am J Psychiatry 1995; 152: 1097-8
56. Shulman LM, Singer C, Weiner WJ. Risperidone in Gilles de la Tourette syndrome [letter]. Neurology 1995; 45: 1419
57. Lombroso PJ, Scahill L, King RA, et al. Risperidone treatment of children and adolescents with chronic tic disorders: a prelimininary report. J Am Acad Child Adolesc Psychiatry 1995; 34: 1147-52
58. Bruun RD, Budman CL. Risperidone as a treatment for Tourette's syndrome. J Clin Psychiatry 1996; 57: 29-31
59. Bhadrinath BR. Olanzapine in Tourette syndrome [letter]. Br J Psychiatry 1998; 172: 366
60. Stamenkovic M, Schindler SD, Aschauer HN, et al. Effective open-label treatment of Tourette's disorder with olanzapine. Int Clin Psychopharmacol 2000; 15: 23-8
61. Onofrj M, Paci C, D'Andramatteo G, et al. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. J Neurol 2000; 247: 443-6
62. Caine ED, Polinsky RJ, Kartzinel R, et al. The trial use of clozapine for abnormal involuntary movement disorders. Am J Psychiatry 1979; 136: 317-20
63. Schmider J, Hoff P. Clozapine in Tourette's syndrome [letter]. J Clin Psychopharmacol 1998; 18: 88-9
64. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000; 39: 292-9
65. Singer HS, Gammon K, Quaskey S. Haloperidol, fluphenazine and clonidine in Tourette syndrome: controversies in treatment. Pediatr Neurosci 1986; 12: 71-4
66. Goetz CG, Tanner CM, Klawans HL. Fluphenazine and multifocal tic disorders. Arch Neurol 1984; 41: 271-2
67. Yvonneau M, Bezard P. Sur un cas de maladie des tics bloquee par le sulpiride. Étude psycho-biologique. Encéphale 1970; 59: 439-59
68. Trillet M, Moreau T, Dalery J, et al. Traitement de la maladie de Gilles de la Tourette par l'amisulpride. Presse Méd 1990; 19: 175
69. Robertson MM, Schnieden V, Lees AJ. Management of Gilles de la Tourette syndrome using sulpiride. Clin Neuropharmacol 1990; 13: 229-35
70. Eggers CH, Rothenberger A, Berghaus U. Clinical and neurobiological findings in children suffering from tic disease following treatment with tiapride. Eur Arch Psychiatr Neurol Sci 1988; 237: 223-9
71. Smirnov AI. O primenenii metoklopramida (tserukala) pri sindrome Turetta. Zh Nevropatol Psikhiatr 1989; 89: 105-8
72. Uhr SB, Pruitt B, Berger PA, et al. Improvement of symptoms in Tourette syndrome by piquindone, a novel dopamine-2 receptor antagonist. Int Clin Psychopharmacol 1986; 1: 216-20
73. Jankovic J, Glaze DG, Frost Jr JD. Effect of tetrabenazine on tics and sleep of Gilles de la Tourette's syndrome. Neurology 1984; 34: 688-92
74. Vieregge P. Tetrabenazine in the treatment of senile vocal tics [letter]. J Neurol 1987; 235: 126-7
75. Jankovic J, Orman J. Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias. Neurology 1988; 38: 391-4
76. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997; 48: 358-62
77. Cohen DJ, Young JG, Nathanson JA, et al. Clonidine in Tourette's syndrome. Lancet 1979; 2: 551-3
78. Cohen DJ, Detlor J, Young JG, et al. Clonidine ameloriates Gilles de la Tourette syndrome. Arch Gen Psychiatry 1980; 37: 1350-7
79. Leckman JF, Cohen DJ, Detlor J, et al. Clonidine in the treatment of Tourette syndrome: a review of the data. Adv Neurol 1982; 35: 391-401
80. Leckman JF, Detlor J, Harcherick DF, et al. Short- and long-term treatment of Tourette's syndrome with clonidine: a clinical perspective. Neurology 1985; 35: 343-51
81. Mesulam MM, Petersen RC. Treatment of Gilles de la Tourette's syndrome: eight-year, practice based experience in a predominantly adult population. Neurology 1987; 37: 1828-33
82. Leckman JF, Hardin MT, Riddle MA, et al. Clonidine treatment of Gilles de la Tourette's syndrome. Arch Gen Psychiatry 1991; 48: 324-8
83. Lichter DG, Jackson LA. Predictors of clonidine response in Tourette syndrome: implications and inferences. J Child Neurol 1996; 11: 93-7
84. Gancher S, Conant-Norville D, Angell R. Treatment of Tourette's syndrome with transdermal clonidine: a pilot study. J Neuropsychiatry Clin Neurosci 1990; 2: 66-9
85. Goetz CG, Tanner CM, Wilson RS, et al. Clonidine and Gilles de la Tourette's syndrome: double-blind study using objective rating methods. Ann Neurol 1987; 21: 307-10
86. Leckman JF, Ort S, Caruso KA, et al. Rebound phenomena in Tourette's syndrome after abrupt withdrawal of clonidine: behavioral, cardiovascular and neurochemical effects. Arch Gen Psychiatry 1986; 43: 1168-71
87. Chappell PB, Riddle MA, Scahill L, et al. Guanfacine treatment of comorbid attention-deficit hyperactivity disorder and Tourette's syndrome: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry 1995; 34: 1140-6
88. Gonce M, Barbeau A. Seven cases of Gilles de la Tourette's syndrome: a partial relief with clonazepam: a pilot study. Can J Neurol Sci 1977; 4: 279-83
89. Goetz CG. Clonidine and clonazepam in Tourettes syndrome. Adv Neurol 1992; 58: 245-51
90. Steingard R J, Goldberg M, Lee D, et al. Adjuntive clonazepam treatment of tic symptoms in children with comorbid tic disorders and ADHD. J Am Acad Child Adolesc Psychiatry 1994; 33: 394-9
91. Kurlan R. Tourette syndrome. Treatment of tics. Neurol Clin 1997; 15: 403-9
92. Gillman M A, Sandyk R. Clonazepam-induced Tourette syndrome in a subject with hyperkplexia [letter]. Postgrad Med J 1987; 63: 311-2
93. Jenner P, Pratt JA, Marsden CD. Mechanism of action of clonazepam in relation to effects of GABA and 5-HT. Adv Neurol 1986; 43: 629-43
94. Chung Hwang E, Van Woert MH. Antimyoclonic action of clonazepam: the role of serotonin. Eur J Pharmacol 1979; 23: 31-40
95. Krishnamoorthy PV. Evidence for synergism between the antimyoclonic action of hydroxytryptophan and clonazepam in rats. Eur J Pharmacol 1988; 149: 331-5
96. Tenn CC, Niles LP. Central type benzodiazepines receptors mediate the antidopaminergic effect of clonazepam and melatonin in 6-hydroxydopamine lesioned rats: involvement of a GABAergic mechanism. J Pharmacol Exp Ther 1995; 274: 84-9
97. Tenn CC, Niles LP. Mechanism underlying the antidopaminergic effect of clonazepam and melatonin in striatum. Neuropharmacology 1997; 36: 1659-63
98. Goldstein JA. Nifedipine treatment of Tourettes syndrome [letter]. J Clin Psychiatry 1984; 45: 360
99. Berg R. A case of Tourette's syndrome treated with nifedipine [letter]. Acta Psychiatr Scand 1985; 72: 400-1

100. Walsh TL, Lavenstein B, Licamele W, et al. Calcium antagonists in the treatment of Tourettes syndrome [letter]. Am J Psychiatry 1986; 143: 1467-8
101. Jiménez-Jiménez FJ, García-Ruiz PJ, García de Yébenes J, et al. Nicardipine improves motor tics. Eur J Neurol 1997; 4: 498-501
102. Micheli F, Gatto M, Lekhuniec E, et al. Treatment of Tourettes syndrome with calcium antagonists. Clin Neuropharmacol 1990; 13: 77-83
103. Martí-Masso JF, Carrera N, De la Puente E. Posible parkinsonismo por cinarizina. Med Clin Barc 1985; 85: 614-6
104. Cortelli P, Santucci M, Righetti F, et al. Neuroendocrinological effect of an antidopaminergic effect of flunarizine. Acta Neurol Scand 1988; 77: 289-92
105. Giménez-Roldán S, Mateo D. Cinnarizine induced parkinsonism: susceptibility related to aging and essential tremor. Clin Neuropharmacol 1989; 14: 156-64
106. García-Ruiz PJ, García de Yébenes J, Jiménez-Jiménez FJ, et al. Parkinsonism associated with calcium channel blockers: a prospective follow-up study. Clin Neuropharmacol 1992; 15: 19-26
107. García-Ruiz PJ, Mena MA, Peñafiel N, et al. Cinnarizine induced parkinsonism in primates. Clin Neuropharmacol 1992; 15: 152-4
108. García-Albea E, Jiménez-Jiménez FJ, Ayuso-Peralta L, et al. Parkinsonism unmasked by verapamil. Clin Neuropharmacol 1993; 16: 263-5
109. García-Ruiz PJ. Calcium channel blockers and movement disorders. Eur J Clin Res 1997; 9: 9-20
110. De Vries DJ, Beart PM. Competitive inhibition of H3 spiperone binding to D2 dopamine receptors in striatal homogenates by organic calcium channel antagonists and polyvalent cations. Eur J Pharmacol 1985; 106: 133-9
111. Pileblad E, Carlsson A. The Ca antagonist nimodipine decreases and the Ca agonist BAY K 8644 increases catecholamines synthesis in mouse brain. Neuropharmacology 1987; 26: 101-6
112. Mena MA, García de Yébenes MJ, Tabernero C, et al. Effect of calcium antagonists on the dopamine system. Clin Neuropharmacol 1995; 18: 410-26
113. Gelb D, Lowenstein D, Aminoff M . Controlled trial of Botulinum toxin injections in the treatment of spasmodic torticollis. Neurology 1989; 39: 80-4
114. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. J Neurol Neurosurg Psychiatry 1990; 53: 640-3
115. Greene P, Kang U, Fahn S, et al. Double-blind placebo controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology 1990; 40: 1213-8
116. Koman LA, Mooney JF, Smith BP, et al. Management of spasticity in cerebral palsy with botulinum A toxin: report of a preliminary, randomized, double blind trial. J Pediatr Orthop 1994; 14: 299-303
117. García-Ruiz PJ, Pascual-Pascual I, Sanchez-Bernardos V. Progressive response to botulinum toxin in cerebral palsy. Eur J Neurol 2000; 7: 191-3
118. Jankovic J. Botulinum toxin in the treatment of dystonic tics. Mov Disord 1994; 9: 347-9
119. Awaad Y. Tics in Tourette syndrome: new treatment options. J Child Neurol 1999; 14: 316-9
120. Kwak C H, Hanna PA, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol 2000; 57: 1190-3
121. Scott BL, Jankovic J, Donovan DT. Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. Mov Disord 1996; 11: 431-3
122. Salloway S, Stewart CF, Israeli L, et al. Botulinum toxin for refractory vocal tics. Mov Disord 1996; 11: 746-8
123. Trimble MR, Whurr R, Brookes G, et al. Vocal tics in Gilles de la Tourette syndrome treated with botulinum toxin injections. Mov Disord 1998; 13: 617-9
124. Feinberg M, Carroll BJ. Effects of dopamine agonists and antagonists in Tourette's disease. Arch Gen Psychiatry 1979; 36: 979-85
125. Lipinski JF, Sallee FR, Jackson C, et al. Dopamine agonist treatment of Tourette disorder in children: results of an open-label trial of pergolide. Mov Disord 1997; 12: 402-7
126. Gilbert D L, Sheturaman G, Sine L, et al. Tourettes syndrome improvement with pergolide in a randomized double blind, crossover trial. Neurology 2000; 28: 1310-5
127. Goetz CG, Stebbins GT, Thelen JA. Talipexole and adult Gilles de la Tourette's syndrome: double-blind, placebo-controlled clinical trial. Mov Disord 1994; 9: 315-7
128. Dursun SM, Burke JG, Reveley MA. Buspirone tratment of Tourette's syndrome [letter]. Lancet 1995; 345: 1366-7
129. Jankovic J. Deprenyl in attention deficit associated with Tourette's syndrome. Arch Neurol 1993; 50: 286-8
130. Feigin A, Kurlan R, McDermott MP, et al. A controlled trial of deprenyl in children with Tourette's syndrome and attention deficit hyperactivity disorder. Neurology 1996; 46: 965-8
131. Toren P, Laor N, Cohen DJ, et al. Ondansetron treatment in patients with Tourette's syndrome. Int Clin Psychopharmacol 1999; 14: 373-6
132. Bonnier C, Nassogne MC, Evrard P. Ketanserine treatment of Tourette's syndrome in children [letter]. Am J Psychiatry 1999; 156: 1122-3
133. Cath DC, Gijsman HJ, Schoemaker RC, et al. The effect of m-CPP on tics and obsessive-compulsive phenomena in Gilles de la Tourette syndrome. Psychopharmacology (Berl) 1999; 144: 137-43
134. Sanberg PR, Fogelson HM, Manderscheid PZ, et al. Nicotine gum and haloperidol in Tourette's syndrome [letter]. Lancet 1988; I: 592
135. McConville BJ, Fogelson MH, Norman AB, et al. Nicotine potentiation of haloperidol in reducing tic frequency in Tourette's disorder [letter]. Am J Psychiatry 1991; 148: 793-4
136. McConville BJ, Sanberg PR, Fogelson MH, et al. The effects of nicotine plus haloperidol compared to nicotine only and placebo nicotine only in reducing tic severity and frequency in Tourette's disorder. Biol Psychiatry 1992; 31: 832-40
137. Silver AA, Sanberg PR. Transdermal nicotine patch and potentiation of haloperidol in Tourette's syndrome [letter]. Lancet 1993; 342: 182
138. Dursun SM, Reveley MA, Bird R, et al. Long-lasting improvement of Tourette's syndrome with transdermal nicotine. Lancet 1994; 344: 1577
139. Silver AA, Shytle RD, Philipp MK, et al. Case study: long-term potentiation of neuroleptics with transdermal nicotine in Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1996; 35: 1631-6
140. Dursun SM, Reveley MA. Differential effects of transdermal nicotine on microstructured analyses of tics in Tourette's syndrome: an open study. Psychol Med 1997; 27: 483-7
141. Sanberg PR, Shytle RD, Silver AA. Treatment of Tourette's syndrome with mecamylamine [letter]. Lancet 1998; 352: 705-6
142. Polinsky RJ, Ebert MH, Caine ED, et al. Cholinergic treatment in the Tourette syndrome. N Engl J Med 1980; 302: 1310
143. Barbeau A. Cholinergic treatment in the Tourette syndrome. N Engl J Med 1980; 302: 1310-1
144. Stahl SM, Berger PA. Physostigmine in Tourette's syndrome: evidence for cholinergic underactivity. Am J Psychiatry 1981; 138: 240-2

145. Tanner CM, Goetz CG, Klawans HL. Cholinergic mechanisms in Tourette's syndrome. Neurology 1982; 32: 1315-7
146. Rosenberg GS, Davis KL. Precursors of acetylcholine: considerations underlying their use in Tourette's syndrome. Adv Neurol 1982; 35: 407-12
147. Moldofsky H, Sandor P. Lecithin in the treatment of Gilles de la Tourette's syndrome. Am J Psychiatry 1983; 140: 1627-9
148. Sandyk R. The effects of naloxone in Tourette's syndrome [letter]. Ann Neurol 1985; 18: 367-8
149. Kurlan R, Majumdar L, Deeley C, et al. A controlled trial of propoxyphene and naltrexone in patients with Tourette's syndrome. Ann Neurol 1991; 30; 19-23
150. Erenberg G, Lederman RJ. Naltrexone and Tourette's syndrome [letter]. Ann Neurol 1992; 31: 574
151. Meuldijk R, Colon EJ. Methadone treatment of Tourette's disorder [letter]. Am J Psychiatry 1992; 149: 139-40
152. Shapira NA, McConville BJ, Pagnucco ML, et al. Novel use of tramadol hydrochloride in the treatment of Tourette's syndrome [letter]. J Clin Psychiatry 1997; 58: 175
153. Gadoth N, Gordon CR, Streifler J. Naloxone in Gilles de la Tourette syndrome [letter]. Ann Neurol 1987; 21: 415
154. Sandyk R, Awerbuch G. Marijuana and Tourette's syndrome [letter]. J Clin Psychopharmacol 1988; 8: 444-5
155. Hemming M, Yellowlees PM. Effective treatment or Tourette's syndrome with marijuana. J Clin Psychopharmacol 1993; 7: 389-91
156. Müller-Vahl KR, Kolbe H, Dengler R. Gilles de la Tourette syndrome. Einfluss von nikotin, alkohol un marihuana auf die klinische symptomatik. Nervenartz 1997; 68: 985-9
157. Müller-Vahl KR, Kolbe H, Schneider U, et al. Cannabinoids: possible role in patho-physiology and therapy of Gilles de la Tourette syndrome. Acta Psychiatr Scand 1998; 98: 503-6
158. Müller-Vahl KR, Schneider U, Kolbe H, et al. Treatment of Tourette's syndrome with delta-9-tetrahydrocannabinol [letter]. J Clin Psychiatry 1999; 156: 495
159. Peterson BS, Leckman JF, Scahill L, et al. Steroid hormones and Tourette's syndrome: early experience with antiandrogen therapy. J Clin Psychopharmacol 1994; 14: 131-5
160. Sandyk R, Bamford CR. Estrogen as adjuvant treatment of Tourette syndrome [letter]. Pediatr Neurol 1987; 3: 122
161. Izmir M, Dursun SM. Cyproterone acetate treatment of Tourette's syndrome [letter]. Can J Psychiatry 1999; 44: 710-1
162. Leckman JF, Scahill L. Possible exacerbation of tics by androgenic steroids [letter]. N Engl J Med 1990; 322: 1674
163. Peterson BS, Zhang H, Anderson GM, et al. A double-blind, placebo-controlled, crossover trial of an antiandrogen in the treatment of Tourette's syndrome. J Clin Psychopharmacol 1998; 18: 324-31
164. Kerbeshian J, Burd L. Differential responsiveness to lithium in patients with Tourette's disorder. Neurosci Biobehav Rev 1988; 12: 247-50
165. Erickson Jr HM, Goggin JE, Messiha FS. Comparison of lithium and haloperidol therapy in Gilles de la Tourette syndrome. Adv Exp Med Biol 1977; 90: 197-205
166. Lombroso CT. Lamotrigine-induced tourettism. Neurology 1999; 52: 1191-4
167. Sotero de Menezes MA, Rho JM, Murphy P, et al. Lamotrigine-induced tic disorder: report of five pediatric cases. Epilepsia 2000; 41: 862-7
168. Chappel PB, Scahill LD, Leckman JF. Future treatments of Tourette's syndrome. Neurol Clin 1997; 15: 924-50
169. Muller N, Riedel M, Erfurth A, et al. Immunoglobulintherapie bei Gilles de la Tourette syndrom. Nervenarzt 1997; 68: 914-6
170. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 1999; 354: 1153-8
171. Leonard HL, Swedo SE, Rapoport JL, et al. Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents: a double-blind crossover comparison. Arch Gen Psychiatry 1989; 46: 1088-92
172. Yaryura-Tobias JA. Chlorimipramine in Gilles de la Tourette's disease [letter]. Am J Psychiatry 1975; 132: 1221
173. Caine ED, Polinsky RJ, Ebert MH, et al. Trial of chlorimipramine and desipramine for Gilles de la Tourette syndrome. Ann Neurol 1979; 5: 305-6
174. Moshe K, Iulian I, Seth K, et al. Clomipramine-induced tourettism in obsessive-compulsive disorder: clinical and theoretical implications. Clin Neuropharmacol 1994; 17: 338-43
175. Riddle MA, Leckman JF, Hardin MT, et al. Fluoxetine treatment of obsessions and compulsions in patients with Tourette's syndrome. Am J Psychiatry 1988; 145: 1173-4
176. Riddle MA, Hardin MT, King R, et al. Fluoxetine treatment of children and adolescents with Tourette's and obsessive compulsive disorders: preliminary clinical experience. J Am Acad Child Adolesc Psychiatry 1990; 29: 45-8
177. Como PG, Kurlan R. An open-label trial of fluoxetine for obsessive-compulsive disorder in Gilles de la Tourette syndrome. Neurology 1991; 41: 872-4
178. Kurlan R, Como PG, Deeley C, et al. A pilot controlled study of fluoxetine for obsessive-compulsive symptoms in children with Tourette's syndrome. Clin Neuropharmacol 1993; 16: 167-72
179. Eapen V, Trimble MR, Robertson MM. The use of fluoxetine in Gilles de la Tourette syndrome and obsessive compulsive behaviours: preliminary clinical experience. Prog Neuropsychopharmacol Biol Psychiatry 1996; 20: 737-43
180. Scahill L, Riddle MA, King RA, et al. Fluoxetine has no marked effect on tic symptoms in patients with Tourette's syndrome: a double-blind placebo-controlled study. J Child Adolesc Psychopharmacol 1997; 7: 75-85
181. McDougle CJ, Goodman WK, Leckman JF, et al. The efficacy of fluvoxamine in obsessive-compulsive disorder: effects of comorbid chronic tic disorder. J Clin Psychopharmacol 1993; 13: 354-8
182. Bajo S, Battaglia M, Pegna C, et al. Citalopram and fluvoxamine in Tourette's disorder [letter]. J Am Acad Child Adolesc Psychiatry 1999; 38: 230-1
183. Ruth U, Mayer-Rosa J, Schlamp D, et al. Tourette-syndrom und antidepressiva-therapie: exazerbation einer ticstorng unter paroxetin. Z Kinder Jugendpsychiatr Psychother 2000; 28: 105-8
184. Hauser RA, Zesiewicz TA. Sertraline-induced exacerbation of tics in Tourette's syndrome [letter]. Mov Disord 1995; 10: 682-4
185. Fennig S. Fennig SN, Pato M, et al. Emergence of symptoms of Tourette's syndrome during fluvoxamine treatment of obsessive-compulsive disorder. Br J Psychiatry 1994; 164: 839-41
186. Delgado PL, Goodman WK, Price LH, et al. Fluvoxamine/pimozide treatment of concurrent Tourette's and obsessive-compulsive disorder. Br J Psychiatry 1990; 157: 762-5
187. McDougle CJ, Goodman WK, Leckman JF, et al. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind placebo-controlled study in patients with and withour tics. Arch Gen Psychiatry 1994; 51: 302-8
188. Sandyk R. Naltrexone suppresses abnormal sexual behavior in Tourette's syndrome. Int J Neurosci 1988; 43: 107-10
189. Sandyk R. Naloxone abolishes obsessive-compulsive behavior in Tourette's syndrome [letter]. Int J Neurosci 1987; 35: 93-4

190. Denckla MB, Bemporad JR, MacKay MC. Tics following methylphenidate administration. A report of 20 cases. JAMA 1976; 235: 1349-51
191. Fras I, Karvalage J. The use of methylphenidate and imipramine in Gilles de la Tourette's disease in children. Am J Psychiatry 1977; 134: 195-7
192. Golden GS. The effect of central nervous system stimulants on Tourette syndrome [abstract]. Ann Neurol 1977; 2: 69-70
193. Pollack MA, Cohen NL, Friedhoff AJ. Gilles de la Tourette's syndrome. Familial occurrence and precipitation by methylphenidate therapy. Arch Neurol 1977; 34: 630-2
194. Bremness AB, Sverd J. Methylphenidate-induced Tourette's syndrome: case report [letter]. Am J Psychiatry 1979; 136: 1334-5
195. Sleator EK. Deleterious effect of drugs used for hyperactivity on patients with Gilles de la Tourette syndrome [letter]. Clin Pediatr (Phila) 1980; 19: 453-4
196. Lowe TL, Cohen DJ, Detlor J, et al. Stimulant medications precipitate Tourette's syndrome [letter]. JAMA 1982; 247: 1168-9
197. Lowe TL Cohen DJ, Detlor J, et al. Stimulant medications precipitate Tourette's syndrome. JAMA 1982; 247: 1729-31
198. Erenberg G, Cruse RP, Rothner AD. Gilles de la Tourette's syndrome: effects of stimulant drugs. Neurology 1985; 35: 1346-8
199. Sverd J, Gadow KD, Paolicelli LM. Methylphenidate treatment of attention-deficit hyperactivity disorder in boys with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1989; 28: 574-9
200. Gadow KD, Nolan EE, Sverd J. Methylphenidate in hyperactive boys with comorbid tic disorder: II. Short-term behavioural effects in school settings. J Am Acad Child Adolesc Psychiatry 1992; 31: 462-71
201. Lipkin PH, Goldstein IJ, Adesman AR. Tics and dyskinesias associated with stimulant treatment in attention-deficit hyperactivity disorder. Arch Pediatr Adolesc Med 1994; 148: 859-61
202. Gadow KD, Nolan E, Sprafkin J, et al. School observations of children with attention-deficit hyperactivity disorder and comorbid tic disorder: effects of methylphenidate treatment. J Dev Behav Pediatr 1995; 16: 167-76
203. Castellanos FX. Controlled stimulant treatment of ADHD and comorbid Tourette's syndrome: effects of stimulant and dose. J Am Acad Child Adolesc Psychiatry 1997; 36: 589-96
204. Castellanos FX. Stimulants and tic disorders: from dogma to data. Arch Gen Psychiatry 1999; 56: 337-8
205. Law SF, Schachar RJ. Do typical clinical doses of methylphenidate cause tics in children treated for attention-deficit hyperactivity disorder?. J Am Acad Child Adolesc Psychiatry 1999; 38: 944-51
206. Freeman RD. Attention deficit hyperactivity disorder in the presence of Tourette's syndrome. Neurol Clin 1997; 15: 411-20
207. Steingard R, Biederman J, Spencer T, et al. Comparison of clonidine response in the treatment of attention-deficit hyperactivity disorder with and without comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 1993; 32: 350-3
208. Singer HS, Brown J, Quaskey S, et al. The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. Pediatrics 1995; 95: 74-81
209. Hoge SK, Biederman J. A case of Tourette's syndrome with symptoms of attention deficit disorder treated with desipramine. J Clin Psychiatry 1986; 47: 478-9
210. Sandyk R, Bamford CR. Beneficial effects of imipramine on Tourette's syndrome. Int J Neurosci 1988; 39: 27-9
211. Spencer T, Biederman J, Wilens T, et al. Nortriptyline treatment of children with attention-deficit hyperactivity disorder and tic disorder or Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 1993; 32: 205-10
212. Frankenburg FR, Kando JC. Sertraline treatment of attention deficity hyperactivity disorder and Tourette's syndrome [letter]. J Clin Psychopharmacol 1994; 14: 359-60
213. Culbertson FM. A four-step hypnotherapy model for Gilles de la Tourette's syndrome. Am J Clin Hypn 1989; 31: 252-6
214. O'Connor K, Gareau D, Borgeat F. Muscle control in chronic tic disorders. Biofeedback Self Regul 1995; 20: 111-22
215. Peterson AL, Azrin NH. An evaluation of behavioral treatments for Tourette syndrome. Behav Res Ther 1992; 30: 167-74
216. Carr JE, Bailey JS. A brief behavior therapy protocol for Tourette syndrome. J Behav Ther Exp Psychiatry 1996; 27: 33-40
217. Michultka DM, Blanchard EB, Rosenblum EL. Stress management and Gilles de la Tourette's syndrome. Biofeedback Self Regul 1989; 14: 115-23
218. Bergin A, Waranch HR, Brown J, et al. Relaxation therapy in Tourette's syndrome: a pilot study. Pediatr Neurol 1998; 18: 136-42
219. Woods DW, Miltenberger RG, Lumley VA. Sequential application of major habit-reversal components to treat motor tics in children. J Appl Behav Anal 1996; 29: 483-93
220. Wageman JR, Miltenberger RG, Williams DE. Treatment of a vocal tic by differential reinforcement. J Behav Ther Exp Psychiatry 1995; 26: 35-9
221. Carr JE. Competing responses for the treatment of Tourette syndrome and tic disorders. Behav Res Ther 1995; 33: 455-6
222. Swerdlow NR, Gierz M, Berkowitz A, et al. Electroconvulsive therapy in a patient with severe tic and major depressive episode. J Clin Psychiatry 1990; 51: 34-5
223. Rapoport M, Feder V, Sandor P. Response of major depression and Tourette's syndrome to ECT: a case report. Psychosom Med 1998; 60: 528-9
224. Wu L, Li H, Kang L. 156 cases of Gilles de la Tourette's syndrome treated by acupuncture. J Tradit Chin Med 1996; 16: 211-3
225. Rauch SL, Baer L, Cosgrove GR, et al. Neurosurgical treatment of Tourette's syndrome: a critical review. Compr Psychiatr 1995; 36: 141-56
226. Leckman JF, de Lotbiniere AJ, Marek K, et al. Severe disturbances in speech, swallowing, and gait following stereotactic infrathalamic lesions in Gilles de la Tourette's syndrome. Neurology 1993; 43: 890-4
227. Kurlan R, Kersun J, Ballentine Jr HT, et al. Neurosurgical treatment of severe obsessive-compulsive disorder associated with Tourette's syndrome. Mov Disord 1990; 5: 152-5
228. Robertson M, Doran M, Trimble M, et al. The treatment of Gilles de la Tourette's syndrome by limbic leucotomy. J Neurol Neurosurg Psychiatry 1990; 53: 691-4
229. Kulisevsky J, Berthier ML, Avila A. Longitudinal evolution of prefrontal leucotomy in Tourette's syndrome. Mov Disord 1995; 10: 345-8
230. Vandewalle V, van der Linden Chr, Groenewegen HJ, et al. Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of the thalamus [letter]. Lancet 1999; 353: 724

Correspondence and offprints: *Félix Javier Jiménez-Jiménez*, C/ Corregidor José de Pasamonte, 24, 3° D, E-28030 Madrid, Spain.
E-mail: fjimenezj@meditex.es