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## Gilles de la Tourette Syndrome: symptomatic treatment based on evidence

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**Abstract** The treatment of the Gilles de la Tourette syndrome has evolved from case reports, clinical experience and more recently blinded trials usually in small numbers of patients. We have reviewed the evidence available to clinicians. The oldest and still most widely prescribed drug, haloperidol, should now not be considered the first-line agent in children as other agents have superior adverse effects profiles. Symptomatic treatment should be targeted to the specific additional psychopathologies seen in the syndrome. For the treatment of tics, sulpiride, tiapride, possibly pimozone and in some cases clonidine may be considered first-line agents. Although a body of data supports pimozone, caution has to be exercised in relation to possible cardiac

effects. Antidepressants and stimulants have an important place in the management of depression, obsessionality and attention deficit hyperactivity disorder. The latter also responds to clonidine making it a rational first choice where ADHD coexists with GTS. There are a multitude of other drugs advocated in the literature in addition to reports of neurosurgery and the novel use of immune modulation. Therapeutic trials for GTS are challenging. However, further data from blinded trials are required before many of these treatments can be considered to be mainstream treatment options.

**Key words** Gilles de la Tourette syndrome – treatment – management – trials

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### Introduction

Gilles de la Tourette Syndrome (GTS) is a model neuropsychiatric disorder characterised by the presence of both multiple motor tics (involuntary jerky muscular movements, such as excessive eye blinking) and one or more vocal tics (phonic tics; involuntary noises, such as repeated throat clearing), which last for longer than a year, though do not necessarily occur concurrently (5, 187).

Before commencing a discussion of GTS it is probably well worth acknowledging that GTS is one of the most important causes of childhood tics which probably also have a variety of other causes. The area is relatively under-researched and

misunderstood. It has been shown in many studies that GTS and tics are genetically related (74), but some more recent studies have not shown this to be the case (43), suggesting that all that tic(k)s is in fact not GTS (44).

GTS used to be considered a rare condition and a somewhat bizarre curiosity, with only case reports documented in the literature (126, 132). Throughout the 1980s and the 1990s, however, the literature on GTS increased vastly, and many cohorts of GTS patients have been described.

It may be considered ironic that the early and now outmoded psychodynamic treatment of GTS was by its very nature based on aetiological theories for tics (e.g. repressed onanism i.e. a psychological disorder), whereas the modern era

of drug treatment has generally relied on empiricism, albeit in the management of a condition increasingly recognized to be “organic”. Indeed the dominant current neuropharmacological hypothesis, centring on an abnormality of the dopaminergic system, has its roots firmly in the successful use of neuroleptic agents over the last three decades rather than vice versa. Treatment issues are complex because of the catalogue of psychopathology that can be associated with GTS. This review concentrates on the clinical data available to clinicians concerning the features of the syndrome and their treatment rather than the hypotheses and biological investigations that may support them.

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### Prevalence and epidemiology

The generally accepted prevalence for GTS for some time has been around 4.2–5/10,000 (17).

Most studies examining prevalence of childhood tics have come from the United States of America, United Kingdom and Europe, but one has also been from the Far East.

One of the first investigations into the frequency reported that in a child psychiatric clinic 5 % of the youngsters were referred to the clinic because of their tics; after the author developed an interest in the area referral bias increased this figure to 17 % (189).

A comprehensive multi-stage investigation in a sparsely populated rural community examined the prevalence of a variety of disorders in 4,500 children aged 9, 11 and 13 years, in an 11-county area in the Appalachian mountains of South Eastern United States of America. Tic disorders were diagnosed in 3.5% of the children (4.3 % for boys and 2.7 % for girls). GTS was found in 0.1 % (33).

An extensive National Child Development Study investigated all children who were living in England and who were born between the 3rd and 9th of March 1958 (73). Information was gathered using questionnaires from schools, mothers and the School Health Services who completed the Medical Questionnaire after taking a medical history and conducting a physical examination of each child. The presence of tics and habit spasms were enquired about in both the Parental and Medical Questionnaires. The number of Parental and Medical Questionnaires that were completed within the stipulated time was 7,985. From the Parental Questionnaire findings, 7.6 % of children had twitches or mannerisms (2.0 % frequently; 5.6 % sometimes) and significantly more boys had tics. The medical history revealed that 5.13 % of the children had tics, the medical examination showed that 3.96 % of children had tics and again, in both instances, more boys than girls had tics (73).

A Dutch investigation of around 2,500 children between the ages of four and 16 years found rates for tics in boys of 10 % and that for girls of 9 %, peaking at the age of 10 to 11 years.

Parents were questioned using the Child Behaviour Checklist (CBCL) and the Teacher Report Form (TRF) was also used (178).

A survey of teachers in Eastern Connecticut in the USA identified tics in 10 % of children between the ages of six and 12 years (52). A thorough study of all 17-year-old adolescents who were being screened for military service in Israel gave prevalence estimates of 4.9/10,000 for boys and 3.1/10,000 for girls (7).

A Japanese study surveyed two groups of children. The index group had parents with a history of childhood tics ( $n = 57$ ) while the parents of the control group ( $n = 178$ ) had not experienced tics. At the age of eight years the prevalence of tics in the index group was 25 %, while that in the control group (representative of the general population) was 10 % (1).

A representative sample of 482 children aged six to 12 years in Buffalo City, New York State, USA were investigated in the years 1956–1957. The children and their mothers were interviewed. Tics were reported in 13 % for boys and 11 % for girls (81).

It has recently also been demonstrated that GTS is more common than previously suggested, especially in children with special needs. For instance, a study of children in a mainstream UK setting using questionnaires in addition to classroom observation and interviews identified GTS in five out of 166 pupils (i.e. 2.9 %), and tics in up to 30/166 (18 %) (94). In a population of children in schooling for emotional and behavioural difficulties a prevalence of tics as high as 65 % has been recorded (78). They are accordingly less common in less disturbed/handicapped children, e.g. 26 % in a survey of special educational needs schools (31).

There have not been many follow-up studies of childhood tics, but there are indications that the prognosis is, or can be, good. One study showed marked improvement on the whole, with 76 % showing marked improvement, 24 % showing no improvement, and 24 % having complete remission after 5 years (189). Another followed up 237 children with tics for between one and 15 years; tics had disappeared in about 50 % and were unchanged in about 6 % (174).

Thus tics are found in a substantial number of children (in many studies around 10 %) and in nearly all studies, tics were more commonly found in boys than in girls. Follow-up indicates that the majority improve.

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### Demography

GTS is found in all cultures and countries (137) and occurs three to four times more commonly in males (126, 132). It is found in all social classes, although some investigations suggest that individuals may socially underachieve (125, 146).

## Aetiology

Although it is now generally recognised that GTS is a genetic disorder the presumed genetic and neuropharmacological lesion are both of an unknown nature. Most evidence suggesting a single major gene locus (9), with autosomal dominant inheritance being most commonly reported (34, 42, 43). More recently, however, mixed/intermediate inheritance (65, 180), bilineality (79) and polygenic inheritance (32) have all been suggested as the inheritance pattern. Evidence for earlier age at onset in maternally transmitted cases has suggested a genomic imprinting effect (48). A world-wide search for the gene(s) has to date only succeeded in excluding much of the genome (67, 110).

There may be several reasons for this non-detection of gene(s), including clinical heterogeneity, incorrect definition of the clinical phenotype, and genetic heterogeneity (i.e. different gene(s) in different families). Currently, there is a large international initiative funded by the USA Tourette Syndrome Association using the sib-pair analysis method to detect the gene(s). As this does not require an assumed mechanism of inheritance, it may lead to areas of interest in the genome, despite genetic heterogeneity.

Other factors have been invoked as important environmental influences. These include perinatal factors (83, 85), streptococcal infections (97, 170), other infections (e.g. viral (20) and autoimmune factors (75)).

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## Clinical characteristics

It may be clinically useful to subdivide GTS into three types (137). The first is simple GTS (with motor and vocal tics being the predominant and almost only symptoms). Secondly, there may be "full blown GTS" (with coprolalia [inappropriate uttering of obscenities], copropraxia [the inappropriate making of obscene gestures], echolalia [copying what other people say], echopraxia [copying other people's movements], palilalia [repeating the end of one's own sentence] and palipraxia [repeating one's own actions/behaviours]). Thirdly there may be "GTS plus" (originally described by Packer (109)) in which the GTS patients may also have Attention deficit hyperactivity disorder (ADHD), Obsessive-compulsive behaviours (OCB), Self-injurious behaviours (SIB) and other psychopathology, such as depression, anxiety and personality disorders.

In the majority of studies GTS starts at the age of seven with motor tics (eye blinking, nose twitching, flicking the hair out of the face), followed by the vocal tics around the age of 11 (throat clearing, sniffing, grunting) and coprolalia (which is actually quite rare, occurring in less than a third of clinic patients), beginning at around the age of 15 (132).

## Psychopathology and associated behaviours

Much is written about the psychopathology of individuals with GTS, but most of the literature concentrates on adults, with relatively few studies addressing the subject in children. Nevertheless, in our clinical experience and reviewing the literature, it is clear that the adult data applies to the younger population in that there are fairly specific psychopathologies and behaviours in children with GTS. These include in particular OCB, ADHD, SIB and depression, all of which have treatment implications.

Several studies have documented the phenomenology and psychopathology of GTS patients. Our group demonstrated (using standardised psychiatric rating scales and interview schedules) that adult GTS patients have significant depression (125), SIB (with a highly obsessional quality (127)) and more anxiety, depression, obsessionalism and personality disorders than control populations (131,136). Others have described significant ADHD (113,164) and non-obscene socially inappropriate behaviours (80).

Despite the fact that GTS starts in childhood and it is acknowledged that these children have behavioural disturbances (185), there are relatively few studies reporting their phenomenology and psychopathology (35, 55, 88, 183), with some papers widely cited, but not employing standardized psychiatric rating scales or interview schedules (e.g. 50).

There is conflicting evidence as to whether or not tic severity is associated with behavioural problems, with Erenberg et al. (50) finding no link, and Rosenberg et al. (138) indicating a positive correlation between tic severity and behaviour problems.

Only two studies have examined depression or depressive symptomatology in GTS children (55, 186); neither however used instruments which are completed by the children themselves. Ferrari et al. (55) investigated 10 GTS children whose parents reported high levels of depression in the children. Wodrich et al. (186) used the Personality Inventory for Children to study 33 GTS children, which is completed by parents/carers rather than the children. Results indicated that the GTS children, when compared to 66 normal control children, were rated as having high psychopathology especially depression (73 %), anxiety and "peculiar behaviour/excessive worry". Our group (Robertson et al. – submitted for publication) has shown that clinic GTS children have significantly more depression and obsessionalism than their peers.

OCS (obsessive compulsive symptomatology) in children with GTS is well established, probably occurring in around 40 % of children although there are reports documenting up to 80% of patients (126). Indeed, cases of "pure" obsessive compulsive disorder (OCD) may be contaminated by tics following the earlier onset of obsessive symptoms (88). De Groot et al. (35) studied 92 children with GTS in a postal survey. OCS were determined by a 40-item questionnaire adapted from the

Leyton Obsessional Inventory (LOI) which has been widely used to assess OCS in GTS (56), but which was not specifically designed to assess children's psychopathology. There was a significant positive relationship between tic severity and OCS. Obsessions contributed to the prediction of learning problems, perfectionism, and antisocial behaviour. Compulsions contributed to the prediction of hyperactivity, psychosomatic symptoms, perfectionism and muscular tension.

Many studies have now demonstrated that the OCS/OCB seen in GTS are phenomenologically, clinically and significantly different to those seen in primary OCD (47, 56, 118, 133). It is also our clinical impression that the OCS/OCB encountered in GTS are not particularly egodystonic. Some OCS/OCB occur normally in children and decrease with age; if the OCS/OCB remain severe (and may well then be pathological), then they are often associated with high levels of anxiety (190).

There is no doubt that ADHD is very common in children with GTS. ADHD occurs in about 8–15 % of children in the general population, but in individuals with GTS it occurs in as much as 20–90 % of clinic populations (130). It is also important to note in this context that ADHD has been found to be higher than normal individuals in at least two epidemiological studies (7, 94), suggesting that ADHD may be a more integral part of GTS in at least some individuals and not merely a reflection of severity and referral bias.

Only one study to date has compared children with GTS+ADHD, compared to children with pure ADHD (164). They found that in GTS children there were high rates of OCD and ADHD. In contrast to the comorbidity with OCD, the other comorbidities (e.g. disruptive behaviours, mood disorders and anxiety disorders) were indistinguishable in comparison between children with GTS+ADHD and children with ADHD alone. These results not only suggest (once again) that there is a specific association between GTS and OCD, but also that the other psychopathology (e.g. mood and anxiety problems) could be secondary to the comorbidity with ADHD. In addition, the findings also suggested that children with GTS+ADHD had lower psychosocial functioning than children with ADHD alone (164).

There may be several reasons for GTS patients, and children in particular, having more, and in some cases fairly specific, psychopathology compared to control populations. Firstly, GTS may indeed be particularly linked with a variety of psychopathologies, e.g. SIB. Secondly, the conditions may be genetically related; for example, OCB seems particularly and genetically related to GTS (43). Thirdly, ADHD is also closely related to GTS, but there is debate as to whether all ADHD behaviours and GTS are related (30, 112) or only a subgroup (113). Fourthly, the anxiety and depression may be secondary to having a chronic stigmatising disorder (131). Fifthly, the anxiety and depression may be secondary to bullying and/or teasing at school (which has been described in

non-GTS children (142). Sixth, GTS clinic patients are subject to referral bias (12), as it seems that mild unreferred GTS cases in the community may not have excess psychopathology apart from OCB, ADHD and SIB (94, 128). Seventh, the conditions may be comorbid (i.e. two separate conditions co-existing together). Finally, one or more of these explanations may apply. All individuals are made up of a variety of complex inherited and environmental factors, and any number of these probably result in the particular makeup of an individual at a particular time of life.

Only when the GTS gene(s) are found, however, will it be clearer as to which of the above explanations are correct, and in fact, what precisely constitutes the GTS phenotype and whether or not it includes only tic phenomena or whether it includes behaviours and psychopathology as well.

Only one study has examined the psychopathology of children with tics in the general population using standardized psychiatric rating scales (94). In this recent epidemiological study in a mainstream school the psychopathology of "tic possible" children was studied, comparing them to the school population as a whole. The only observed positive association between tics and psychopathology was with teacher ratings of conduct and/or emotional disorder which were higher in tic children. In contrast to clinic proband or family populations there was no evidence of an association with depression, OCS/OCB nor ADHD.

Of importance however, is that nearly all the psychopathologies and behaviours described above when present may necessitate treatment in their own right. In our clinical experience, few, if any, children are brought to the clinic merely because of their motor and vocal tics; in the majority of cases it is because of the other difficulties, be it behaviour or psychopathology.

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## Treatment

The current treatment options include behavioural strategies, drug treatment and neurosurgery. Many agents and strategies have been advocated on the basis of case reports resulting in a rather anarchic situation.

The gathering of evidence to support the optimal management of individual patients is challenging. As detailed above, fluctuation in the severity and nature of symptoms over time is the norm. In any case the *objective* measurement of symptom severity at any one time is difficult, although improved by rating scales. In addition to these problems both clinicians and researchers face not only a wide spectrum of severity but also variations in individual responses to treatments between and within subject. Despite these difficulties in recent years several randomized treatment trials have been published. The conduct of trials varies widely, particularly in older work. Endpoints

and assessments range from self-rating subjective scales of varying complexity to standardised counting of tics using video recordings to discontinuation of drugs and measures of social intrusiveness. Much work includes both children and adults and so there is no evidence base to suggest that they should be treated in different ways apart from drug dosages. In addition many drugs are not specifically licensed for paediatric use and therefore clinicians are obliged to draw on their own clinical experience to some extent. There is also an understandable preference to cautiously protect children from the extrapyramidal effects of neuroleptics and the uncertain arena of stereotactic surgery. Further complicating the therapeutic options are small scale reports of augmentation effects between different classes of drugs, untested in trials. Likewise there are documented instances of adverse drug interactions including ECG abnormalities. With regard to this point as far as the individual drugs are concerned, one review has suggested that monitoring of cardiac and ECG parameters should be undertaken regularly with stimulants, tricyclics and clonidine (172). Many clinicians believe this to be the case for pimozide.

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## General

GTS is under-diagnosed by non-specialists and in mild cases the correct label and information about the disorder may provoke considerable relief and may be all that is required. Support organisations provide a useful role in many countries.

There is no evidence to suggest any form of treatment with the exception of surgery is any more than symptomatic in the long term. Management must therefore focus on specific symptoms and be targeted by an analysis of psychopathology and associated behaviours in individual patients. The management of "GTS plus" is significantly more challenging and multimodal than simple GTS.

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## Behavioural

Psychobehavioural methods have been applied to tics, OCD and ADHD. Despite decades of reports their use is uncertain. They are probably most useful in combination with drugs. Much of the literature relates to single cases or small series. These techniques are less easily transportable than drugs and so in practice may not be a ready part of a clinician's armamentarium particularly where a multidisciplinary approach is an ideal rather than reality. Enthusiasm for their use for tics is not now widespread, reflecting the patchy evidence.

The two most commonly invoked specific treatments for tics are "massed practice" and more recently "habit reversal

training". Massed practice essentially encourages the repetitive voluntary rehearsal of a particular tic with the aim of leading to its extinction or unlearning (26, 167, 172). As a strategy targeted to a particular anatomical location it is vulnerable to the waxing and waning nature of the syndrome; a treated tic may be replaced by another one elsewhere. Unsuccessful use of the technique has also been documented (69).

Habit reversal training uses an incompatible muscular or vocal response that physically interferes with the target tic preventing its manifestation during rehearsal (8,115). Other techniques are more general in their scope. Relaxation therapy in a controlled trial against "minimal therapy" of 23 children (mean 11.8 years) showed a trend to improvement after six weeks of weekly individual hour-long training sessions but this was not sustained at three months (11). Although this formal intervention was of limited value many patients do develop their own strategies to aid relaxation which have a bearing on tic severity. This is not an altogether simple relationship though, as children with GTS are often worse at home compared to school, relaxation at home may include the release of tics that can, or have to be, suppressed outside the family environment. Biofeedback and acupuncture have also been reported (101, 188).

Failure of behaviour therapy to have an impact in individual cases has also been reported (23, 145). Indeed, adverse effects have been noted in two cases in which motor symptoms *increased* with behavioural interventions. The authors credibly hypothesize that in focussing attention on the tics the treatments may increase the "inhibitory energy" expended leading to a worsening in the irrepressible urge to tic (21). It may be that cases like this are under-reported.

Cognitive-behavioural therapy specifically directed at OCD has a stronger foundation and is reviewed elsewhere (93). Behaviour management in ADHD using contingency reinforcement techniques (e.g. point reward system) may offer a minor and labour intensive contribution with a possible drug-sparing effect (114).

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## Neuroleptics

The butyrophenone haloperidol was the first drug treatment for GTS and remains the most widely used agent world-wide. The first report of its empirical usage was in an adult with GTS who had already undergone a frontal lobectomy (123). There followed a number of case reports and small series through the 1960s and 1970s documenting efficacy of haloperidol along with some more disappointing results. One of these favourable reports describes a patient that had been obliged to undergo a catalogue of unsuccessful treatments including insulin coma (66) illustrating the important advance for patients that an effective drug treatment must have represented.

Dosage should be kept to a minimum as 2–3 mg/day is often sufficient. To avoid excessive sedation starting doses of 0.25–0.5 mg with subsequent weekly titration are recommended. The use of intramuscular long-acting haloperidol decanoate has also been advocated (111) including a case where the oral preparation was ineffective (27).

The most feared reactions in children and adults are the extrapyramidal effects – acute dystonia, parkinsonism, akathisia and tardive dyskinesia. The commonest unwanted results are sedation and drowsiness, increased appetite, dysphoria and depression. In addition to these, “fog states”, aggression, social and school phobia, amenorrhoea, galactorrhoea and gynaecomastia have also been reported. There is also the theoretical risk of neuroleptic malignant syndrome which has not yet been reported in GTS. These adverse effects are reviewed in detail elsewhere (134).

In a study of 208 GTS children on neuroleptics 34 experienced dose-related dysphoria, nine akathisia, five aggression, three “fog states” that cleared with discontinuation or treatment with primidone, and three tardive dyskinesia that resolved with time (18).

The side effects that most commonly led to discontinuation in a retrospective analysis of 28 patients (aged 10–48) using neuroleptics (haloperidol in 24 cases) were dysphoric reactions, akathisia, nervousness, sedation, dystonic reactions and cognitive dulling (157). It has been suggested, based on a retrospective analysis of 196 patients, that females are more likely to stay on haloperidol treatment (152).

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## Pimozide

The adverse effects risked with haloperidol form an incentive for each new wave of neuroleptics to be used experimentally. Pimozide, a diphenylbutylpiperidine is used extensively in North America. Pimozide antagonises both dopamine receptors with selectivity for the D1 subtype, and calcium channels but exerts less noradrenergic antagonism than haloperidol. Pharmacokinetic study has shown faster elimination in children compared to adults and significant individual variability in both groups (140). There are now several blinded placebo/crossover trials indicating that pimozide does demonstrate efficacy and has fewer adverse effects in practice.

An early trial which was a double-blind placebo-controlled study of pimozide v. haloperidol in nine patients (age 8–28 mean 18.7 years) of whom five had been previously been prescribed haloperidol unsuccessfully concluded that both drugs significantly reduced tic frequency using a tic counting endpoint. Pimozide (seven patients) was associated with fewer reports of lethargy (139).

A subsequent open label trial of 31 patients (10–50 years median 15) showed better efficacy and fewer side effects than

haloperidol using a self rating scale (154). A further 59 patients (ages 6–54 mean 17.8) treated with open label pimozide (0.5–9 mg/day) alone or in combination with clonidine or tetrabenazine showed a good clinical response in 81 % without side effects. However sedation, weight gain, depression, parkinsonism, akathisia, acute dystonia, blurred vision, slurred speech and xerostomia did occur (122).

A placebo-controlled crossover trial of 57 patients (21.1 years  $\pm$  11) with a three-week washout (single-blind placebo), then study medications for six weeks showed that both agents are more effective than placebo (max pimozide 20 mg, haloperidol 10 mg). Haloperidol was slightly more effective compared to placebo but more frequent adverse affects. The QTc interval was prolonged with pimozide, although not in the abnormal range (156).

Another double-blind placebo-controlled crossover trial using equivalent dose titration of haloperidol and pimozide (3.5, 3.4 mg/day respectively) in 22 subjects (7–16 years old) favoured pimozide with regard to both efficacy and side effects. The study design employed a two-week placebo baseline, six-week treatment arms separated by a two-week washout, and assessments using the total GTS Global Scale. Unlike haloperidol, pimozide was associated with significant differences from placebo on the primary outcome. Haloperidol caused three times as many extrapyramidal and other serious effects. Treatment limiting side effects in haloperidol were encountered in 41 %. Therefore pimozide was judged to be superior (141).

ECG abnormalities, in particular QT interval prolongation are associated with pimozide, probably related to calcium channel blocking properties and have been observed in GTS patients (57). In combination with fluoxetine, pimozide has also been reported to cause sinus bradycardia (3). For these reason regular ECG monitoring is often undertaken on an empirical basis. However, in a long-term follow-up study of 33 patients treated with haloperidol or pimozide over 1–15 years no ECG abnormalities were seen. In this report the adverse effects of both agents were similar apart from a higher incidence of acute dyskinesias and dystonias with haloperidol. Haloperidol was discontinued in 47 % compared to 8 % for pimozide (146)

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## Sulpiride

Sulpiride is used in the UK. It is a substituted benzamide with selective dopamine D2 antagonist effects again with lower incidence of extrapyramidal and autonomic adverse effects. A retrospective analysis of 63 GTS patients (6–68 mean age 29.3) treated with sulpiride (started at 100 mg bd) showed beneficial effects in 59 %. The main adverse effects were sustained drowsiness and depression which could not be

definitely linked to the medication. There were no tardive dyskinesias (129). A subsequent 14-week double-blind placebo-controlled crossover trial against fluvoxamine in 11 adult patients with GTS and OCD confirmed sulpiride's efficacy against tics with a trend towards improvement of OC symptoms (61). Tardive dyskinesia has subsequently been reported in an adult with GTS (42).

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### Tiapride

Another substituted benzamide, tiapride is commonly used in Europe. It is supported by a double-blind placebo-controlled trial in 17 children indicating a positive therapeutic effect (49).

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### Atypical neuroleptics

The atypical neuroleptics are characterised by a reduced risk of acute or subacute extrapyramidal side effects with a wider receptor pharmacology than the traditional agents.

Risperidone, a benzisoxale has a lower affinity for D2 antagonism than haloperidol, combined with 5-hydroxytryptamine (serotonin) 5-HT<sub>2A</sub> antagonism. The serotonergic action may be particularly relevant in cases with comorbid OCD making this drug a rational choice. Its use in children was reported in 1995 in a study of five subjects whose tics improved significantly. Where OCD was comorbid it improved in one of three subjects (92). There have been several further reports including an open-label trial of risperidone in 38 subjects with GTS aged 8–53 years (median 22) who had failed or experienced adverse reactions with haloperidol and clonidine. The Yale Global Tic Severity Scale was measured before and a month into treatment with 0.5–9 mg/day (mean 2.7 mg). Eight patients discontinued because of side effects, 22 (59 %) improved, seven (18 %) saw no change and one (3 %) became worse (19). However in a retrospective study of 19 patients (7–52 years, mean 24) many with OCD treated with an average daily dose of 1.5 mg, only 41 % felt that the drug had been helpful, 35 % felt that it made no difference and 24 % felt worse. Side effects were experienced by over half of the patients although there were no extrapyramidal effects (135). Although risperidone might even worsen some cases of OCD with GTS (135) it has been used in a small group of “pure” OCD (70) and as an augmenting combination with SSRIs (165).

There is also a case report of the use of olanzapine in GTS (13). Clozapine, a dibenzodiazepine with 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>3</sub> and weaker D1 antagonist properties, has not been found to be helpful in several reports which also documented the serious side effects associated with this agent (22).

Piquindone a novel pyrroloisoquinoline D2 antagonist potent in animal models but chosen for its lower potency in models of extrapyramidal symptoms was reported in three adult patients in a one month double-blind placebo-controlled crossover trial showing a “clinically obvious” effect on tics, with mild sedation being the only side effect (176).

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### Other dopaminergic agents

Tetrabenazine depletes presynaptic monoamines and antagonises postsynaptic dopamine receptors without risk of dystonia or tardive dyskinesia. Its use was reported long ago (171) and has recently been substantiated in a retrospective analysis of 47 patients of whom over half showed a marked improvement (72).

Treatment with dopamine agonists has also been successful. Pergolide has been used in open label studies (64, 90). Improvement in the latter study seemed to be correlated with the presence of restless legs syndrome which itself can be treated with pergolide. Paradoxical limb movements during sleep have been seen to be common in a small group of drug-free GTS sufferers (179). The paradoxical benefit of dopamine agonism has been explained by hypothesising a reversal of depolarising block, or a reduction of dopaminergic outflow mediated by presynaptic D2 receptors which are more sensitive to agonists than postsynaptic receptors (90). This would be consistent with a case of unsuccessful treatment with L-DOPA in a patient refractory to haloperidol (37).

The monoamine oxidase B inhibitor selegiline which has weak dopaminergic properties has also been studied in a double-blind placebo-controlled crossover study in GTS with ADHD. It included 24 subjects (mean age 12) of which 15 completed an eight-week treatment and six-week washout resulting in an improvement in ADHD and a marginal effect on tics (53).

Another illustration of the apparent two-way effect of dopaminergic drive is that “tardive Tourettism”, i.e. the emergence of features of GTS secondary to neuroleptics, have been seen after both acute and chronic usage, often on withdrawal (166).

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### Clonidine

Clonidine is a centrally acting alpha 2-noradrenergic agonist. It is active against both ADHD and tics, although its use for the latter is more common in America than the UK. It has been assessed to be the drug of first choice by one commentator (102). An early study of 25 patients was positive (29) but subsequently published views have been mixed as far as tics

are concerned. An open label comparison with haloperidol showed inferior efficacy in general (155).

In a single-blind placebo controlled trial of 13 patients aged 9–16 treated with 0.125–0.3 mg/day for more than 60 days, six responded with significant improvements in motor and phonic tics and behavioural problems with no serious side effects. Six subjects had an equivocal response (82).

However, a double-blind placebo-controlled crossover study of the effectiveness of clonidine in 30 GTS patients (both children and adults) over a six-month study period with three weekly video recordings and objective rating scales showed no efficacy in either low ( $0.0075 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) or high doses ( $0.015 \text{ mg kg}^{-1} \text{ day}^{-1}$ ) (62).

In a double-blind placebo-controlled study of desipramine and clonidine in the control of ADHD in GTS in children aged 7–13 years, desipramine was found to be superior but significantly clonidine did not alter tic severity (160). A retrospective study from the same centre, comparing clonidine, haloperidol and fluphenazine however did suggest that clonidine was helpful for tics in 47 % with few side effects. Fluphenazine was found to be effective in 24/31 patients and to have fewer side effects than haloperidol (159).

Finally, 47 GTS patients (7–48 years old) taking 3–5 mg/kg were studied in a double-blind placebo-controlled trial. Clinical ratings of tic severity improved in both groups, but more in the treatment group indicating better efficacy than placebo although not a dramatic effect (86).

A transdermal preparation is also available and has been tested in nine patients in a placebo-controlled crossover trial. Although no objective improvement was recorded, most subjects felt they had improved (60).

Although the side effect profile of clonidine is preferable to neuroleptics it includes sedation, insomnia, dry mouth, headaches and postural hypotension. It has been suggested that ECG, pulse and blood pressure should be monitored (172).

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## Guanfacine

Guanfacine, a newer and well-tolerated alpha-2 adrenergic agonist may have beneficial effects on attention without the hypotensive or sedative effects of clonidine. An open label study in 10 children (8–16 years old), the majority on 1.5 mg for four to 20 weeks, demonstrated a significant decrease in severity of motor and phonic tics and improvement in attention (25).

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## Stimulants

The use of stimulants (e.g. methylphenidate, dextroamphetamine, pemoline) in GTS is controversial (130). The majority

of reports cite methylphenidate. In a survey of over 200 Canadian GTS patients over 20 % had used stimulants (182). They are the most used class of drug for childhood ADHD but in the context of GTS the situation is complicated by the risk of exacerbating motor symptoms. Given their monoaminergic pharmacology this would be predicted, and has been observed both in the exacerbation and precipitation of tics (119). However, there are reports of tics reducing with stimulants (58, 91). Moreover, there is evidence that school functioning is more influenced by ADHD than tics (2), and so the effective control of this symptom is paramount.

Four boys with GTS and ADHD in a single-blind placebo-controlled trial of methylphenidate improved on clinical ratings and “playroom observation”, no adverse effects on tics were seen at higher doses, although some were exacerbated at lower dose (168).

A nine week placebo-controlled double-blind crossover of methylphenidate and dextroamphetamine was conducted in 20 boys with ADHD + GTS. 14 continued for one to three years, generally in combination with other psychotropics. A substantial minority experienced a consistent worsening of tics, reversible in all cases, although the majority had improvement in ADHD with acceptable effects on tics (24). An earlier double-blind study did not show clinically significant exacerbation of tics (59). Whilst this treatment has been documented to produce significant improvements in ADHD in children with tics in a double-blind study of 34 children (aged 6.1–11.9 years), complete “behavioural normalization” is often not achieved (108).

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## Antidepressants

As outlined in the first sections above, children in the GTS plus category may have comorbid depression in its own right meriting the use of antidepressants. These drugs, particularly clomipramine, also have serotonin reuptake inhibition properties which can be directed towards OCS in the context of pure OCD (28) or with GTS (120). This symptom usually requires chronic maintenance treatment. GTS without OCD in an adult has also been reported to respond to clomipramine (39) although exacerbation of GTS with antidepressants has also been reported (104). The use of tricyclic antidepressants (TCA) is limited by the common muscarinic side effects and danger in overdose.

This class of drugs is also active against ADHD in lower doses than those used in depression with reports detailing the use of desipramine, nortriptyline and imipramine (38, 68, 161–163). As mentioned above a double-blind placebo-controlled study of desipramine versus clonidine in children found the former to be superior for ADHD with no effect on tics (160). It has been suggested that TCA should not be combined



with pimozide to avoid the increased risk of intraventricular conduction delay (172).

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### Selective serotonin reuptake inhibitors (SSRIs)

The selective serotonin reuptake inhibitors (SSRIs) have been an appealing therapeutic candidate, particularly for OCD due to their serotonergic action, favourable side effect profile and safety in overdose.

Ten GTS patients (8–15 years) with primary OCD, or OCD in the context of GTS received fluoxetine at 10 or 40 mg/day for 4–20 weeks. This was well tolerated although agitation was noted in four subjects and mild gastrointestinal symptoms in two. Half the subjects responded, three of which had GTS (124). An open label study of 30 children and adults showed overall improvement in OCB in three quarters of the cases (45).

Another illustration of the variability of responses and possible augmentation effects in this group of patients is provided by the case of an adult with OCD and GTS – fluvoxamine worsened GTS and did not improve his OCD. The addition of pimozide dramatically reduced both symptoms and subsequent double-blind sequential discontinuation showed pimozide alone reduced only tics (36).

Two patients (21 and 32 years old) are reported to have responded to a combination of fluoxetine and clomipramine (a TCA) in terms of both abnormal movements and obsessive-compulsive behaviour (158). One must note however that TCA plasma levels may be substantially raised if they are used in conjunction with SSRIs.

Negative results for OCD are also available. A double-blind placebo-controlled trial of fluoxetine (20–40 mg/day) in 11 children with GTS and OCS demonstrated no significant changes in OCS but a trend towards improvement in tic severity, attention and social functioning (77).

In contrast a double-blind placebo-controlled trial of fluoxetine in 14 subjects (8–33 years), three with no obsessive compulsive features, showed no major effect on tic symptoms, although a reduction in OCD (150).

Fluvoxamine has showed an improvement of OCD with a non-significant beneficial effect on tics in a controlled trial (61) with further supportive data in a retrospective case-controlled study although patients with pure OCD fared better (96).

The side effects of SSRIs include gastrointestinal effects, headaches, restlessness and anxiety but sedation and muscarinic effects are less prominent than with the older TCA. They can however be associated with extrapyramidal effects (89), especially when used with neuroleptics (16). Fluvoxamine was reported to precipitate GTS in a 14-year-old boy with OCD. He was unresponsive to neuroleptics, but improved after withdrawal of fluvoxamine. The symptoms re-emerged with a second trial of fluvoxamine (54).

### Botulinum toxin

Botulinum toxin inhibits acetylcholine release at the neuromuscular junction, reducing muscle activity when given by intramuscular injection. This is a reversible effect lasting weeks to months in dystonias. It may be most applicable to painful dystonic tics of the face and neck but interestingly its effects sometimes seem to be more general than would be expected following a local treatment. The premonitory urge often experienced before tics are also attenuated indicating an interruption of a reflex arc by reduction of local build up of tension (71). Vocal cord injections are also possible and have been used for coprolalia (151, 175).

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### Opiates

The opioid system has been hypothesized to be of importance in GTS via modulation of the nigrostriatum (184). Opiates are a little used treatment but have been reported as case reports, e.g. oxycodone for self injurious behaviour in a 15-year-old boy whose tics were successfully treated with clonidine (147), methadone (99) and tramadol (153). In addition a double-blind randomised trial of propoxyphene (260 mg/day), naltrexone (50 mg) and placebo in 10 adults using a self reported scale showed the antagonist naltrexone to have a significant effect on tics (76).

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### Calcium antagonists

There are several reports of the successful use of calcium antagonists for tics, often with rapid responses but no controlled trials. The agents cited have been nifedipine (10, 14, 63), flunarizine (100), and verapamil (181) with an unsuccessful report of diltiazem (181). Side effects can include headache and depression. Nifedipine has also been reported to augment haloperidol (4).

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### Nicotine

Cannabinoids have been reported to strongly potentiate neuroleptic induced bradykinesia in animal models. This has been hypothesised to be mediated through a nicotinic cholinergic mechanism, raising nicotine as a therapeutic candidate (103). Nicotine gum improved GTS not controlled by neuroleptics (143). An open label study of nicotine gum in 10 patients on haloperidol and nine untreated showed significant reductions in tics (on video) during 30 min chewing and one hour fol-

lowing treatment. There was a shorter-lived effect with nicotine alone (95). These potentiating effects can last for days to weeks using nicotine patches (41).

The nicotine antagonist mecamylamine (an antihypertensive) was used in doses of up to 5 mg a day in a retrospective study of 13 patients including nine children with a mean age of 14 years. Improvements were seen in tics, mood, irritability and aggression. The authors speculate that both nicotine agonists and antagonists could be effective through prolonged inactivation of nicotinic receptors (144).

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## Hormonal

The significantly higher incidence of GTS in boys compared to girls has fuelled speculation of a hormonal influence on GTS. Some evidence of pre-menstrual exacerbation and relief at menarche has been reported (148) and it has been suggested that oestrogen may augment neuroleptics (148). The anti-oestrogen clomiphene has also been reported to be successful (149).

A preliminary trial of flutemide, a selective androgen receptor antagonist, in three adults showed an improvement in tic score of 45 to 60 %. One man's symptoms returned after five weeks of use whereas a woman has a sustained response but became depressed and suffered diarrhoea (116). This was followed by a double-blind placebo-controlled crossover trial in thirteen adults over six weeks. The drug was well tolerated producing significant reduction in motor but not phonic tic severity. The effects were modest and short-lived possibly because of physiological compensation for androgen receptor blockade (117).

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## Immunotherapy

A theory of autoimmune contribution to the aetiology of GTS has been built on an analogy with Sydenham's chorea which follows group A B-Streptococcal infection. A subgroup of children with GTS have been found to show a similar association and the presence of antineural antibodies (170). This hypothesis has supported the investigation of immune-modulating strategies including plasmapheresis, intravenous immunoglobulin, corticosteroids and penicillin all with apparent success which has sometimes been sustained, in very small numbers (169,105). This approach is an intriguing prospect for the future but should be regarded as experimental until more data is presented.

## Other drug treatments

A number of other treatments have been used in single cases or small trials on an empirical basis. Marijuana has been anecdotally recommended for tics by patients and is currently under investigation (106, 107). Lithium has been used (51, 98) but failure has also been described (15). There have been several reports of clonazepam, a benzodiazepine which acts primarily on the GABAergic system, including a single-blind comparison with clonidine which found clonazepam superior for tics in 20 children (40). To complete the deck of neuro-active drugs for which efficacy has been claimed, physostigmine, carbamazepine and buspirone have been cited but we will not discuss them further here. Details of other case reports and non-blinded trials can be found elsewhere (134).

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## Surgery

Stereotactic surgery can be considered for very severe cases. The procedures fall into four groups. Limbic and frontal procedures (e.g. anterior cingulotomy, limbic leucotomy, frontal leucotomy) can be used in combination with drug and behavioural treatments for disabling OCD or self-injurious behaviour. Procedures directed at the basal ganglia motor loop may be appropriate for tics and include ventral thalamotomy and high frequency thalamic stimulation using implanted deep brain stimulators (177). Thalamic procedures are in the majority in the literature. Lastly a case of bilateral cerebellar dentatotomy has been recorded.

Dramatic results have been presented but a comprehensive review in 1995 of published and unpublished reports covering 36 patients over the last 30 years concluded that the procedure of choice is unclear due to limited evidence and that the procedures remain experimental in this application (121). Only two paediatric cases were reviewed. A 16-year-old girl underwent bilateral ventrolateral thalamotomy in 1962 with impressive results and a 12-year-old boy received a bilateral cerebellar procedure in 1972 which was not well documented.

It may well be that selected children with a very severe disorder could benefit from life-long relief with one of these procedures but sadly the data is lacking and so surgery cannot be recommended lightly. Quite clearly it is vital that any future cases need to be rigorously documented, whatever the outcome, and should probably only take place within institutional ethically approved protocols.

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## Conclusions

The broad literature account must be made of accumulated clinical experience and the methodology of trials, with due

weight being given to randomized placebo-controlled crossover comparison studies. Whilst it is premature to state that neuroleptics should not be first-line agents because of their side effects this is probably the case for haloperidol which is still the most used agent. We would recommend instead sulpiride or tiapride. As these substituted benzamides are not available in the US and elsewhere, pimozide, for which more evidence to date has actually been presented, may also be used although the possibility of the adverse cardiac effects argue for caution. There is patchy evidence for clonidine although in the presence of ADHD this would be a sensible first choice. The stimulants continue to excite debate. The evidence justifies their judicious use for the attentional symptoms which may be most disabling. We feel that tricyclic and SSRI antidepressants are probably not significantly active against tics but obviously

should be used to treat depression in addition to their important role in OCD. In our opinion these well-documented treatments should be used first with the more *recherché* options being reserved for refractory cases, except in the context of blinded controlled and preferably randomized studies. Calcium antagonists need to be further investigated as they apparently offer the opportunity of efficacy in a comparatively benign class of drugs and the same may apply to clonazepam and the more practical modalities of immunotherapy. There are numerous intriguing case reports in the literature and these have been historically crucial in introducing neuroleptics as the first effective treatments. Patients will now be best served by larger trials which will allow clinicians to act on better evidence. The challenge of this in GTS should not be underestimated.

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