
INVITED REVIEW

Tourette syndrome, associated conditions and the complexities of treatment

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Summary

Tourette syndrome (TS) is characterized by multiple motor tics plus one or more vocal (phonic) tics, which characteristically wax and wane. It can no longer be considered the rare and bizarre syndrome that it was once thought to be. The concepts surrounding TS, and our understanding of it, are also becoming increasingly complex and, in some individuals, TS is now recognized to be associated with a wide variety of associated behaviours and psychopathologies. It is suggested that TS is heterogeneous from a variety of standpoints including

clinical presentation and psychopathology, and thus neuropharmacological responses and possibly even aetiological and genetic mechanisms. In this paper, mention is made of recent findings in epidemiology and genetics, highlighting the complexities of the disorder; these have been chosen because findings in both areas have clinical and management implications. The literature on the clinical manifestations, associated behaviours, psychopathology (and/or comorbid conditions) and management, in particular, is reviewed in detail.

Keywords: Tourette syndrome; clinical phenomenology; psychopathology; treatment

Abbreviations: ADHD = attention deficit hyperactivity disorder; BNF = British National Formulary; CCEI = Crown Crisp Experimental Index; DBT = double-blind trial; DSMs = Diagnostic and Statistical Manuals; EPSE = extrapyramidal side-effect; GAD = generalized anxiety disorder; 5-HT = 5-hydroxytryptamine; MDD = major depressive disorder; NMS = neuroleptic malignant syndrome; NOSI = non-obscene complex socially inappropriate behaviours; OCB = obsessive-compulsive behaviour; OCD = obsessive-compulsive disorder; OCS = obsessive-compulsive symptoms; PANDAS = paediatric autoimmune neuropsychiatric disorders associated with group A β -haemolytic streptococcal infections; SIB = self-injurious behaviour; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TD = tardive dyskinesia; TS = Tourette syndrome; YGTSS = Yale Global Tic Severity Scale

Introduction

Tourette syndrome (TS) used to be considered rare (see Robertson 1989, 1994), with, for many years, case reports being the only documentations in the medical literature. Recently, the literature on TS has mushroomed, with substantial cohorts of TS patients and scientifically rigorous investigations being commonly described. It used to be thought that the clinical phenomenology of TS was fairly simple and standard, e.g. as defined by the Diagnostic and Statistical Manuals (DSMs) criteria (American Psychiatric Association, 1980, 1987, 1994), but it is now recognized that TS is far from simple. There is no doubt that TS is genetic, but the precise inheritance pattern is as yet unclear. Comorbid conditions, associated behaviours and psychopathologies are

increasingly being described, but it is unclear whether or not they all represent the 'genetic' expression of the TS gene(s). Recent epidemiological studies also indicate that TS is no longer rare; but is the mild phenotype being described in family and population studies merely a forme fruste of that seen in TS clinics? In addition, apart from the inherited genetic vulnerability to TS, it has also been suggested that perinatal insults (e.g. birth injuries) and more recently (and somewhat speculatively) infections with streptococci or viruses may affect the expression of TS; clearly this has both aetiological and treatment implications.

A MEDLINE search performed in August 1998, covering the period since January 1997, using 'Tourette' as the title

keyword, identified 108 articles; as many as 31, however, were reviews of the literature. With this in mind it was decided that this review should be very specific and the review will therefore concentrate on the clinical presentation, comorbid clinical conditions and psychopathology, and then focus, in particular, on the complexities of treatment of TS.

The clinical presentation of TS will be dealt with in detail and the effects of stress on TS will also be discussed. The more common comorbid conditions such as attention deficit hyperactivity disorder (ADHD), obsessive-compulsive behaviours (OCB), self-injurious behaviours (SIBs), anxiety, depression and personality disorder will be examined. Comments will be made on the less common, but also important, aspects, such as oppositional defiant disorder, conduct disorder, aggression, learning difficulties, rage and autism. The main focus of the paper will then be on the complexities of management which have evolved alongside the recognition of the clinical complexities.

For recent reviews about other aspects the readers are referred to the following articles: genetics (Patel, 1996; Alsobrook and Pauls, 1997); epidemiology (Staley *et al.*, 1997; Tanner and Goldman, 1997); phenomenology and classification of tics (Jankovic, 1997); neurobiology (Baker *et al.*, 1995; Singer, 1997); social and educational resources (Packer, 1997); reviews of instruments used to measure aspects of TS (Kompolti and Goetz, 1997); neuropsychology (Como, 1997); autism and pervasive developmental disorders (Stern and Robertson, 1997); secondary tic disorders (Kumar and Lang, 1997); structural (Robertson, 1998) and functional (Buitelaar *et al.*, 1998) neuroimaging; and recent articles highlighting mainly current findings (Robertson and Stern, 1997, 1998).

History, prevalence and epidemiology

The first case of TS, the Marquise de Dampierre, was documented by Itard (Itard, 1825) and later by Georges Gilles de la Tourette (Gilles de la Tourette, 1885). There have been translations of some of these early case reports (e.g. Goetz and Klawans, 1982; Robertson and Reinstein, 1991) and ideas (Kushner *et al.*, 1999), but the recent and scholarly exposition of the history of TS (Kushner, 1999) is recommended for anyone interested in either TS or indeed the history of neuropsychiatry.

Originally, TS was thought to be very rare. The generally accepted prevalence figure for TS has for some time been 0.5 per 1000 (5 per 10 000) (Bruun, 1984). A careful population-based epidemiological study that systematically screened for the presence of TS among Israeli armed forces personnel reported an overall prevalence estimate of 4.28 per 10 000 (Apter *et al.*, 1992, 1993). Another recent, substantial, multistage epidemiological study reported TS in 0.1% of 4500 randomly selected children (aged 9, 11 and 13 years) in south-eastern USA (Costello *et al.*, 1996). A more recent study was undertaken by Mason and colleagues (Mason *et al.*, 1998) who examined all year 9 pupils (aged 13

and 14 years) in a randomly selected regular mainstream secondary school in West Essex, UK, in a two-stage procedure. Standardized questionnaires were completed by parents, teachers and pupils. Classroom observations were also employed to identify tics. Those pupils identified as having tics underwent a semi-structured interview, using a shortened version of the National Hospital Interview Schedule (Robertson and Eapen, 1996), by a research psychologist. Five out of 166 pupils (2.9%) satisfied DSM-III-R criteria for TS (three definite, two probable). Of importance is that only one showed no evidence at all of any hyperactivity, depression, emotional disorder or conduct disorder; four of the five were hyperactive (one satisfied DSM-IV criteria for ADHD). The Yale Global Tic Severity Scale (YGTSS) (Leckman *et al.*, 1989) scores did, however, indicate mild TS in all subjects. Tic-possible children (30 out of 166, 18%) in the same study were also evaluated. The prevalence of psychopathology such as depression, OCB and ADHD were no different in tic possibles when compared with the total school population; teachers, however, did rate them as having more emotional and conduct disorders (Mason *et al.*, 1998). The study, resulting in such a high prevalence, was criticized (Traverse, 1998), but was well defended and justified by the original authors (Banerjee *et al.*, 1998). Interestingly, however, Traverse did suggest that in his own personal experience there has been an increase in the prevalence of TS over the last 12 years (Traverse, 1998). Banerjee and colleagues pointed out in particular that the lower figures documented before (e.g. Lucas *et al.*, 1982) had relied on TS cases admitted to hospital (the Mayo clinic) (Banerjee *et al.*, 1998). In the author's experience in community research settings, the number of TS cases seen by a doctor are very few (eight out of 50; Robertson and Gourdie, 1990).

In studies in children with special educational needs in particular, the prevalence of TS has been demonstrated to be very high. Thus, Comings and colleagues working in a southern Californian school district, screened 3034 pupils referred for psycho-educational assessment from three schools over a 2-year period; they estimated that 12% of all children in special education classes had TS and that 28% fell within a broader tic diagnostic category (Comings *et al.*, 1990). Kurlan and colleagues directly examined 35 children from special education classes and 35 regular classroom children in Monroe County, New York, for the presence of tics (Kurlan *et al.*, 1994a). Of the special education students, nine (26%) had definite or probable tics, while two (6%) of the regular school children had tics; about one-third of those with tics met diagnostic criteria for TS. Eapen and colleagues directly examined children from schools in West Essex, UK. They studied 20 children from a residential school for emotional and behavioural difficulties, 27 from a residential school for children with learning difficulties, 17 'problem' children and 19 normal children from a mainstream school. Of the students with emotional and behavioural difficulties, 65% were judged to have tics, compared with 24% of students with learning difficulties ($P < 0.05$), 6% of problem children ($P < 0.003$)

and none of the normal children ($P < 0.006$); most of the affected students met diagnostic criteria for TS (Eapen *et al.*, 1997a).

To complement these recent findings, a retrospective study examining other factors in 138 children with TS found that 64 (46%) experienced a school-related problem. Regression analysis of subjects without a diagnosis of learning disability revealed that the presence of ADHD served as a significant predictor of school problems (Abwender *et al.*, 1996).

Thus, it seems that TS is more common than was previously estimated; it is more common in children, especially in those with special educational needs; and in mainstream children TS is generally mild, but may well even then be associated with hyperactivity or, in some cases, ADHD.

TS is found in all cultures, countries and racial groups and is three to four times more common in males (Robertson, 1989, 1994; Staley *et al.*, 1997; Tanner and Goldman, 1997; Robertson and Baron-Cohen, 1998). TS is found in all social classes, although some studies suggest that TS patients may well underachieve socially (Robertson *et al.*, 1988; Sandor *et al.*, 1990).

Clinical characteristics and complexities

It has been pointed out that TS is difficult to investigate as the syndrome has no definitive 'gold standard'. There is no hallmark imaging abnormality, no neuropathological lesion at post-mortem and no genetic test yet to aid symptom based clinical diagnosis (e.g. Tanner and Goldman, 1997).

TS is characterized by both multiple motor and one or more phonic tics which occur many times a day in bouts; the number, frequency and complexity of the tics change over time and they are present for at least 1 year (World Health Organization, 1992; American Psychiatric Association, 1994). The DSM-IV criteria have, however, been criticized (Comings, 1995; Freeman *et al.*, 1995; Erenberg and Fahn, 1996; Kurlan, 1997b) as, in brief, DSM-IV criteria stipulate, amongst other things, the presence of significant impairment and personal distress, which is clearly not evident in non-clinic studies (e.g. epidemiological and school populations and/or family members in genetic studies).

The main characteristics of TS appear to be independent of culture and, by and large, symptoms are similar worldwide (Robertson, 1994; Staley *et al.*, 1997; Tanner and Goldman, 1997). Motor and phonic tics are the hallmark of TS; Jankovic makes the point that the term phonic tic is preferred to vocal tic, as not all abnormal sounds and noises in TS are produced by the vocal cords (Jankovic, 1997). It is important to note that symptoms fluctuate in severity and change character within the same person; this variability of expression may contribute to diagnostic confusion and misdiagnosis (Jankovic, 1997). Jankovic elegantly describes the intimate phenomenology of tics showing how most tics encountered in TS are semi-voluntary (unvoluntary) or involuntary (suppressible). Jankovic also suggests that the characteristics of tics are such that premonitory feelings or sensations

precede the tic, they are temporarily suppressible, they are suggestible, they increase with stress but also increase with the relaxation after stress, they decrease with distraction and concentration, they wax and wane with transient remissions and they persist during sleep (Jankovic, 1997).

The age of onset of TS symptoms ranges from 2 to 21 years, with a mean of 7 years being commonly reported, and symptoms usually begin with motor tics. The onset of phonic tics is later, with a mean age of onset of 11 years. Patients also often demonstrate a variety of complicated movements including touching, licking, spitting, jumping, smelling, squatting, abnormalities of gait and forced touching (Robertson, 1994; Staley *et al.*, 1997). Premonitory feelings or 'sensory' experiences, which are distinct from the actual motor or phonic tics and precede the tics, occur in over 80% of TS patients (Cohen and Leckman, 1992; Leckman *et al.*, 1993). Tics may be abrupt in onset, fast and brief (clonic tics) or may be slow and sustained (dystonic or tonic tics) (Jankovic, 1997). Dystonic tics are more likely to be associated with premonitory sensations (Jankovic, 1997).

Coprolalia (inappropriate involuntary uttering of obscenities) occurs in less than one-third of clinic TS patients, but in few children or mild cases (Robertson, 1994), and it usually manifests itself by 15 years of age. There is some suggestion that it may be culturally determined as only 4% have true coprolalia in Japan (Nomura and Segawa, 1982) and some countries show higher figures than in USA or Europe (Staley *et al.*, 1997). Copropraxia (involuntary inappropriate obscene gestures), echolalia (imitation of sounds or words of others), echopraxia (imitation of actions of others) and palilalia (repetition of the last word, phrase or last syllable of a word uttered by the patient) occur in a substantial proportion of TS clinic patients. Whilst these clinical features are not essential to make the diagnosis, their presence would strengthen the clinician's diagnostic confidence (Robertson, 1994).

Non-obscene complex socially inappropriate behaviours (NOSI) (Kurlan *et al.*, 1996) and 'disinhibition behaviours' (Cohen and Leckman, 1992) have also been described in TS. Kurlan and colleagues surveyed 87 adolescent and adult TS patients (mean age 28 years) and reported NOSI such as insulting others (22%, e.g. aspersions on weight, height, intelligence, general appearance, breath or body odour, parts of the anatomy, racial or ethnic slurs), other socially inappropriate comments (5%) and socially inappropriate actions (14%). More often subjects described having an urge to carry out the NOSI (insulting others, 30%; other socially inappropriate comments, 26%; socially inappropriate actions, 22%), which they attempted to suppress. NOSI were usually directed at a family member (31%) or familiar person (36%), at home or in a familiar setting such as work or school; less commonly NOSI were directed at a stranger (17%) in public settings (20%). Social difficulties such as verbal arguments, school problems, fist-fights, job problems, removal from a public place and legal trouble or arrest commonly resulted. NOSI were more common in young boys and were closely

related with ADHD ($P < 0.005$) and conduct disorder ($P < 0.005$), but not OCB, and it was suggested that they may well represent part of a more general dysfunction of impulse control in TS (Kurlan *et al.*, 1996).

The course of TS is important to examine, as not only do symptoms wax and wane in the short term, but symptom patterns may well change over the individual's lifetime. By late adolescence or early adulthood, follow-up studies have consistently demonstrated an improvement in tic frequency or severity in the majority of TS patients (Bruun *et al.*, 1976; Erenberg *et al.*, 1987); this may be especially so in treated patients, as it has been shown that untreated TS patients demonstrate virtually no sustained change in their tics over time (Sandor *et al.*, 1990). A recent study (Leckman *et al.*, 1998) has demonstrated that in a single birth cohort of 36 TS patients, the mean tic onset was earlier than previously reported, being at 5.6 years ($SD = 2.3$), which was followed by a progressive pattern of tic worsening. The average age of the most severe tics was 10 years ($SD = 2.4$). In eight patients (22%) the tics were so severe during the 'worst ever' period that school functioning was significantly impaired. In most cases the severe period was followed by a decline in tic severity. By 18 years nearly half of the cohort was virtually tic free (Leckman *et al.*, 1998).

Of importance is that some investigators document a reduction of the tic-related phenomena with time, but a persistence or increase in the behavioural disorders (Erenberg *et al.*, 1987; Singer and Rosenberg, 1989; de Groot *et al.*, 1994) which will be described below.

It has been suggested (Robertson and Baron-Cohen, 1998) that it may be useful to clinically subdivide TS into: (i) 'pure TS', consisting primarily and almost solely of motor and phonic tics; (ii) 'full blown TS' which includes coprophenomena, echophenomena and paliphenomena; (iii) 'TS-plus' (originally coined by Packer, 1997), in which an individual also has ADHD, significant OCB or obsessive-compulsive disorder (OCD) and SIB. Others with severe psychopathology (e.g. depression, anxiety, personality disorders and other difficult and antisocial behaviours) may also be included in this group.

In summary, it can be seen that although the basic clinical picture of TS, i.e. the motor and phonic tics, is remarkably consistent irrespective of country of origin, an in-depth analysis of symptomatology reveals marked heterogeneity.

Psychopathology and associated behaviours

Many types of behaviours and psychopathologies have been reported to occur frequently in TS individuals. It is important to acknowledge once again (see Robertson, 1989) that in the author's opinion, some types of behaviour such as OCB and SIB are strongly linked to TS (see below) and are probably an integral part of the syndrome; this may now also be true for at least some types of ADHD. The other behavioural disturbances (see below) occur in a substantial proportion of TS patients and are often the reason for referral to a physician.

It is important to question whether these antisocial (in the broadest sense) behaviours are truly increased in TS or not. There are those who argue that they are increased and are therefore integral to TS (e.g. Comings and Comings, 1987; Comings, 1990). However, in the author's own experience in clinical (e.g. Robertson *et al.*, 1988, 1989, 1993, 1997), family-pedigree (Robertson and Gourdie, 1990) and school settings (Mason *et al.*, 1998), and in epidemiological (Caine *et al.*, 1988) and family-pedigree (Kurlan *et al.*, 1986, 1987; McMahon *et al.*, 1992) studies of others, the TS cases are often of mild severity, unknown to medical professionals, and are not associated with major behavioural disturbances. They may well have emotional problems, but these are probably not of the severity necessitating referral. Clinic populations of TS, on the other hand, may include severe, full blown and often TS-plus individuals, which may be reflective of referral bias (Berkson, 1946). Until the putative gene(s) is identified, however, the precise phenotype (and whether or not it includes the associated behaviours and psychopathologies) will remain unclear.

Let us now examine the individual associated behaviours and psychopathologies encountered in TS patients. The reason for considering this in detail is that recently there have been controlled studies which employ standardized rating scales and are thus more probing into the exact nature of the pathologies and their relationship to TS.

ADHD

ADHD is probably one of the most common psychiatric disorders affecting children, with prevalence estimates ranging from 2 to 15%; the aetiology of ADHD is not fully understood. As ADHD begins in early childhood, parents are often the first to note clumsiness, excessive activity, low frustration tolerance and 'accident proneness' (Towbin and Riddle, 1993). For a careful review of stand-alone hyperkinetic disorder (which includes ADHD), influences on pathogenesis, prevalence, diagnosis, comorbidity, differential diagnosis, work-up and treatment guidelines, readers are referred to the review by Taylor and colleagues (Taylor *et al.*, 1998). The present author suggests that as ADHD and TS are so intimately related, it is valuable to familiarize oneself with this ADHD literature.

As early as 1973, it was generally accepted that many children who progress to TS first manifest various behavioural disturbances often labelled as minimal brain dysfunction, hyperactivity or attention deficit disorder (Shapiro *et al.*, 1973a, b). Although diagnostic criteria have changed over time, in this review, for the sake of convenience, all these types of symptom, unless otherwise specified, will be referred to as ADHD. Components of this are a short attention span and impulsivity; hyperactivity may or may not be present (American Psychiatric Association, 1987). For a detailed history of ADHD through the DSM variants, the reader is referred to Towbin and Riddle (Towbin and Riddle, 1993).

It has been pointed out that of all the comorbid conditions

ADHD is probably the most commonly encountered in TS, as evidenced by a vast literature on the subject (Towbin and Riddle, 1993; Freeman, 1997). Although early studies found ADHD in as few as 13% of TS patients (Mak *et al.*, 1982), it is now evident that ADHD occurs in a substantial proportion of TS patients, ranging from 21 to 90% of clinic populations (Robertson and Eapen, 1992), clearly far in excess of the 2–15% (Towbin and Riddle, 1993) or 4–19% (Taylor *et al.*, 1998) in the general population. Two epidemiological studies have, however, also examined ADHD in TS. Apter and colleagues examined all those recruited into the Israeli Defence Force during 1 year and reported the rate of ADHD in people with TS to be 8.3% compared with a population point prevalence of 3.9% in individuals without TS (Apter *et al.*, 1993). Recently, Mason and colleagues undertook a school epidemiological study examining TS and tics. Of the 30 out of 167 (18%) tic possibiles, there was no increase in ADHD in tic possibiles compared with the other children, as rated by the short Connors scale; there was also no increase in hyperactivity as assessed by both the General Health and Behaviour Questionnaire, and Strength and Difficulty Questionnaire of Goodman (1994, 1997). Four out of five (80%) of the identified TS individuals (definite and probable) were, however, reported as hyperactive by their teachers, parents or both; one satisfied DSM-IV criteria for ADHD (Mason *et al.*, 1998).

It has also been pointed out that it is the symptoms of ADHD which often contribute to the behavioural disturbances, poor school performance and impaired executive functioning testing in children with TS (Singer *et al.*, 1995a).

Attentional problems and difficulties with hyperactivity and impulse control frequently precede the emergence of the actual tics (Jagger *et al.*, 1982; Singer *et al.*, 1995a). In fact, for the DSM-IV diagnosis to be made, symptoms of ADHD must be present in two or more settings before the age of 7 years; the TS tic symptoms, however, often begin later (Robertson, 1989, 1994).

Only one study to date has examined the phenomenology of 'pure' (primary) ADHD and compared it with that of TS plus ADHD (Spencer *et al.*, 1998). It was demonstrated that in TS there were increased rates of both OCD and ADHD. In contrast to the comorbidity with OCD, it was found that the other comorbidities (such as disruptive behaviours, mood disorder, anxiety disorder) were indistinguishable in the comparison between children with TS plus ADHD and children with ADHD alone. This suggests that some psychopathology (e.g. mood and anxiety) could be secondary to the comorbidity with ADHD, rather than the TS *per se*. In addition it was shown that children with TS plus ADHD had lower psychosocial functioning than children with ADHD alone (Spencer *et al.*, 1998). A more recent paper (Spencer *et al.*, 1999) compared 128 male children and adolescents with 110 controls, at baseline and 4 years later; when compared with controls, ADHD youngsters had more tic disorders initially and more new onsets at follow-up. Of

interest is that tic disorders and ADHD had independent courses, with ADHD showing markedly less remission.

Three fairly recent studies (Weiss *et al.*, 1985; Mannuzza *et al.*, 1993, 1998) in non-TS youngsters, have all demonstrated that childhood ADHD was predictive of antisocial personality disorder in adulthood. As so many TS children have ADHD symptoms, this may well account for the apparent increase in at least some of the adulthood psychopathologies in TS (e.g. personality disorder) (see below).

The precise relationship between ADHD and TS is thus complex and has stimulated debate for a long time; there appear currently to be four possibilities as to the nature of the relationship. First, there have been suggestions that the two disorders are genetically related (e.g. Comings and Comings, 1984, 1987; Knell and Commings, 1993), although this has been disputed (Pauls *et al.*, 1986a, 1988; Eapen and Robertson, 1996). The data from another study, however, have suggested a second possibility—that there may be two types of individuals with TS plus ADHD, one in whom ADHD is independent of TS and others in whom ADHD is secondary to TS (Pauls *et al.*, 1993). A third possibility is that pure ADHD and TS plus ADHD are different phenomenologically, but the exact relationship is unclear. A fourth possibility as to the cause of the apparent relationship has been put forward by Towbin and Riddle, who suggested that TS individuals may have reduced capacities for concentration, attention and impulse control, but at a level subthreshold for a DSM diagnosis of ADHD; the frequency of comorbidity therefore depends on where the cut-off point for ADHD is set (Towbin and Riddle, 1993). The three latter possibilities may well be related in some way and more research needs to be undertaken.

In the author's opinion, ADHD or similar symptoms are common in people with TS and it appears that they may occur in even mild TS cases who are identified in epidemiological studies. It is unlikely therefore to be wholly due to referral bias. Whether or not the symptoms are sufficient to warrant an actual ADHD diagnosis is as yet unknown, and whether or not the symptoms in TS plus ADHD are identical to those seen in pure ADHD has to be investigated further.

Obsessive–compulsive behaviours, symptoms and disorder

Obsessive-compulsive disorder (OCD) is characterized by persistent obsessions [recurrent, intrusive, senseless thoughts, which are egodystonic (internally uncomfortable)] or compulsions (repetitive and seemingly purposeful behaviours which are performed according to certain rules or in a stereotyped fashion); they are a significant source of distress to the individual or interfere with social or role functioning (American Psychiatric Association, 1987, 1994). Early studies reported a prevalence rate in the general population of 0.05%, but recent research suggests a lifetime prevalence rate of

between 1.9 and 3.2% (Dinan, 1995). It has been suggested that there are essentially three types of OCD: (i) familial type related to tic disorders; (ii) familial type unrelated to tics; (iii) non-familial type (Pauls *et al.*, 1995).

It is becoming increasingly evident that there is a clear and strong association between TS and OCD, both in TS patients and in their family members, with evidence for the association being obtained from phenomenological, genetic and epidemiological investigations (Robertson and Yakeley, 1993; Robertson, 1995).

At the outset the author wishes to make the point that the obsessive-compulsive symptoms (OCS) and obsessive-compulsive behaviour (OCB) encountered in TS may well be describing one and the same phenomenon, but that they are clinically and significantly different from the OCS encountered in pure OCD.

Twelve studies undertaken between 1969 and 1985 reported TS patients with obsessive-compulsive traits or illnesses, varying from single case reports to significant percentages of TS populations ranging from 11% to as high as 80% (Robertson, 1989). Substantial studies in the late 1980s also indicated that OCS/OCB were common in TS, occurring in 37% (Robertson *et al.*, 1988), 47% (van de Wetering *et al.*, 1988) and 49% (Caine *et al.*, 1988) of TS patients. One controlled study in children also suggested significant OCS/OCB in 28% of the TS group (Grad *et al.*, 1987). Clearly, all these figures are far in excess of the 1.9–3.2% for OCD in the general population (Dinan, 1995); even though the OCS/OCB in TS are different from those in OCD (see below), the high rates in TS individuals are remarkable.

Three studies have suggested that OCS/OCB in TS change with age or duration of TS. Montgomery and colleagues and Nee and colleagues both suggested that OCS/OCB increased in frequency with the duration of TS (Montgomery *et al.*, 1982; Nee *et al.*, 1982). Frankel and colleagues suggested that younger TS patients exhibited OCS/OCB related to impulse control, while older patients were more concerned with checking and arranging (Frankel *et al.*, 1986).

Robertson and colleagues reported that coprolalia and echophenomena were significantly related to OCS/OCB (Robertson *et al.*, 1988). The only study to control for depression showed that TS patients are disproportionately obsessive, which is not accounted for by depression (Robertson *et al.*, 1993).

Several elegant investigations have demonstrated significant phenomenologic differences between 'pure' (primary) OCD and the OCS/OCB encountered in TS (Frankel *et al.*, 1986; Pitman *et al.*, 1987; George *et al.*, 1993a; Holzer *et al.*, 1994; Leckman *et al.*, 1994–5; Eapen *et al.*, 1997b; Miguel *et al.*, 1997; Müller *et al.*, 1997; Zohar *et al.*, 1997; Petter *et al.*, 1998). In essence, the obsessions seen in TS have to do with sexual, violent, religious, aggressive and symmetrical themes; the compulsions are to do with checking, ordering, counting, repeating, forced touching, symmetry ('evening up'), getting things 'just right' and self-damage or

SIB. In contrast, the obsessions seen in pure OCD are to do predominantly with contamination, dirt, germs, being neat and clean, fear of something going wrong or bad happening and the fear of becoming ill; compulsions in pure OCD are mainly to do with cleaning and washing. In addition, the compulsions in OCD are preceded by cognitions and autonomic anxiety and have fewer prior sensory phenomena. Certainly, at a clinical level, the OCS/OCB in TS appear to be egosyntonic (personally comfortable), rather than the egodystonic (subjectively uncomfortable) symptoms which characterize OCD.

Other investigations have also highlighted the special phenomenology of the OCS/OCB seen in TS. Leckman and colleagues have described the 'just right' phenomenon in TS. For example, an individual would have to arrange, re-arrange and even re-arrange things further in a particular order and in certain positions or patterns until they looked 'just right' to the individual; the subtle differences in this re-arranging would probably not be discernible to other people watching (Leckman *et al.*, 1994). In another study of TS subjects with OCS/OCB, the most common obsessions concerned the fear that one might harm oneself or others, intrusive nonsense sounds, words or music, and thoughts that something terrible such as fire, death or illness might happen; common compulsions included checking, excessive washing and toothbrushing, rituals of cleaning household or inanimate objects, and counting, hoarding or collecting rituals (Hebebrand *et al.*, 1997).

In one study (George *et al.*, 1993a) the TS group reported that their compulsions arose *de novo* or spontaneously, while the pure OCD group reported that their compulsions were frequently preceded by stimuli such as guilt or worry. In another study (Eapen *et al.*, 1997b), those probands who shared a similar symptom profile to TS subjects all had a positive family history of OCD; all other OCD probands were isolated cases.

There is general agreement now that at least some forms of OCS/OCB are genetically related to TS and may well be a phenotype of the putative TS gene(s) (Pauls and Leckman, 1986; Pauls *et al.*, 1986a, b, 1991; Eapen *et al.*, 1993a). Other studies have also showed that there were elevated rates of OCB/OCD in family members of TS probands (Walkup *et al.*, 1996). In contrast, one study found no increase of OCB/OCD in family members of TS probands (Hebebrand *et al.*, 1997).

In summary, and in the author's opinion, it does appear that there are specific OCS/OCB in the majority of TS patients, but that they are significantly different to the obsessions and compulsions seen in pure OCD. In addition, the OCS/OCB in TS seem clinically less egodystonic than in pure OCD. Finally, there may well be a genetic relationship between some types of OCS/OCB/OCD and TS.

SIB

In his original paper in 1885, Georges Gilles de la Tourette described that two out of nine patients injured themselves

(Gilles de la Tourette, 1885). From 1916 to 1989 there were over a dozen case reports of SIB in TS patients (Robertson *et al.*, 1989). Investigations have reported SIB to occur in 33% (Robertson *et al.*, 1989), 34% (Steffl, 1984), 43% (Van Woert *et al.*, 1976), 48% (Nee *et al.*, 1980) and 53% (Moldofsky *et al.*, 1974) of TS patients.

In the most detailed investigation into SIB to date, Robertson and colleagues (Robertson *et al.*, 1989) reported that over one-third of clinic TS patients carried out SIB. Twenty-three types of SIB were described; 14 patients showed more than one type of SIB. The types of SIB seemed to be non-specific and were similar to that found in learning disabled/mentally retarded populations; they included head banging (47%, the most common), body punching/slapping, head or face punching/slapping, banging or poking sharp objects into the body, scratching parts of the body and, curiously, inflicting severe eye injuries. SIB was related to the severity of TS, a past psychiatric history and to psychopathology, particularly hostility and obsessionality, as measured on standardized psychiatric rating scales (Robertson *et al.*, 1989). This association between SIB and obsessionality has also been described by others both in general (e.g. McKerracher *et al.*, 1968; Gardner and Gardner, 1975) and OCD (Stinnet and Hollender, 1970; Gardner and Gardner, 1975; Primeau and Fontaine, 1987) populations. Of note is that in severe TS patients who also have OCS/OCB characterized by SIB, psychosurgery has been life-saving (e.g. Kurlan *et al.*, 1990; Robertson *et al.*, 1990a).

Of importance, however, is that even individuals with mild TS, encountered in epidemiological (Caine *et al.*, 1988) and pedigree (Robertson and Gourdie, 1990) settings, have also exhibited such SIBs.

In summary, and in the author's opinion, SIB is an important part of TS which may well be integral and not merely reflective of severity or referral bias. SIB in TS is particularly related to OCS/OCB and this clearly has treatment implications.

Anxiety

Anxiety is also common in TS patients and has been examined frequently. Zausmer studied 96 children with tics. Anxiety symptoms in the group were of four types including: sleep difficulties; tension habits; motor unrest; phobias, worries, poor concentration; they were recorded in over 80% of patients (Zausmer, 1964). Corbett and colleagues investigated children and adults with tics by means of chart reviews. In 52%, tics were the initial complaint; anxiety was documented as the most frequent symptom (Corbett *et al.*, 1969). Erenberg and colleagues reported 45% of 58 TS individuals to have extreme anxiety (Erenberg *et al.*, 1987). Coffey and colleagues investigated 84 TS patients, of whom 11 (13%) had TS with OCD and 16 (19%) had TS with non-OCD anxiety disorder (Coffey *et al.*, 1992). Chee and Sachdev reported on 50 TS adult patients using a structured schedule; 30% were found to have GAD (Chee and Sachdev, 1994).

Thibert and colleagues examined 98 responses to a mailed questionnaire and showed that the group of TS patients with high OCS/OCB scored higher on social anxiety than the general population (Thibert *et al.*, 1995).

Pitman and colleagues examined 16 TS patients, 16 OCD patients and 16 controls; results indicated that TS subjects had significantly more generalized anxiety disorder (GAD) than controls (Pitman *et al.*, 1987). Comings and Comings studied anxiety disorders in 246 patients with TS and 47 controls. Sixteen per cent of the TS patients and none of the controls experienced more than three panic attacks per week. Nineteen per cent of TS patients and none of the controls had phobias which interfered with their life; 26% of TS subjects had more than three phobias in contrast with 8.5% of controls. Fourteen per cent of TS patients and 4.2% of controls had both panic attacks and phobias (Comings and Comings, 1987).

Robertson and colleagues have examined four different TS cohorts for the presence of anxiety. First, Robertson and colleagues examined 90 clinic patients with TS using the Crown Crisp Experimental Index (CCEI, previously known as the Middlesex Hospital Questionnaire) and the Mood Adjective Checklist, both of which include anxiety subscales, as well as the Spielberger State Trait Anxiety Inventory; TS patients scored much higher on anxiety than the normative data on all three scales (Robertson *et al.*, 1988). Using the Spielberger State Trait Anxiety Inventory in two separate controlled studies, adult TS patients had significantly more state and trait anxiety than the control subjects (Robertson *et al.*, 1993, 1997). In contrast, in a group of mild TS cases (relatives of a TS proband in the family study previously referred to), the scores of the TS cases on the three anxiety subscales of the CCEI were no different from the scores of non-TS cases (Robertson and Gourdie, 1990).

In a careful genetic study, Pauls and colleagues interviewed 338 biological first degree relatives of 85 TS probands, 92 biological first degree relatives of 27 unaffected control probands and 21 non-biological first degree relatives of six adopted TS probands. The relatives of the unaffected probands and adopted TS probands served as a control sample for the whole data set. The rates of GAD were not significantly higher in the TS probands than controls; also, the rates of GAD were not significantly different between relatives of TS probands and controls, suggesting that GAD and TS are not genetically related (Pauls *et al.*, 1994).

Once again, in the author's opinion, it seems that anxiety is common in clinic TS patients, but its exact relationship to TS is as yet unclear; it may well be secondary to having moderate or severe TS.

Depression

Depression is a common disorder with a lifetime risk of ~10%, with rates almost doubled in women. It may be a mild disorder, but if severe the lifetime suicide risk is ~15%. The aetiology of depression is often multifactorial and

includes genetic factors as well as psychosocial variables such as recent adverse life events, adverse childhood circumstances (e.g. parental loss, stress or abuse), adverse current social circumstances and physical illness (Katona and Robertson, 1995).

Several studies have found both children (Ferrari *et al.*, 1984; Wodrich *et al.*, 1997) and adult TS patients to be depressed, and this may be more so in older individuals with a longer duration of illness (Robertson *et al.*, 1988). Robertson and colleagues examined 90 adult TS patients using standardized psychiatric rating scales including the Beck Depression Inventory, the Mood Adjective Checklist and the CCEI, both with depression subscales; on all three measures the TS patients' scores were substantially higher than normative data (Robertson *et al.*, 1988). TS patients have, in addition, also been found to be significantly more depressed than control groups (Comings and Comings, 1987; Robertson *et al.*, 1993, 1997); in the two studies by Robertson and colleagues, once again the Beck Depression Inventory was employed (Robertson *et al.*, 1993, 1997).

In the genetic study referred to previously, Pauls and colleagues studied TS probands and controls, examining for rates of major depressive disorder (MDD), which were significantly higher for TS probands than control subjects. MDD was also significantly increased among relatives of TS probands. When this association was examined further, however, the rate of MDD in relatives of TS plus MDD probands was higher than controls, but the rate of MDD in relatives of TS probands without MDD was no higher than controls (Pauls *et al.*, 1994). This is compatible with MDD being genetic in its own right, but not with the notion that TS and MDD are genetically related. These results are in contrast to the findings of Comings who has always considered TS and depression to be genetically related (Comings, 1990).

In a recent clinic study, bipolar affective disorder was found to occur commonly in 30% of TS patients (Berthier *et al.*, 1998). A previous epidemiological study, however, had shown only a trend towards such an association (Kerbeshian *et al.*, 1995).

In a group of mild TS cases (relatives of a TS proband in a family study by Robertson and Gourdie, referred to earlier), the scores of the TS cases on the depression subscale of the CCEI were no different from the scores of non-TS cases (Robertson and Gourdie, 1990).

This depression in TS clinic patients and probands could be explained, at least in part, by the fact that sufferers have a chronic, socially disabling and stigmatizing disease (Robertson, 1994). This depression in clinic TS patients may also be due to the side-effects of neuroleptics (depression, dysphoria; see below). In addition, it has been shown that children who have been bullied (as have many TS children encountered in clinic) may become anxious and depressed (Salmon *et al.*, 1998). Finally, it may reflect the fact that clinic attenders often have more than one problem/disorder. One must not forget, however, that depression is a common

illness and for this reason a certain proportion of TS patients could be depressed in any event, i.e. it may be a chance association.

In the author's opinion, depression is certainly associated with TS but the exact relationship is unclear. It may well be a secondary phenomenon, i.e. secondary to having moderate or severe TS, or bullying in children. In the authors' opinion, the depression in TS is highly likely to be multifactorial in origin, as is depression in non-TS populations.

Personality disorder

There is only one investigation of personality disorder in TS, but as it is an important clinical issue, the results will be discussed in detail. Robertson and colleagues examined 39 adult TS patients of whom 31 (79%) were male, with 34 age- and sex-matched controls. The TS patients were of moderate severity (YGTSS; mean 26.2, range 11–55). TS patients and controls were examined using the Structured Clinical Interview for DSM-III-R Personality Disorders II (Spitzer *et al.*, 1987; Nussbaum and Rogers, 1992) to systematically determine personality axis II personality disorders. Subjects also completed a self-rated scale for personality disorders (Dowson, 1992). Results showed that, using the Structured Clinical Interview for DSM-III-R Personality Disorders II, 25 out of 34 (64%) TS cases had one or more DSM-III-R personality disorders, compared with only two of 34 (16%) control subjects ($\chi^2 = 22.7$, $P < 0.0001$). TS cases were also more likely to have multiple personality disorders. Using the STCPD scale, 27 (71%) of the 38 TS cases completing the scale were identified as having one or more personality disorders compared with five (15%) of the control group (Robertson *et al.*, 1997). The cause of this increase in personality disorder may well be the result of the long-term outcome of childhood ADHD, referred to earlier. Thus, it does appear that at least some clinic TS populations have personality disorders which have both treatment and prognosis implications.

Other associated behaviours

Other behaviours such as aggression (Moldofsky *et al.*, 1974; Stefl, 1984; Robertson *et al.*, 1988; van de Wetering *et al.*, 1988; Palumbo *et al.*, 1997), antisocial behaviours (Nee *et al.*, 1980; Stefl, 1984), learning disabilities, oppositional defiant disorder, conduct disorder (Comings and Comings, 1987; Palumbo *et al.*, 1997), severe temper outbursts (Erenberg *et al.*, 1987), schizoid symptoms (Comings and Comings, 1987), inappropriate sexual behaviour (Moldofsky *et al.*, 1974; Nee *et al.*, 1980; Robertson *et al.*, 1988) and rage (Bruun and Budman, 1997) are also seen in TS clinic patients. No studies to date, however, have examined these types of behaviour in either epidemiological settings, in mild TS patients or in a controlled setting.

A number of case reports (e.g. Realmuto and Main, 1982; Barabas and Matthews, 1983) and a systematic pilot study

by our group (Baron-Cohen *et al.*, 1999a), have suggested an association between TS and autism. In the latter study three of 37 (8.1%) pupils with autism were found to have TS; the presence of TS was not associated with superior intellectual, language or social development. In a more recent large scale study, 447 pupils from nine schools for youngsters with autism were examined in a six-stage investigation involving combined observational and family interview/history methods (Baron-Cohen *et al.*, 1999b). Results showed that definite TS was confirmed in 19 children giving a prevalence rate of 4%; 10 more children were diagnosed as having probable TS (2.2%). Many others (34%) showed tics on observation (but not both motor and vocal tics) and thus the observed rate of 6.48% of TS in autism may well be an underestimate. Of interest is that family histories for tics or OCB were positive in 25 out of 32 youngsters (78%). TS was not related to the severity of autism in the youngsters (Baron-Cohen *et al.*, 1999b). The presence of TS in people with autism may well have treatment implications and should therefore be examined for.

Conclusions

The above conditions are no doubt found in many TS cases, but the precise relationships between them and TS are as yet unclear. Further studies will have to be undertaken on mild TS individuals in non-clinic settings to see whether or not they are more depressed and anxious, and have more personality disorders than control subjects. Further genetic studies are also called for. The clinic population, as said, may well reflect referral bias (Berkson, 1946). Only when the putative gene(s) are identified can one be absolutely sure of the TS phenotype and which associated behaviours, if any, form part of the phenotype.

Aetiological aspects

Genetics

It is now generally agreed that TS is genetically determined. The assertion was made as there are large families documented (Kurlan *et al.*, 1986; Robertson and Gourdie, 1990; McMahon *et al.*, 1992) which, at least at face value, suggested autosomal dominant inheritance and on their own should have been large enough to enable detection of linkage. Indeed, TS was shown to be autosomal dominant by complex segregation analysis techniques (e.g. Curtis *et al.*, 1992). To date, however, no linkage studies have been replicated and much of the genome has been excluded (over 80% by 1993; Heutink *et al.*, 1993). The question then is why has this proven so difficult? This may be so for several reasons, including the fact that the model for inheritance is wrong, the phenotype cannot be accurately determined or there are other non-genetic factors at play. These are some of the reasons why so many different models for inheritance have been proposed

and why the definition of the phenotype has taken on such crucial importance.

Thus, more recently, a mixed model has been proposed (Hasstedt *et al.*, 1995; Walkup *et al.*, 1996) in which it is suggested that there is a genetic predisposition involving one copy of the gene which renders the individual vulnerable, and other factors (e.g. infections, perinatal factors) which determine the extent of the expression of the gene; the number of genes (one or two) may determine the severity of TS. Polygenic inheritance (involving many genes) (Comings *et al.*, 1996), which is more controversial, and bilineality (Kurlan *et al.*, 1994b) (both matrilineal and patrilineal inheritance) have also been suggested. Two studies have shown the effects of genomic imprinting (Lichter *et al.*, 1995; Eapen *et al.*, 1997c). Many authorities believe that an individual may inherit a vulnerability to a spectrum disorder including TS and OCB (Eapen *et al.*, 1993a). Pauls and colleagues suggested that, although ADHD is not a variant expression of TS, the two conditions may be aetiologically related in some individuals, such that there may be two types of people with TS and ADHD; those in whom ADHD is independent of TS (with onset of ADHD before onset of TS) and others in whom ADHD is secondary to the occurrence of TS (concurrent or later onset of ADHD) (Pauls *et al.*, 1993).

There may also be genetic heterogeneity, i.e. different genes may be responsible for TS in different families. Future research in the area will also concentrate on the precise definition of the phenotype. To date, as has been said before, it is not clear which manifestations of TS the putative gene(s) will be responsible for in the phenotype; e.g. will the gene for 'pure TS' be the same as that for 'full blown' or 'TS-plus'?

A possible new approach to solving the problems of identifying the genetic mechanisms involved may be sib-pair analysis. A large international investigation spearheaded by the Tourette Syndrome Association (USA) is now employing this technique. As this method is more robust to mis-specification of models of inheritance, it should eventually either find linkage to chromosomal loci or not.

In the first publication from the group and the first complete genome scan in TS, two areas are suggestive of linkage (Tourette Syndrome Association International Consortium for Genetics, 1999). These results are exciting and further research is under way.

Perinatal factors and infections

Recently there have been suggestions that a variety of other factors are involved in the aetiopathogenesis of TS, including pre- and perinatal stressors/insults, and, somewhat later, various bacterial and viral infections.

Perinatal factors

Based on observations that stressors at various times of the life cycle could influence TS symptoms, Leckman and colleagues suggested a stress-diathesis model for the

pathogenesis of TS, according to which the clinical expression of TS is a product of the interaction of an inherited vulnerability (such as that discussed above) with environmental factors; these may include CNS stimulants or intermittent, uncontrollable stress during a critical period of brain development (Leckman *et al.*, 1986). Thus, it has been proposed that prenatal events or exposures such as maternal life stress during pregnancy, severe nausea and vomiting during pregnancy, and antiemetic medication may lead to changes in the sensitivity of some dopaminergic receptors and this could partially determine the eventual severity of expression of the diathesis to TS (Leckman *et al.*, 1987, 1990). Others have also reported a high incidence of birth complications in 25% of 53 TS patients (Lees *et al.*, 1984), which included induced labour, umbilical cord round the neck, neonatal jaundice, caesarian section, forceps delivery, prolonged labour, prematurity and a twin sibling dying at birth. Unfortunately, none of these were controlled studies, so it is not possible to say whether or not these factors are found more with TS individuals than any other group or the general population.

Neuroimmunology and infections

Several groups have recently investigated the possible role of infections in the aetiopathology of TS and related disorders. These will all be discussed as they have important, though as yet novel, treatment implications (see below).

There have been recent suggestions that paediatric autoimmune neuropsychiatric disorders associated with group A β -haemolytic streptococcal infections (PANDAS) (Swedo *et al.*, 1998) may be of importance in the understanding of the aetiopathology of TS. Robertson and Stern suggest a possible clinical spectrum between TS and Sydenham's chorea, a variant of rheumatic fever with neurological involvement (Robertson and Stern, 1998); this theory is strengthened by the findings of both OCD symptoms (Swedo *et al.*, 1989, 1993) and vocal tics (Mercadante *et al.*, 1997) in Sydenham's chorea.

The PANDAS disorders, associated with either abrupt onset or exacerbations of tics or OCS/OCB symptoms, have been described in a series of reports (Allen *et al.*, 1995; Swedo *et al.*, 1997, 1998). Carrying on related research, studies have now also examined a trait marker of rheumatic fever susceptibility (a β -lymphocyte antigen labelled D8/17) and have found it to be increased in patients with both TS and OCD (Murphy *et al.*, 1997; Swedo *et al.*, 1997).

The neuroimmune diathesis of TS has been of interest for some time (Hallett and Kiessling, 1997). Antineuronal antibodies were found to be increased in the sera of children with movement disorders including Sydenham's chorea and TS (Kiessling *et al.*, 1993, 1994). The same group later developed a sensitive and specific assay for the determination of these human antineuronal antibodies in TS and related disorders (Laurino *et al.*, 1997).

Although the idea of PANDAS is intriguing, it is still

speculative and only a few cases have been described which support the hypothesis. The topic has been well reviewed by Kurlan who suggests that further research is required to establish more clearly the role of post-infectious and immune-mediated mechanisms in TS (Kurlan, 1998, 1999). He also suggests that with the present state of knowledge, testing and treating of patients should not form part of a routine clinical work-up and should only be used in the context of research protocols (Kurlan, 1998, 1999).

Moving on to other infections, Budman and colleagues reported an 11-year-old girl who had no family history of TS, but who, at the age of 5 years, began to have symptoms of TS including motor and vocal tics, ADHD and OCD. Gestation, birth and early development were normal. At 3 years she developed herpes simplex type 1 oral lesions; she continued to have these periodically. Over the years her response to traditional anti-TS medication was variable. Acyclovir was given twice for tic exacerbations and she improved markedly on both occasions (Budman *et al.*, 1997).

Riedel and colleagues documented a boy who began blinking excessively at the age of 4 years; it resolved within a year without treatment. At the age of 9 years he developed multiple motor tics, a vocal tic and poor impulse control, and was hospitalized 11 months after the onset. The results of all special investigations suggested an infection with *Borrelia burgdorferi* (Lyme disease). He was treated with an intravenous antibiotic (ceftriaxone 2 g) daily for 14 days which resulted in both a decrease of symptoms and a decrease in *Borrelia*-specific antibody titres. The authors suggested that such an infection should be considered in all cases of TS in endemic areas (Riedel *et al.*, 1998).

In summary, several recent investigations have identified some TS patients associated with streptococcal infections; others have reported TS symptoms to be associated with Lyme disease and a viral infection. All of these findings, although interesting, must be considered as speculative and almost anecdotal as yet, and although they have treatment implications, these also must be considered to be in their infancy. This, once again, highlights the heterogeneity of so many aspects of TS, including aetiology.

Course and prognosis

TS has a life-long course. Characteristically, the course of TS is punctuated by the appearance of new tics and the disappearance of older ones; during adolescence the symptoms tend to be more unpredictable from day to day, but it is estimated that in 30–40% of cases the tic symptoms will remit completely by late adolescence (Robertson, 1994).

A recent study by Leckman and colleagues demonstrated that there was a mean tic onset at age 5.6 years which was followed by a progressive pattern of tic worsening. The period of greatest tic severity occurred at 10 years. In eight of 36 cases (22%) the frequency and forcefulness of the tics during the worst period were so severe that functioning in school was impossible; in practically every case this period

was followed by a steady decline in tic severity. By the age of 18 nearly half of the cohort was virtually tic free. The onset of puberty was not associated with either the timing or severity of tics (Leckman *et al.*, 1998).

There is little doubt that stress is involved in the pathogenesis and worsening of TS, but the topic has received relatively little systematic attention in the literature. Stress has been implicated in the pathogenesis (e.g. Leckman *et al.*, 1986, 1990) as well as the perpetuation or increase of TS symptoms.

Stress has been shown to increase the severity of tics. Case reports have documented an increase in TS symptoms following the death of a parent, personal illness, birth of a sibling (Eisenberg *et al.*, 1959), beginning school (Eisenberg *et al.*, 1959; Surwillo *et al.*, 1978), parental separation (Stevens, 1964), illness of a parent (Faux, 1966), personal illness (Eisenberg *et al.*, 1959; Faux, 1966), premenstrual tension (Lees *et al.*, 1984), thermal stress (Lombroso *et al.*, 1991), conflicting family interactions (Edell and Motta, 1989; Malatesta, 1990) and traumatic war experiences (Witzum *et al.*, 1996). Three long-term single case studies have investigated stress and TS and shown that increased stress increases tics, whereas reduced stress (e.g. by relaxation) reduces tics (Goforth, 1974; Surwillo *et al.*, 1978; Michultka *et al.*, 1989).

Other evaluations of substantial TS cohorts have found that increased stress or events which produce anxiety such as emotional trauma and social gatherings worsen tics (Jagger *et al.*, 1982; Lees *et al.*, 1984; Robertson *et al.*, 1988; Bornstein *et al.*, 1990; Chappell *et al.*, 1994; Silva *et al.*, 1995).

Management of TS

Management can range from education to supportive reassurance to intricate pharmacological interventions, and ideally management should be multidisciplinary. At the outset it must be pointed out that education is mandatory and psychobehavioural methods and reassurance may well be sufficient for many patients, especially those with mild symptomatology.

Psychological techniques

A variety of psychological techniques have been used in the treatment of TS. The first technique used was 'massed negative practice' (over-rehearsal of the target tic by the patient, which would eventually disappear by a mechanism called reactive inhibition). Subsequent literature has, however, shown inconsistent results using this method (for review, see Evers and van de Wetering, 1994). Other psychological treatments which have proved useful in TS have included assertiveness training (Mansdorf, 1986), self-monitoring (Billings, 1978) and cognitive therapy (O'Connor *et al.*, 1993). Relaxation therapy (Bergin *et al.*, 1998), on the other hand, has not proved useful in the treatment of tics. Evers

and van de Wetering suggested a treatment model based on a specific tension reduction technique in which, instead of a tic which occurs in response to a specific sensory stimulus, the patient is taught a more socially acceptable alternative response which also reduces the sensory stimulus (Evers and van de Wetering, 1994). By and large the author is not greatly impressed with psychological techniques for the treatment of the tics *per se*, as much of the documentation in the literature is anecdotal and, in her experience, results have not been particularly encouraging. The main use for psychobehavioural techniques in TS is for the associated OCS/OCB where it forms an important adjunct to medication.

Pharmacological management

The neurobiology of TS has been thoroughly reviewed (Messiha, 1988; Baker *et al.*, 1995; Singer, 1997; Robertson and Stern, 1998) and many circuits (e.g. frontal-subcortical; basal ganglia-thalamocortical, nucleus accumbens- limbic system) and neurotransmitter and/or neuromodulator systems have been implicated in the aetiopathogenesis. These neurotransmitter systems include catecholamines (dopamine and noradrenaline); tryptophan and its metabolites (serotonin, kynurenine, tryptamine), acetylcholine, the GABA amino acids (glutamate, phenylalanine, *p*-tyrosine), trace amines (e.g. tyramine), opioid peptides (e.g. dynorphin), the second messenger (cyclic AMP), and androgenic hormones.

However, there have been relatively few post-mortem TS brains studied pathologically. Many parts of the brain have been invoked as abnormal in TS. Studies of eye movements have implicated basal ganglia dysfunction. MRI studies have implicated corpus callosum size and loss of normal asymmetrical predominance of the caudate. Much of the imaging and neurochemical data has been potentially conflicting. In fact, it has been pointed out that the efficacy of neuroleptics in treating tics (see below) was the main factor behind the prevailing theory of dysfunctional dopaminergic basal ganglia circuitry (Robertson and Stern, 1998).

Chemotherapy is, at present, the mainstay of treatment of the motor and vocal symptoms of TS, as well as some of the associated behaviours. Thus, this communication will concentrate on pharmacological manoeuvres in the treatment of TS. Many studies and case reports will be reviewed, not only to demonstrate drug efficacy, but also to indicate the most favoured drugs and reasons for this.

The pharmacological treatment of TS can be complex and may be difficult in many cases. It can be hampered by the fact that there have been relatively few double-blind medication studies and the controlled trials that there are have been conducted on relatively small numbers of patients. Combination strategies are often required according to which symptoms are being primarily targeted, and relatively few studies of these exist; augmentation strategies are also used for certain symptom groups. Some patients, however, with

multiple symptom profiles (e.g. TS-plus) appear refractory to many of the treatments.

Pharmacological treatment of the motor and vocal tics

The most commonly prescribed medications for the motor and vocal tics have historically been the dopamine antagonists, but prescribing habits and efficacy vary widely. The most successful agents in this group are haloperidol, pimozide, sulpiride and tiapride. Other drugs such as clonidine, clonazepam and, more recently, risperidone are widely used but efficacy is still open to question. Some drugs, including nicotinic agents, have some appeal but have had little exposure, while others such as clozapine and talipexole, have been found not to be useful.

MEDLINE searches followed by cross-referencing indicated that there are around 20 double-blind trials (DBT) investigating the treatment of TS (see separately under each individual drug). The most common DBTs have involved standard neuroleptics. Let us examine the drugs separately in detail. Trade names have been obtained from British National Formulary (1998) and Martindale Pharmacopoeia (Reynolds, 1996).

Dopamine-modulating drugs

Typical neuroleptics (dopamine antagonists). The neuroleptics are most often used as antipsychotic agents and are also misleadingly referred to as major tranquilizers. They are considered to act primarily by interfering with dopaminergic transmission in the brain by blocking dopamine receptors. They also affect cholinergic, α -adrenergic, histaminergic and serotonergic receptors (British National Formulary, 1998).

Haloperidol (Dozic, Haldol, Halperon, Peridol, Serenace). Haloperidol, a butyrophenone derivative, is primarily a dopamine D2 receptor blocker (Messiha, 1988). It is one of the most widely used agents used in treating in TS in the USA, Canada, UK, Europe, Australasia and the Far East. Seignot first documented its use in the treatment of TS (Seignot, 1961), but it has recently been shown that the patient previously had a frontal lobotomy (Rickards *et al.*, 1997). Since then, however, it has been the most tried and tested medication, with many case reports of its successful use (Caprini and Melotti, 1961; Challas and Brauer, 1963; Chapel *et al.*, 1964; Stevens and Blachly, 1966; Fernando, 1967; Lucas *et al.*, 1967; Boris, 1968; Shapiro and Shapiro, 1968; Stanciu *et al.*, 1972; Shapiro *et al.*, 1973c; Perera, 1975; Feinberg and Carroll, 1979; Singer *et al.*, 1986; Wright and Peet, 1989). Shapiro and colleagues reviewed 41 reports of its use over a 14-year period and found its efficacy to be between 78 and 91% (Shapiro *et al.*, 1988). It has also, however, withstood the rigours of DBTs (Connell *et al.*,

1967; Shapiro *et al.*, 1989) when it has been shown to be superior to comparator agents.

Monitoring of haloperidol treatment in a research setting has included measuring serum haloperidol levels which, with the low dosages in use, are remarkably small; this can be compared with both high doses and consequent high serum levels in patients with schizophrenia (Singer *et al.*, 1981).

It has been suggested, however, that haloperidol produces unacceptable side-effects in ~84% of patients and therefore only a minority of 20–30% of TS patients continue treatment for extended periods (Sallee *et al.*, 1997). In addition, in many studies, haloperidol has been shown to produce more side-effects when compared with other neuroleptics (Ross and Moldofsky, 1977, 1978; Singer *et al.*, 1982; Shapiro and Shapiro, 1982; Goetz *et al.*, 1984; Shapiro *et al.*, 1989; Sallee *et al.*, 1997). Side-effects of the neuroleptics in general will be discussed later.

Borison and colleagues conducted placebo-controlled DBTs using fluphenazine and trifluoperazine which were as efficacious as haloperidol, but with fewer side-effects. In other studies, clonidine was shown to be equally as efficacious as haloperidol, but did not produce adverse CNS side-effects. They also compared amantadine and benztropine in a crossover study. Amantadine was superior in treating the side-effects of haloperidol treatment in TS (Borison *et al.*, 1983).

It does appear that if medications other than haloperidol are available they should be used as first-line agents, not because of increased efficacy, but because it now seems undisputed that haloperidol produces excessive adverse side-effects, as in controlled situations haloperidol produces more side-effects than other agents.

Pimozide (Antalon, Opiran, Orap). Pimozide is a diphenylbutylpiperidine derivative which possesses post-synaptic blocking activity with a preference for the dopamine D1 receptor (Messiha, 1988). It is widely used in the USA, Canada, UK, Europe, Australasia and the Far East.

Ross and Moldofsky conducted a placebo-controlled DBT, in which both pimozide and haloperidol significantly decreased tic frequency in nine TS patients. Follow-up at 4–20 months later showed that six of seven patients receiving pimozide and one of two receiving haloperidol had >75% improvement in symptoms (Ross and Moldofsky, 1978).

Regeur and colleagues reviewed their management with 65 TS patients. Fifteen patients (23%) received no medication. Pimozide was their most popular medication (given in 46 out of the 65 cases, 71%) because of relative lack of side-effects. Thirty-seven were treated with pimozide alone, five with pimozide and tetrabenazine and four with pimozide and clonidine. The dose ranges of pimozide were 0.5–9 mg per day. Eighty-one per cent experienced a good clinical response without side-effects (Regeur *et al.*, 1986).

Shapiro and colleagues treated 57 TS patients in a DBT comparing haloperidol, pimozide and placebo. The active agents were more effective than placebo, but haloperidol was slightly more effective than pimozide. Adverse effects

occurred more frequently with haloperidol versus placebo than with pimozide versus placebo, but the frequency was not significantly different for haloperidol compared with pimozide. Of importance is that clinically significant cardiac effects did not occur at a maximum dosage of 20 mg/day for pimozide and 10 mg/day for haloperidol (Shapiro *et al.*, 1989).

Sallee and colleagues conducted a 24-week placebo-controlled DBT, with double crossover comparison of pimozide and haloperidol therapy, and measured prolactin levels, tic severity and extrapyramidal side-effects (EPSEs) in 22 TS children and adolescents (aged 7–16 years). Pimozide was significantly superior to placebo, whereas haloperidol failed to reach significance. Haloperidol produced a 3-fold higher frequency of side-effects and significantly more EPSEs than pimozide. The patients experienced clinical response rates of 69% on 3.4 mg/day of pimozide and 65% on 3.5 mg/day of haloperidol. Pimozide responders demonstrated significantly raised prolactin compared with pimozide non-responders and haloperidol treated patients, suggesting that prolactin may be a marker for tic response to pimozide and conversely, a potential marker for haloperidol-related incidence of EPSEs (Sallee *et al.*, 1996, 1997). Sallee and colleagues had previously reported results of cognitive testing in 66 TS patients, of whom one-third had comorbid ADHD, when pimozide was found to be significantly superior to haloperidol in improving cognitive functioning (Sallee *et al.*, 1994).

Sandor and colleagues described a long-term follow-up study (1–15 years) of 33 TS patients treated with pimozide (2–18 mg), haloperidol (2–15 mg) or no drugs. Both drugs produced comparable relief of symptoms at follow-up; however, significantly more patients on haloperidol (47%), compared with pimozide (8%), discontinued treatment. Haloperidol resulted in significantly more acute dyskinesias and/or dystonias than pimozide; otherwise, the adverse side-effect profile was similar for the two agents. Of importance is that no increased incidence of ECG abnormalities with pimozide were found (Sandor *et al.*, 1990).

Substituted benzamides. The substituted benzamides, selective D2 antagonists, have also become popular worldwide, excluding the USA and Canada, for the treatment of motor and vocal tics. This group is popular as the drugs produce less EPSEs and less tardive dyskinesia (TD).

Sulpiride (Dogmatil, Dolmatil, Eglonyl, Sulparex, Sulpitil). The most widely documented benzamide in the treatment of TS is sulpiride, first used by Yvonneau and Bezard in 1970 (Yvonneau and Bezard, 1970). Subsequently, it has been extensively used and documented (Robertson *et al.*, 1990b; George *et al.*, 1993b). Robertson and colleagues managed 63 out of 114 (55%) TS patients with a mean age of 29.3 years (range 10–68) with sulpiride and worthwhile beneficial effects occurred in 59%. Positive effects were: decreased motor and vocal tics, decreased OCS/OCB, decreased aggression, decreased echophenomena and tension, and finally, an improved mood. The dose of sulpiride commenced at 200 mg

daily and increased to a limit of 1 g daily (Robertson *et al.*, 1990b). George and colleagues undertook a 14-week DBT with placebo-controlled crossover of fluvoxamine versus sulpiride, followed by single-blind combined therapy in 11 subjects with comorbid TS and OCD. Sulpiride monotherapy significantly reduced tics and non-significantly improved OCS/OCB. Fluvoxamine, either alone or combined with sulpiride, non-significantly ameliorated tics and reduced OCS/OCB (George *et al.*, 1993b).

Tiapride (Equilium, Tiapridal). Tiapride, not licensed in the USA, Canada or UK, is widely used in Europe for the treatment of TS. A case report of a 17-year-old TS female (Lipsey, 1983) and a study including extrapyramidal hyperkinetic syndromes (Klepel *et al.*, 1988) showed that tiapride was useful in reducing symptoms.

Chouza and colleagues gave tiapride to 25 patients with various forms of dyskinesia for 3 months. Maximal dosage was 900 mg/day. A DBT of tiapride versus placebo showed significantly better results in the tiapride group. The forms of dyskinesia which responded best to tiapride included those of TS patients. An unequivocal, although minor, tiapride-induced parkinson syndrome was recorded in a few patients. No instances of tiapride-induced dyskinesia or akathisia were seen (Chouza *et al.*, 1982).

Eggers and colleagues conducted a placebo-controlled study on 10 children followed by a double-blind crossover study on 17 children using tiapride; tiapride was shown to have a positive therapeutic effect on tics and it had no adverse effects on neuropsychologically measurable cognitive performances in children. Neurophysiological parameters such as the EEG frequency analysis and sensory evoked potentials were not affected by tiapride; nor was the neurosecretory, hypothalamic–hypophyseal regulation of the sex hormones, thyroid stimulating hormone, growth hormone or thyroid hormone impaired. The hyperprolactinaemia caused by tiapride's dopaminergic properties was moderate and restricted to the duration of therapy (Eggers *et al.*, 1988).

Other benzamides. Other benzamides which have also been used successfully in smaller numbers of TS patients include amisulpiride (Trillet *et al.*, 1990), metoclopramide (Desai *et al.*, 1983; Smirnov, 1989) and remoxipride (Buitelaar *et al.*, 1995; Sandor *et al.*, 1996). In the UK remoxipride can only be prescribed on a named patient basis because of blood dyscrasias (aplastic anaemia, cytopenia). To the best of the author's knowledge, there have been no reports of the use of the other benzamides such as raclopride and nemonapride for TS treatment.

Other typical neuroleptics less commonly used in TS. Other neuroleptics such as the diphenylbutylpiperidine penfluridol (Shapiro *et al.*, 1983a, 1988), the phenothiazines, fluphenazine (Goetz *et al.*, 1984; Singer *et al.*, 1986), trifluoperazine (Polites *et al.*, 1965; Fernando, 1967; Prabhakaran, 1970) and thioproperazine (Lechin *et al.*, 1982) have also been used successfully. In a few patients depot neuroleptics such as haloperidol (Paolucci *et al.*, 1984; Clarke and Ford, 1988) or flupenthixol (in our own TS clinic;

M. M. Robertson, unpublished data) have been used successfully.

Atypical neuroleptics. It may well be that the relatively new 'atypical' neuroleptics may be of potential use in TS. It has been pointed out that what exactly should be included in the definition of an atypical neuroleptic remains controversial, but the majority of investigators would agree that an essential requirement is a reduced risk of acute or subacute EPSEs (Chappell *et al.*, 1997), as well as a different receptor profile to the traditional/typical neuroleptics. Only three of these have been tried in TS patients, namely risperidone, clozapine and olanzapine.

Risperidone (Belivon, Risperidal, Risperidol). Risperidone, a benzisoxazole, has a higher affinity for 5-hydroxytryptamine (5-HT) 2A receptors and lower dopamine D2 receptor binding than haloperidol (Leysen *et al.*, 1992). As the 5-HT_{2A} receptor has been suggested as important in the pathophysiology of TS, risperidone may be of theoretical benefit in TS, especially if the patient has OCS/OCB in which 5-HT has been implicated. Several groups have recently reported success in treating TS symptoms with risperidone (Bruggeman *et al.*, 1994; Stamenkovic *et al.*, 1994; van der Linden *et al.*, 1994; Giakas, 1995; Lombroso *et al.*, 1995; Shulman *et al.*, 1995; Bruun and Budman, 1996), with the majority (i.e. 68% of 57 patients) doing well. The results of a study by Robertson and colleagues in 19 TS patients were, however, somewhat disappointing, with 41% responding positively and 35% feeling that it had made no difference, while it made symptoms worse in 24%. At follow-up several months later, very few patients were still taking the drug. Of importance is that no patients suffered EPSEs (Robertson *et al.*, 1996). Finally, it is also of interest that risperidone has been used successfully in the treatment of OCD (Jacobsen, 1995) and has been used as an augmenting agent alongside a selective serotonin reuptake inhibitor (SSRI) in both TS and OCD (Stein *et al.*, 1997). Interestingly, tics have also been reported following risperidone withdrawal (Rowan and Malone, 1997).

Clozapine (Clozaril, Leponex). Clozapine is a dibenzodiazepine compound that is also a potent 5-HT_{2A}, 5-HT_{2C}, 5-HT₃ and, weaker, D₁₋₄ receptor antagonist. Patients taking it must have their blood monitored regularly as they may develop agranulocytosis, which occurs in ~2% of cases (McDougle *et al.*, 1995); in the UK an official Clozaril Patient Monitoring Service has been set up by the manufacturing company to regularly check the patients for blood dyscrasias.

To date there have been only two reports of the use of clozaril in the treatment of TS. Schmider and Hoff documented its use in an atypical TS patient with comorbid schizophreniform disorder (Schmider and Hoff, 1998). Caine and colleagues conducted a unique study when they treated 12 patients with abnormal involuntary movement disorders, including seven with TS and others with Huntington's disease and atypical persistent dyskinesia, with clozapine in a

placebo-controlled DBT. Two dropped out due to complications. The TS patients were treated with clozapine (average dose 371 mg/day; range 150–500) for 4–7 weeks. Overall, clozapine was found not to be effective; on the contrary, at doses of 50–150 mg clozapine was actually associated with transient increased tics. There were also, however, serious unacceptable side-effects (Caine *et al.*, 1979).

Much later, McDougle and colleagues studied 10 OCD patients who were treated with clozapine and it was found to be ineffective (McDougle *et al.*, 1995). There have, however, been two case reports of the beneficial use of clozapine in tardive TS (see below) (Kalian *et al.*, 1993; Jaffe *et al.*, 1995). In the latter report, the patients were treated with a combination of clozapine and propranolol, or clozapine and tetrabenazine (Kalian *et al.*, 1993).

Olanzapine (Zyprexa). Bhadrinath documented the successful use of olanzapine in a 16-year-old TS girl with coprolalia and SIB. She had been treated unsuccessfully with haloperidol, pimozide and risperidone; all were discontinued either due to poor control of TS symptoms or unacceptable side-effects. The patient was started on olanzapine 5 mg daily which was raised to 10 mg after 1 week. Over 9 weeks of treatment partial control of tic symptoms was achieved. Increased appetite lasted for 4 weeks and drowsiness improved when the medication was taken at night (Bhadrinath, 1998).

There are other atypical neuroleptics such as sertindole [Serlect, Serdolect (now withdrawn from the UK market)] and quetiapine (Seroquel), but to the best of the author's knowledge there have been no publications documenting the use of these drugs for the treatment of TS.

Side-effects of the neuroleptics. Neuroleptics are useful in the treatment of TS as has been shown, but unfortunately are often associated with unacceptable side-effects. For example, approximately 84% of haloperidol-treated patients experience adverse effects during the course of treatment and only a minority (as low as 20–30%) are able to continue to take the drug for continued periods (Erenberg *et al.*, 1987; Chappell *et al.*, 1995a).

The side-effects will be discussed in detail as they are not only important, but may be subtle, unusual and somewhat different to those seen in other conditions. Sixteen groups of side-effects are described in the following section.

(i) *Acute dystonic side-effects* including 'lock-jaw' and oculogyric crises can occur with the administration of any of the neuroleptic drugs, especially in drug naive patients. Depending on the severity of the dystonic reaction, there are agents such as the anticholinergic drugs (Barnes and McPhillips, 1996) which can be given as 'antidotes', either orally, intramuscularly or intravenously; these include orphenadrine (Disipal) (Connell *et al.*, 1967), benztropine (Cogentin) (Kurlan, 1997a), diphenhydramine (Benadryl) (Kurlan, 1997a) and procyclidine (Kemadrin) (M. M. Robertson, unpublished data).

It has been suggested that some patients with tics may have an increased risk of dystonia, as it was reported to occur in 5% of TS patients seen at a clinic (Stone and Jankovic, 1991). However, none of 46 TS cases were reported to have acute dystonic reactions with pimozide (Regeur *et al.*, 1986).

(ii) *Parkinsonian side-effects* (e.g. tremor, bradykinesia) can occur, but are rare at low doses and may be helped by decreasing the dose (Kurlan, 1997a) or adding an anticholinergic such as benzhexol (Eapen *et al.*, 1993b), benztropine, biperiden, orphenadrine or procyclidine (Barnes and McPhillips, 1996).

(iii) *Neuroleptic-induced akathisia* or motor restlessness occurs in 23–75% of neuroleptic-treated patients (Barnes *et al.*, 1992). It can also occur in neuroleptic-treated TS patients and may exacerbate the TS symptoms (Bruun, 1988). It may be helped by neuroleptic dose reduction and withdrawal (Barnes and McPhillips, 1996; Kurlan, 1997a), or prescription of propranolol (George *et al.*, 1993b), clonidine (Zubenko *et al.*, 1984; Adler *et al.*, 1987) or the 5-HT₂ antagonists cyproheptadine (Weiss *et al.*, 1995) and ritanserin (Miller *et al.*, 1990). Of interest is that a boy with TS who had a positive family history of restless legs syndrome (Ekbom's syndrome)—his mother suffered with restless legs syndrome—was particularly vulnerable to neuroleptic-induced akathisia with haloperidol, pimozide and tiapride (Müller *et al.*, 1994).

(iv) *Sedation and drowsiness* are particularly common with haloperidol and may be avoided by taking the medication at bedtime or drinking caffeine containing beverages in the morning (Kurlan, 1997a). They have also been reported as the most common side-effects occurring with sulpiride—20 out of 63 patients (32%); in half of these patients the side-effects were transient, while in the other half they were sustained and required discontinuation of the drug (Robertson *et al.*, 1990b). Sedation has been reported with pimozide (Regeur *et al.*, 1986), but is less evident than with haloperidol (Ross and Moldofsky, 1978).

(v) *Cognitive effects*: butyrophenones such as haloperidol may also impair concentration and scholastic achievement (Bruun, 1988), and have been associated with lower IQ in structured settings such as neuropsychological testing with the Wechsler Adult Intelligence Scale (Robertson *et al.*, 1988).

(vi) *Dysphoria and depression* have been reported with haloperidol (Erikson *et al.*, 1977; Caine and Polinsky, 1979; Bruun, 1982, 1984, 1988), pimozide (Regeur *et al.*, 1986; Bruun, 1988), fluphenazine (Bruun, 1988), tiapride (Chouza *et al.*, 1982) and sulpiride (Robertson *et al.*, 1990b; George *et al.*, 1993b). This is important as individuals with TS have been shown to be particularly prone to depression (Robertson *et al.*, 1988, 1993, 1997). This may be dose related and thus treated by reducing the dose (Kurlan, 1997a), by discontinuing the drug (Robertson *et al.*, 1990b) or by adding an appropriate antidepressant (Robertson *et al.*, 1990b).

(vii) *TD*: it seems that, in general, TD is fairly uncommon in TS patients treated with neuroleptics, as evidenced by the

documentation of case reports of its occurrence (Caine *et al.*, 1978; Mizrahi *et al.*, 1980; Caine and Polinsky, 1981; Seeman *et al.*, 1981; Golden, 1984; Riddle *et al.*, 1987). Of importance, however, is that TD side-effects have been reported in children exposed to haloperidol with dosages as low as 4 mg/day for 4 years (Silva *et al.*, 1993). Tardive dystonia can occur occasionally after short-term treatment with low doses (British National Formulary, 1998). Tardive dystonia has been reported with haloperidol (Singh and Jankovic, 1988) while TD has been reported in one patient treated with sulpiride (Eapen *et al.*, 1993b). This latter case was unusual, as sulpiride has actually been successfully used in relieving symptoms of TD (Haggstrom, 1980; Gerlach and Casey, 1984; Quinn and Marsden, 1984; Schwartz *et al.*, 1990; Chaplin, 1991). To put this into context, in a series of 46 TS cases treated with pimozide (Regeur *et al.*, 1986) and 63 treated with sulpiride (Robertson *et al.*, 1990b), no cases of TD were encountered. Treatment of TD and tardive dystonia can be difficult, but manoeuvres include reduction and eventual stoppage of the neuroleptic (Miyasaki and Lang, 1995), prescribing a combination of clozapine and clonazepam (Shapleske *et al.*, 1996), clonazepam (Thaker *et al.*, 1990), vitamin E (tocopherol; Egan *et al.*, 1992; Lohr and Caligiuri, 1996), nifedipine, reserpine and tetrabenazine (Shale and Tanner, 1996). Yassa and Ananth reviewed the efficacy of lithium therapy in the treatment of TD. A few well-designed studies indicate that lithium is useful in certain TD patients and that the plasma lithium level may be related to the therapeutic response (Yassa and Ananth, 1980).

(viii) *Social and school phobia* have both been triggered by both haloperidol (Mikkelsen *et al.*, 1981; Bruun, 1988) and pimozide (Linet, 1985) in TS patients. Mikkelsen and colleagues described 15 TS patients who developed school and work avoidance syndromes when treated with low dose haloperidol (mean 2.5 mg daily) for relatively short periods of time (mean 8 weeks). The phobic symptoms disappeared completely with discontinuation or reduction of the haloperidol dose (Mikkelsen *et al.*, 1981). Linet proposed the term 'neuroleptic separation anxiety syndrome', which he suggested was clinically indistinguishable from DSM criteria for school phobia or separation anxiety disorder. It was suggested that tricyclic antidepressants (TCAs) may have a therapeutic or indeed prophylactic effect (Linet, 1985). Others, however, have suggested that the syndrome may actually be one of the many faces of neuroleptic-induced akathisia (Heiser and Sramek, 1986), while Munro suggested that it was a variant of depression (Munro, 1986) and Bruun suggested that it is always associated with dysphoria (Bruun, 1988). This is important as TS children have been demonstrated to be more phobic than controls with chronic tic disorder (Spencer *et al.*, 1995), while TS adults have been shown to be more anxious than control populations (Robertson *et al.*, 1993, 1997).

(ix) *'Fog states'* have also been described with haloperidol (even at very low doses) and consist of episodes during which the patients felt out of touch with, but not unaware

of, their surroundings for seconds to hours at a time, accompanied by depersonalization, paranoia and slowed thinking (Bruun *et al.*, 1976; Feldman, 1977; Bruun, 1988). These patients respond to the antiepileptic drug, primidone, which suggests that they are probably partial seizures (Bruun, 1988).

(x) *Hostility and aggression*: a few children reported by Bruun have become hostile and aggressive with haloperidol or pimozide. With this symptom there was a particular 'threshold dose' above which aggressive behaviour was encountered and below which the children were 'normal' (Bruun, 1988).

(xi) *Appetite*: an increase in appetite with a resultant increase in weight is not uncommon in patients treated with neuroleptics and has been reported with pimozide (Regeur *et al.*, 1986) and sulpiride (Robertson *et al.*, 1990b). It must be borne in mind, however, that the aetiology of weight gain is not fully understood. One strategy for counteracting the weight gain is by a strict diet and exercise programme (Kurlan, 1997a).

(xii) *ECG abnormalities* such as prolongation of the QT interval can occur with pimozide (Fulop *et al.*, 1987); this can deter some clinicians from prescribing it, especially in higher doses. If prescribed, however, baseline ECG as well as regular ECG monitoring is recommended. This side-effect is probably related to its calcium channel blocking activity (Messiha, 1988). As many TS patients require more than one medication, the physician must always be aware of the potential difficulties of using drugs in combination with pimozide because of the effects on the ECG and therefore the heart. These include, for example, the reporting of sinus bradycardia with the combination of pimozide and fluoxetine (Ahmed *et al.*, 1993).

(xiii) *Amenorrhoea, galactorrhoea and gynaecomastia* have been reported in 17% of 63 TS patients treated with sulpiride (Robertson *et al.*, 1990b). Galactorrhoea has also been subsequently reported (George *et al.*, 1993b). In the author's clinical practice in adult psychiatry, patients receiving sulpiride have had particularly high prolactin when they have had these three side-effects. Endocrine dysfunction such as impotence has also been reported with pimozide (Ananth, 1982).

(xiv) *The neuroleptic malignant syndrome (NMS)*, first reported by French psychiatrists in 1960 (Delay *et al.*, 1960), is a rare but serious adverse effect of neuroleptic medication which is potentially fatal. It is basically an idiosyncratic reaction to neuroleptics characterized by muscular rigidity, fever, autonomic dysfunction, labile blood pressure, sweating, urinary incontinence, fluctuating level of consciousness, leucocytosis and an elevated serum creatine phosphokinase level (the latter being brought about by rhabdomyolysis, i.e. breakdown of muscle tissue). It affects males more than females, and patients between the ages of 12 and 78 years with NMS have been described. Most of the affected patients have had psychiatric diagnoses, but cases of NMS with narcolepsy, Huntington's and Parkinson's disease have also

been documented. The neuroleptics most implicated are haloperidol and depot fluphenazine (Levenson, 1985; British National Formulary, 1998). NMS has been reported with metoclopramide. Successful treatments include essential discontinuation of the neuroleptic and prescription of drugs such as dantrolene, bromocriptine and amantadine (Levenson, 1985; Jee, 1987; British National Formulary, 1998). Differential diagnosis includes severe dystonic reactions. One of the major aetiological theories is central dopaminergic blockade, although the exact underlying mechanism remains unclear (Levenson, 1985).

(xv) *Hypotension and hypothermia*: although not many TS patients presenting for treatment are elderly, it is worth mentioning that hypotension and interference with temperature are dose related side-effects of some neuroleptics and can cause falls and hypothermia in the elderly; serious thought and consideration should be given to prescribing these drugs to anyone of over 70 years (British National Formulary, 1998).

(xvi) *Tardive TS*: neuroleptics are, of course, given for other conditions such as behavioural problems, autism and psychotic illness. During treatment for some of these disorders, 'tardive TS' (Stahl, 1980) has been described following treatment with several neuroleptics (Stahl, 1980; De Veugh-Geiss, 1980; Seeman *et al.*, 1981; Mueller and Aminoff, 1982; Munetz *et al.*, 1985; Kuniyoshi *et al.*, 1992). Neuroleptics implicated include chlorpromazine (Klawans *et al.*, 1978) and haloperidol (Karagianis and Nagpurkar, 1990).

Other agents acting as dopamine antagonists

Tetrabenazine (Nitoman, Tetrabenazine). Tetrabenazine, a benzoquinolizine derivative, which depletes presynaptic storage of monoamines and blocks post-synaptic dopamine receptors, was initially used as an antipsychotic drug in 1960 (Jankovic and Beach, 1997) and then successfully in tic and hyperkinetic disorders (Pakkenberg, 1968; Sweet *et al.*, 1974; Jankovic and Orman, 1988; Shapiro *et al.*, 1988). Jankovic and colleagues have used tetrabenazine for some time (Jankovic *et al.*, 1984) and recently it has been used successfully in a substantial series of TS patients (Jankovic and Beach, 1997). There have been some suggestions that tetrabenazine plus a dopamine antagonist, which acts post-synaptically, could be used together, as they may have a more lasting effect and fewer side-effects, because both drugs can be given in lower doses (Fog and Regeur, 1986). More commonly recognized side-effects of tetrabenazine include depression (Jankovic and Beach, 1997; BNF, 1998), drowsiness, fatigue, parkinsonism, insomnia, nervousness, anxiety and akathisia (Jankovic and Beach, 1997). In its favour, it has not been reported to cause TD (Jankovic and Beach, 1997).

Piquindone (RO 22-1319). Piquindone is a pyrroloisoquinoline derivative with D2 receptor antagonist properties (Messiha, 1988). Uhr and colleagues treated four TS patients with piquindone. All four experienced clinically obvious

reductions of tics; motor tics responded at lower doses than vocal tics. Sedation that decreased over time was the only adverse effect and therefore piquindone produced therapeutic effects without disabling side-effects. All patients expressed a strong subjective preference for piquindone over haloperidol (Uhr *et al.*, 1986). To the best of the author's knowledge this agent is not licensed for use.

Inosine (Immunovir, Isoprinosine, Viralin). Inosine has been used traditionally in the treatment of viral infections (Reynolds, 1996), has some immunomodulation properties (Grieco *et al.*, 1984) and is also said to mimic the action of some dopamine antagonists (Cheng and Jiang, 1990).

Cheng and Jiang treated 36 TS patients with inosine in divided doses of 50–90 mg/kg daily. Tic scores obtained from a crossover DBT (11 cases) and open study (25 cases) suggested that the tics were well controlled in 75% of patients. At follow-up a year later the efficacy of inosine was still impressive in 50% of patients (Cheng and Jiang, 1990).

Side-effects of inosine include transient nausea and vomiting (Reynolds, 1996) and reversible increases in serum and urinary uric acid (British National Formulary, 1998).

Dopamine agonists

Pergolide (Celance, Parkotil, Permax). Pergolide is a dopamine agonist with its agonist properties both at D2 and, to a lesser extent, at D1 receptors, and is used mainly in Parkinson's disease (Reynolds, 1996). Lipinski and colleagues used pergolide in 32 TS patients aged 17–19 years in a 6-week open-label fixed-flexible dosing schedule. Overall 75% of patients (24 out of 32) had a drop of >50% in all aspects of tic severity with a mean treatment dose of 177 ± 61 µg/day. Of interest is that the presence of restless legs syndrome comorbidity (59%) was highly associated with a positive response (Lipinski *et al.*, 1997).

Side-effects pertinent to TS include dyskinesia and NMS (British National Formulary, 1998). Abrupt withdrawal of pergolide may precipitate hallucinations and confusion (Reynolds, 1996).

Amantadine (Mantadix, Symadine, Symmetral). Amantadine, another dopamine agonist which also has antiviral properties, has modest effects when used in Parkinson's disease, but not drug induced extrapyramidal symptoms (Reynolds, 1996; British National Formulary, 1998). Trials with amantadine are under way in the USA in the treatment of TS. To the best of the author's knowledge there is only one publication of its use in TS in which it was found not to be useful (Walsh *et al.*, 1986).

Selegiline (Deprenyl, Eldepryl, Movergan). Selegiline is a dose-dependent selective irreversible inhibitor of monoamine oxidase, type B, which is another dopamine agonist (Reynolds, 1996). The main use of this agent is in the treatment of Parkinson's disease (Reynolds, 1996; British National Formulary, 1998).

Jankovic first reported the successful use of selegiline (8 mg/day) in 26 out of 29 (i.e. 90%) youngsters with TS and ADHD, in an open trial (Jankovic, 1993).

Feigin and colleagues conducted a placebo-controlled crossover DBT using selegiline for ADHD in 24 youngsters with a mean age of 12 years with comorbid TS. The design included two 8-week treatment periods separated by a 6-week washout period. Measures for ADHD and tic severity were total scores on the DuPaul Attention Deficit Hyperactivity Scale and the YGTSS. Fifteen subjects completed the study. The primary analysis revealed, from the DuPaul Attention Deficit Hyperactivity Scale, no statistically significant beneficial effect of selegiline. However, further *post hoc* analyses revealed that the effect of selegiline in the first period was substantial. There was also a marginally statistically significant beneficial effect of selegiline on the motor tics as evidenced by the YGTSS total score. Some patients, however, had an increase in tics (Feigin *et al.*, 1996).

Talipexole. Talipexole is a new dopamine agonist that is under investigation for use in Parkinson's disease and schizophrenia (Reynolds, 1996).

Goetz and colleagues evaluated talipexole in a placebo-controlled DBT in 13 TS adult men. The drug was poorly tolerated because of clinically significant sedation and dizziness. Tics did not improve at tolerable doses (Goetz *et al.*, 1994). To the best of the author's knowledge this drug is not licensed for use in patients with TS.

SKF 39393. Braun and colleagues used a selective D1 dopamine receptor autoagonist, SKF 39393, in patients including TS individuals, and no consistent changes of tics could be discerned (Braun *et al.*, 1989). To the best of the author's knowledge this agent is not licensed for use in patients with TS.

Treatment of TS and its comorbid conditions with special reference to ADHD, OCB and SIB

Noradrenergic-modulating drugs

Clonidine (Barclayd, Catapres, Catapresan, Dixarit). Inconsistent with the dopamine hypothesis is the fact that other agents have proved useful in treating TS, especially clonidine, an α -2 adrenoceptor agonist (Leckman *et al.*, 1985; Lichter and Jackson, 1996), which is of special use when the TS patient also has ADHD (Robertson and Eapen, 1992).

Clonidine is conventionally used as an oral preparation, but can also be used as a transdermal patch (Dillon, 1990; Gancher *et al.*, 1990). Clonidine is not licensed in the UK for the treatment of TS, although the BNF sanctions its use (British National Formulary, 1998); its main indications are migraine, menopausal flushing and hypertension. Although many clinicians worldwide now use clonidine, its effectiveness for the motor and vocal tics of TS has been questioned (Goetz, 1992). In the author's TS clinic it is the preferred drug for children with TS and ADHD, commencing at a dose of 25 µg/day and building up the dose slowly to around 100–150 µg/day. For hypertension, the maximum daily dose can be 1.2 mg (British National Formulary, 1998).

One of the earliest reports of the successful use of clonidine

in TS was that of Cohen and colleagues in which clonidine reduced TS symptoms in 70% of a sample of 25 patients; symptoms which responded included not only the tics, but associated behaviours such as OCS/OCB, irritability, aggressiveness, frustration tolerance, oppositional behaviours as well as difficulties in family and peer functioning (Cohen *et al.*, 1980, 1981).

There have been several DBTs which have shown clonidine to be superior to comparator agents (McKeith *et al.*, 1981; Borison *et al.*, 1983; Leckman *et al.*, 1991), while others have found it not to be effective (Dysken *et al.*, 1980; Goetz *et al.*, 1987; Singer *et al.*, 1995b).

Leckman and colleagues suggest that ~50% or more TS patients experience substantial, long-term symptomatic improvement with minimal side-effects with clonidine. However, their profile of response is often variable, with behavioural symptoms appearing to show the most consistent improvement. Maximal benefit may not be evident for 4–6 months. A minority of patients do not respond and a few worsen on clonidine (Leckman *et al.*, 1982).

Shapiro and colleagues conducted an open trial of clonidine and neuroleptics in patients with TS. Neuroleptics resulted in greater improvement across the range of symptoms in a larger proportion of patients than did clonidine (Shapiro *et al.*, 1983b).

Leckman and colleagues treated 13 TS patients with clonidine (0.125–0.3 mg/day) for at least 60 weeks. In a single-blind, placebo-controlled trial, six of the 13 patients (46%) were judged to be unequivocal responders to clonidine and six other patients had an equivocal response. There was significant improvement in motor and phonic tics, as well as in associated behaviour problems, and there were no serious side-effects. Tolerance to clonidine did not develop (Leckman *et al.*, 1985).

Goetz and colleagues evaluated 30 TS patients during a 6-month placebo-controlled crossover study of clonidine. Videotapes were obtained at each 3-week visit and were evaluated randomly at the end of the study for distribution, frequency and severity of motor and vocal tics. Quantifiable psychometric examinations were also performed. Clonidine did not significantly reduce motor tics, vocalizations or behaviour. The effect of a low dose was no different from that of a high dose, children's responses were no different from adults', and those also receiving neuroleptic agents showed the same lack of efficacy as seen in patients on no other medication (Goetz *et al.*, 1987).

Leckman and colleagues compared clonidine (3–5 µg/kg/day) with placebo in 47 TS patients aged 7–48 years. Twenty-four subjects took clonidine and 23 placebo. Forty individuals (21 clonidine, 19 placebo) completed the 12-week trial. Clinical ratings of tic severity improved for both groups. The magnitude of response was greater in the clonidine group. Clinician-rated measures of motor tic severity, the degree to which the tics are 'noticeable to others,' motor tic counts from videotaped interviews, and parent-rated measures of

impulsivity and hyperactivity were the most responsive to clonidine (Leckman *et al.*, 1991).

Thus, it appears that clonidine improves tics and ADHD and may also exert beneficial effects on the behavioural abnormalities, perhaps more so than on the motor and vocal tics (Cohen *et al.*, 1980; Leckman *et al.*, 1982, 1985; Messiha, 1988).

Side-effects of clonidine important in TS include sedation, dizziness, depression, bradycardia, nocturnal unrest and euphoria, and sudden withdrawal can lead to a hypertensive crisis (British National Formulary, 1998). It has been recommended that ECG, blood pressure and pulse baseline, in addition to regular monitoring, should be carried out if clonidine is used (Taylor *et al.*, 1998). In the author's clinic, however, only blood pressure and pulse are regularly monitored.

Guanfacine (Tenex). Guanfacine is also an α -2 adrenoceptor agonist, but possibly without the hypotensive or sedative effects of clonidine, and it has been shown to be useful in the treatment of both ADHD (Horrigan and Barnhill, 1995; Hunt *et al.*, 1995; Cohn and Caliendo, 1997) and TS (Chappell *et al.*, 1995b).

Chappell and colleagues conducted an open-label study of guanfacine in 10 children with TS plus ADHD, aged 8–16 years. The duration of follow-up was 4–20 weeks and the majority of patients were treated with 1.5 mg/day. Standardized ratings of tic severity and ADHD symptoms were obtained. Blind Continuous Performance Tests were performed at baseline and at two follow-up intervals in eight subjects. Guanfacine was associated with significant decreases in both commission and omission errors on the Continuous Performance Test. In addition, guanfacine caused a significant decrease in severity of motor and phonic tics. The most common side-effects were transient sedation and headaches (Chappell *et al.*, 1995b).

Stimulants. The use of stimulants such as methylphenidate (Ritalin, Ritaline, Rubifen), dexamphetamine (Dexamin, Dexidrene, Dextrostat) and pemoline (Cylert, Dynalert, Volital) in children with TS and ADHD has long been controversial (Robertson and Eapen, 1992), as they may worsen the tics, while improving the hyperactivity and concentration. This was felt to represent an absolute contraindication, but recently cautious use of these agents in this context has been advocated (Freeman, 1997).

Borcherding and colleagues reported the occurrence of abnormal movements (orofacial, stereotypic, tics, tremor) and perseverative/compulsive behaviours, or both, in 34 out of 45 (76%) ADHD boys (mean age 8.6 years), during a crossover DBT of methylphenidate and dexamphetamine. Chronic motor tics and TS were exclusionary criteria. All subjects were medication free for 3 weeks before the study. These adverse effects were often subtle and transient, and they usually occurred only on one drug. This necessitated discontinuation in only one case. Dexamphetamine tended to produce more compulsive behaviours, which were also more

likely to resemble clinical OCD, than did methylphenidate. Abnormal movements and compulsive behaviours tended to co-occur on methylphenidate only (Borcherding *et al.*, 1990).

Gadow and colleagues studied 11 prepubertal hyperactive boys with tic disorder who received placebo and three doses of methylphenidate (0.1, 0.3 and 0.5 mg/kg) for 2 weeks each, under double-blind conditions. Each boy was observed for ~20 h in the school setting. Results indicated that methylphenidate effectively suppressed hyperactive/disruptive behaviours and physical aggression. Methylphenidate also reduced the occurrence of vocal tics in two settings. None of the motor tic measures revealed drug effects. On an operationally defined minimal effective dose, only one boy experienced motor tic exacerbation (Gadow *et al.*, 1992).

Gadow and colleagues also studied 34 prepubertal children with ADHD and tic disorder who received placebo and three doses of methylphenidate twice daily for 2 weeks, each under double-blind conditions. Methylphenidate resulted in marked reductions of hyperactive, disruptive and aggressive behaviour; there were no 'non-responders.' The only observed changes in tics were a small but statistically significant increase in the frequency of motor tics and a tendency for fewer vocal tics. However, these changes in motor tic frequency were not perceived by care providers as a worsening in the severity of the child's tic disorder. Most dose-response relationships were linear, but the mean minimal effective dose was 0.3 mg/kg (Gadow *et al.*, 1995).

Castellanos and colleagues conducted a 9-week placebo-controlled crossover DBT in 20 subjects in three cohorts, evaluating the effect of methylphenidate and dexamphetamine on tic severity in boys with ADHD and TS. Fairly high doses of methylphenidate and dexamphetamine in the first cohort resulted in significant increases in tic severity which were sustained on higher doses of dexamphetamine, but which attenuated on methylphenidate. Fourteen of 20 subjects continued stimulant treatment for 1-3 years, generally in combination with other psychotropics. Stimulant-associated adverse effects, including tic exacerbations, were reversible in all cases (Castellanos *et al.*, 1997).

It has been suggested that when treating ADHD with stimulants, controlled release preparations and the adjunctive use of clonidine are helpful to extend stimulant effects and control the adverse effects (Carrey *et al.*, 1996). Clinicians have been successfully using a combination of clonidine and stimulants safely, for many years, to treat children with ADHD; it has been suggested that clonidine both works synergistically with stimulants to reduce behavioural symptoms, and helps with the initiation of sleep (Popper, 1995). Consequent on three deaths reported in children receiving the combination, Popper carefully goes through all the evidence, and ends by suggesting that the deaths were probably not in fact due to the combination (Popper, 1995). He very carefully thereafter considers the safety and sense of the combination, providing valuable guidelines for the clinician.

In the UK pemoline has been withdrawn from the market. Side-effects of the stimulant include dependence, psychotic states and growth retardation (British National Formulary, 1998).

Antidepressants. Antidepressants have been used to treat the depression, the ADHD and particularly the OCS/OCB aspects of TS.

TCA. (i) *Desipramine* [*Norpramine*, *Pertofran* (*discontinued in UK because of lack of commercial viability*)]. Desipramine, a TCA, has been shown to be useful in treating ADHD symptoms (Biederman *et al.*, 1986) and has also withstood the rigours of DBTs (Biederman *et al.*, 1989*a, b*; Gualtieri *et al.*, 1991), in which it was shown to be significantly superior to placebo. An early report suggested that desipramine helped the ADHD and tic symptoms of a boy with TS (Hoge and Biederman, 1986).

Subsequently, Singer and colleagues compared clonidine and desipramine, used to modify ADHD behaviours in 37 children with TS plus ADHD, in a placebo-controlled DBT. Several markers for ADHD were shown to improve significantly after treatment with desipramine, and desipramine was always superior to clonidine. On measures of tic severity, neither drug made tics worse. Desipramine showed a statistically significant improvement on a global linear analogue scale, but not with standardized tic severity ratings. Clonidine did not significantly alter tic severity with any measure (Singer *et al.*, 1995*b*). Problems such as acute collapse and sudden death have, however, been reported with the use of desipramine in children (Riddle *et al.*, 1991).

Other TCAs such as imipramine (Imipramine, Tofranil) (Dillon *et al.*, 1985) and nortryptiline (Allegron) (Spencer *et al.*, 1993) have also been used successfully in children with TS and ADHD.

(ii) *Clomipramine* (*Anafranil*). The most widely investigated antidepressant for the treatment of pure OCD is the TCA clomipramine (Montgomery, 1980; Thoren *et al.*, 1980; Flament *et al.*, 1985). The main problem with the drug, however, is the side-effect profile (e.g. drowsiness, dry mouth, blurred vision, constipation, urinary retention, sweating) and the danger in overdose [cardiac (arrhythmias, heart block), seizures; British National Formulary, 1998]. In the author's experience, it is therefore not first choice.

Selective serotonin reuptake inhibitors. OCD is generally now thought to be unresponsive to psychodynamic psychotherapies, but it does respond to behaviour therapy, especially exposure and response prevention, and to medications such as clomipramine and the SSRIs (Greist *et al.*, 1995).

The SSRIs such as fluoxetine (Fluoxetine, Prozac, Prozac), fluvoxamine (Faverin, Fevarin, Luvox), sertraline (Lustral, Zoloft), paroxetine (Aropax, Paxil, Seroxat) and citalopram (Cipramil, Seropram) appear to be effective as antidepressants, are less sedative than TCAs, and have few antimuscarinic effects and low cardiotoxicity. They are

particularly useful in targeting the depression and OCS/OCB of TS and are used regularly. By and large, the doses given for depression are lower (e.g. fluoxetine 20 mg per day), while the doses for OCD are higher (e.g. fluoxetine 60 mg per day) (British National Formulary, 1998). Fluoxetine and fluvoxamine have been documented most frequently in TS.

Delgado and colleagues described a 25-year-old man with TS who presented for treatment of OCD symptoms. Fluvoxamine worsened tics, led to coprolalia and did not help the OCD. The addition of pimozide reduced both OCD and TS symptoms. Double-blind sequential discontinuation of fluvoxamine and pimozide confirmed that pimozide alone reduced only tics and the combination of fluvoxamine and pimozide was required for the improvement in OCD (Delgado *et al.*, 1990).

Following a report of the successful use of fluoxetine in the OCS/OCB in TS patients (Riddle *et al.*, 1988), Riddle and colleagues subsequently gave fluoxetine 10–40 mg per day to 10 consecutive youngsters below the age of 15 years with either OCD or TS. Five of the 10 patients were responders. Response rates were similar in the pure OCD group (two out of four, 50%) and the TS plus OCD group (three out of six, 50%). Fluoxetine was well tolerated, with adverse effects including behavioural agitation or activation in four patients and mild gastrointestinal symptoms in two (Riddle *et al.*, 1990).

Como and Kurlan undertook an open-label trial of fluoxetine (20–40 mg/day) in 32 TS patients who also had OCD. After 1 week of treatment, six (15%) withdrew due to perceived lack of benefits. Data were therefore analysed on 26 patients (13 children, 13 adults) who were treated for 3–8 months. There was a significant reduction in Leyton Obsessional Inventory scores for both groups and 81% of patients reported a subjective improvement in obsessions and compulsions (Como and Kurlan, 1991).

Kurlan and colleagues conducted a randomized 4-month DBT of fluoxetine (20–40 mg/day) and placebo in 11 children with TS and OCS/OCB. No significant differences between treatment groups were observed for measures of OCS/OCB. Fluoxetine therapy, however, was associated with a trend towards some improvement in tic severity, attentional abilities and social functioning (Kurlan *et al.*, 1993).

McDougle and colleagues conducted a retrospective case-controlled analysis and evaluated fluvoxamine in 33 patients with OCD and a comorbid tic disorder, and 33 patients also with OCD but without a comorbid tic disorder. Both groups of patients demonstrated statistically significant reductions in OCS/OCB, depressive and anxiety symptoms with fluvoxamine. The frequency and magnitude of response of OCS/OCB was, however, significantly different between the groups. A clinically meaningful improvement in OCS/OCB occurred in only 21% of OCD patients with comorbid chronic tics compared with a 52% response rate in OCD patients without chronic tics. Moreover, OCD patients with a concurrent chronic tic disorder showed only a 17%

reduction in Yale–Brown Obsessive–Compulsive Scale scores compared with a 32% decrease in the severity of OCS in those OCD patients without chronic tics (McDougle *et al.*, 1993). McDougle and colleagues then undertook a study involving 62 patients with a principle DSM diagnosis of OCD and gave placebo for a week followed by 8 weeks of fluvoxamine in identical capsules. There had been no 1-week placebo responders. Thirty-four patients were refractory to fluvoxamine and were then entered into a 4-week double-blind placebo-controlled 2 mg haloperidol addition phase. Haloperidol addition was significantly superior to the placebo in reducing the severity of OCS/OCB on the Yale–Brown Obsessive–Compulsive Scale; of particular importance is that all eight of the patients (i.e. 100%) with comorbid chronic tics such as in TS, responded to the haloperidol. Haloperidol was not useful in treating OCD symptoms in the absence of tics. Fluvoxamine blood levels were not related to treatment response (McDougle *et al.*, 1994).

Silvestri and colleagues described two TS patients in whom treatment with fluoxetine in association with clomipramine led to a marked reduction of both abnormal movements and OCS/OCB (Silvestri *et al.*, 1994).

Fluvoxamine (George *et al.*, 1993b) and fluoxetine (Eapen *et al.*, 1996) were particularly useful in patients with TS and OCS/OCB, often in combination with DA antagonists such as sulpiride (George *et al.*, 1993b; Eapen *et al.*, 1996), haloperidol and pimozide, as well as with clonidine (Eapen *et al.*, 1996).

A recent study has demonstrated that fluoxetine has no effect on reducing the tic symptomatology of TS, but has very good effects on the OCS/OCB aspects, with the only real side-effect being transient behavioural activation, which occurred in about 50% of subjects and was more common in children (Scahill *et al.*, 1997).

As a note of caution, however, the emergence of symptoms of TS and the aggravation of the OCS/OCB during fluvoxamine treatment of a 14-year-old boy with OCD has been described (Fennig *et al.*, 1994).

Side-effects of the SSRIs include gastrointestinal side-effects (diarrhoea, nausea and vomiting, which are dose related), headache, restlessness and anxiety; they do not cause weight gain (British National Formulary, 1998). It is particularly important when discussing treatment of TS, however, to note that EPSEs have been reported with the SSRIs when used alone (Lipinski *et al.*, 1989; Reccoppa *et al.*, 1990; Choo, 1993) and especially when used in combination with neuroleptics in both adults and children (Bouchard *et al.*, 1989; Tate, 1989; Shihabuddin and Rapport, 1994; Budman *et al.*, 1995).

Of note is that the exacerbation of tics following antidepressant therapy has been reported (Müller, 1992). A confusional state has been reported in TS patients receiving diazepam with fluvoxamine (Wright and Peet, 1989) and by the addition of fluvoxamine to tiapride and clonazepam (Müller, 1992).

Less commonly used agents in TS

Benzodiazepines and GABA modulating agents

Diazepam (Valium). A DBT of diazepam (a benzodiazepine) versus placebo at 2 mg t.d.s. (three times a day) showed no effect, but at 5 mg was helpful in reducing TS symptoms (Connell *et al.*, 1967). *Lorazepam (Ativan)* 1.5–10 mg/day may also be used to help TS symptoms (Bazire, 1997). Whether or not this is due to a direct action on TS symptoms or is merely an anxiolytic effect is not clear. There are, however, problems with long-term prescription of benzodiazepines including addiction and tolerance.

Clonazepam (Anteplepsin, Klonopin, Rivotril). Clonazepam, a benzodiazepine which acts primarily as an agonist on α -2 adrenoceptors, but also acts on GABA receptors (Messiha, 1988), has been used to treat all forms of epilepsy (BNF, 1998) and other movement disorders such as myoclonus, dystonia and blepharospasm (Browne, 1978; Merikangas and Reynolds, 1979).

Gonce and Barbeau first reported the successful use of clonazepam in seven TS patients (Gonce and Barbeau, 1977), followed by Dion and Chouinard (Dion and Chouinard, 1987, 1988). In general, it was felt that clonazepam was well tolerated and produced no TD. Drtilkova and colleagues compared clonazepam and clonidine in 20 children (mean age 11 years), 14 with chronic tic disorder and six with TS. Clonazepam was significantly superior to clonidine and produced fewer side-effects (Drtilkova *et al.*, 1994). Merikangas and colleagues conducted a single-blind investigation of 20 TS patients. As TS patients had previously been reported to have high red blood cell choline levels, red blood cell choline was measured. Patients with high red blood cell to plasma choline ratios responded significantly better to clonazepam than to haloperidol, and the clonazepam responders were significantly more likely to have a family history of TS or tics (Merikangas *et al.*, 1985). Of 54 TS patients treated with clonazepam in three studies, there was a good response of between 53 and 71% (Goetz, 1992). Jankovic and Rohaidy reported that TS patients with mild symptoms improved with clonidine or clonazepam, whereas those with more severe symptomatology required fluphenazine, pimozide, haloperidol or tetrabenazine (Jankovic and Rohaidy, 1987). On the other hand, clonazepam-induced TS symptoms in a 37-year-old subject with hyperreflexia or abnormal startle response have been described (Gillman and Sandyk, 1987). Clonazepam has also been used to treat tardive Tourette-like syndrome (Kuniyoshi *et al.*, 1992).

Side-effects of clonazepam important in TS include drowsiness, fatigue, dizziness, paradoxical aggression, irritability and mental changes (British National Formulary, 1998).

Other GABA modulating drugs

Progabide. Mondrup and colleagues evaluated progabide (a GABA receptor agonist) in 17 patients with hyperkinetic movement disorders, including four with TS. Doses ranged

from 900 to 3600 mg/day (median 2400 mg/day) and treatment lasted from 2 to 52 weeks; improvement in tics occurred in two of four (50%) TS patients (Mondrup *et al.*, 1985). Others have also suggested its use (Fog and Regeur, 1986).

Baclofen (Baclofen, Lioresal). Baclofen is also a derivative of GABA but this GABA agonist has not proved useful in a small number of patients (Shapiro *et al.*, 1988).

Other medications

Nicotine. It has been suggested that the pathophysiology of TS may be linked to a relative imbalance between cholinergic and dopaminergic activity within the striatum and that nicotine may alter this imbalance (Dursun and Reveley, 1996).

Animal experiments in the late 1980s and early 1990s demonstrated that nicotine potentiated haloperidol-induced catalepsy and reduced locomotor activity (Manderscheid *et al.*, 1988; Sanberg *et al.*, 1989; Emerich *et al.*, 1991). At around the same time, there was a case report that chewing nicotine gum reduces tics (Brill, 1988). Devor and Isenberg reported a male TS patient whose symptoms reduced markedly when he smoked cigarettes (Devor and Isenberg, 1989).

In open studies involving small numbers of TS patients who were being treated with haloperidol, the frequency of tics was reduced significantly during a 30-min nicotine gum (Nicorette) chewing period and the hour afterwards, suggesting once again that nicotine appears to potentiate the effects of haloperidol (Sanberg *et al.*, 1988, 1989; McConville *et al.*, 1991); the methods involved, however, have been criticized (Arevalo *et al.*, 1992; Rickards, 1992). In addition, many discontinued the gum because of side-effects, especially nausea and a bitter taste in the mouth (Sanberg *et al.*, 1989; McConville *et al.*, 1991). Subsequent DBTs suggested that nicotine markedly potentiated haloperidol effects in treating TS and showed lesser effects on symptoms when used alone; placebo gum had no effect (McConville *et al.*, 1992). Mainly because of the unacceptable side-effects of gum, transdermal nicotine patches (TNP) were subsequently used (Silver and Sanberg, 1993; Dursun *et al.*, 1994; Reveley *et al.*, 1994); at a dose of 7–10 mg/24 h, although there was a broad range in individual response, TS patients improved significantly for up to 1–4 weeks, but not as long as 16 weeks, and side-effects were transient (Silver *et al.*, 1996; Dursun and Reveley, 1997). Other side-effects of TNPs include headache, light-headedness, sweating, tremor and sleep disturbances (Davila *et al.*, 1994).

A recent study, on the other hand, evaluated the effect of nicotine smoking in 47 TS patients; of the 28 smoking patients only two (7%) reported a tic reduction when smoking cigarettes (Muller-Vahl *et al.*, 1997).

Nicotine is also available as a nasal spray and an inhaler is under development (Benowitz, 1996); to the best of the author's knowledge, neither of these applications has been used in TS.

A nicotine antagonist, mecamyline (marketed as an antihypertensive agent in the USA), was prescribed in 13 TS patients. Improvements were noted in tics, mood, irritability and aggression (Sanberg *et al.*, 1998).

It does appear that agents acting on the nicotine receptors may well be useful in the treatment of TS, especially when used as an augmenting agent to neuroleptics. More research, however, is needed in the area.

Calcium channel blockers (Verapamil, nifedipine, flunarizine). Goldstein and Berg both documented the successful use of nifedipine (Adalat, Adipine, Cardilate) in TS (Goldstein, 1984; Berg, 1985). Walsh and colleagues reported tic, irritability and compulsive symptom reduction with Verapamil (Cordilox, Securion, Univer, Verapress; 20 mg t.d.s.) in an 11-year-old boy, and tic and inner tension reduction in a woman by treatment with nifedipine (10 mg t.d.s.), but not with diltiazam (Adizem, Tildiem) (180 mg/day) (Walsh *et al.*, 1986).

After a suggestion that nifedipine augments haloperidol in the treatment of TS, the successful combination of nifedipine and haloperidol in treating a patient with TS was reported (Alessi *et al.*, 1988, 1989). Micheli and colleagues evaluated seven TS patients aged 12–31 years, before treatment, after 1 month on placebo, after a single 10 mg nifedipine dose (three subjects) and monthly while on flunarizine 10–15 mg (mean dose 13 mg). None of the patients receiving nifedipine improved, but treatment with flunarizine significantly decreased both motor and phonic tic severity and frequency in all but one patient. Adverse effects occurred in four patients and included mild transient headaches, depression and bradykinesia (Micheli *et al.*, 1990).

Buspirone (Axoren, Buspar). Buspirone is an anxiolytic/antidepressant which is a 5-HT_{1A} partial agonist and a dopamine D₂ presynaptic autoreceptor antagonist. As there is some evidence that tic-like movements in animals (such as head shakes and wet dog shakes) are blocked by buspirone (Handley and Dursun, 1992), buspirone was tried and found to be useful in a patient who was refractory to other treatment (Dursun *et al.*, 1995).

Botulinum toxin (Botox, Dysport, Oculinum). Botulinum toxin injections were pioneered by Scott and colleagues (Scott, 1981; Scott *et al.*, 1990), and in TS by Jankovic and colleagues (see below). They have been used for some time in focal dystonia (Jankovic and Brin, 1991) and oral–lingual dyskinesia (Ludlow *et al.*, 1988). More recently they have proved useful in TS, targeting the symptoms of blepharospasm, neck and facial muscles (Jankovic, 1994; Jankovic and Hallett, 1994; Pongvarin *et al.*, 1995; Awaad and Michon, 1996). Scott and colleagues reported on a 13-year-old boy with severe coprolalia, OCD and ADHD who was considerably improved by unilateral vocal cord injections of botulinum toxin; not only was his coprolalia improved, but also the premonitory sensations that were associated with the vocal tics and coprolalia (Scott *et al.*, 1996). Trimble and colleagues reported a 34-year-old man who had severe TS with OCS/OCB and disabling coprolalia. He was injected with

3.75 mouse units of botulinum toxin into both thyroarytenoid muscles via an anterior cricothyroid puncture technique under local anaesthetic using EMG control. His therapeutic response was excellent and not only reduced coprolalia, but also aided the general symptoms (Trimble *et al.*, 1998). On the other hand, Chappell and colleagues treated two males with botulinum toxin, both of whom had frequent and forceful tics involving a specific body area (shoulder in one patient, lower thigh in the other); an injection of botulinum toxin was given into these areas. Neither patient had a reduction of tics or premonitory urges (Chappell *et al.*, 1997).

Drugs affecting the opioid system. Early work by Sandyk reported the successful use of naltrexone, naloxone and oxycodone on TS symptoms (Sandyk, 1986a, b; Sandyk *et al.*, 1986a, b).

Kurlan and colleagues investigated the effect of drugs acting on the endogenous opioid system in 10 TS adults who received propoxyphene (260 mg/day), naltrexone (50 mg/day) and placebo in a randomized DBT. Using a self-report scale, subjects reported a significant reduction of tics after treatment with naltrexone when compared with placebo. An improvement in the Trail Making B test, which is a measure of attention and visuomotor sequencing and planning, occurred after receiving naltrexone when compared with placebo or propoxyphene (Kurlan *et al.*, 1991). Pentazocine has also been reported as a useful drug (Bazire, 1987).

Meuldijk and Colon reported the case of a man whose TS symptoms responded to methadone after he had not responded to many traditional drugs (Meuldijk and Colon, 1992).

McConville and colleagues reported two TS patients who responded to the sequential use of opioid agonists and antagonists. A male responded to naltrexone initially and later codeine sulphate, while a female responded to codeine sulphate initially and naltrexone 100 mg/day later (McConville *et al.*, 1994).

Risks with opioids are the addiction potential and the risk of tic exacerbation after sudden withdrawal (McConville *et al.*, 1994).

Lithium (Camcolit, Liskonum, Lithobid, Priadel, Quilonum). The use of lithium in TS is not common. Few have documented the usefulness of lithium in a small number of TS patients (Erickson *et al.*, 1977; Hamra *et al.*, 1983; Varma and Messiha, 1983), with lithium blood levels at 0.8–0.9 mEq/l. Kerbeshian and Burd described 13 boys with TS some of whom also had bipolar disorder; interestingly, when they were treated with lithium, the tic symptomatology improved in seven; blood levels ranged between 0.8 and 1.2 mEq/l (Kerbeshian and Burd, 1988, 1989). The use of lithium, however, was not useful in controlling tic symptomatology in other cases (Borison *et al.*, 1983).

Drugs affecting cholinergic mechanisms. Cholinergic modulating drugs such as physostigmine (Stahl and Berger, 1980, 1981) have proved useful, while others such as dimethylaminoethanol (Deanol; Finney *et al.*, 1981) and lecithin (Polinsky *et al.*, 1980) have not been useful.

Carbamazepine (Epilex, Tegretol, Timonil). Neglia and

colleagues described three patients who experienced the onset ($n = 1$) or exacerbation ($n = 2$) of multiple motor and vocal tics 2–4 weeks after the commencement of carbamazepine therapy for control of suspected seizures; no patient had signs or symptoms of carbamazepine toxicity (Neglia *et al.*, 1984). On the other hand, cases have been reported where carbamazepine has reduced the TS symptoms (Lutz and Feldman, 1977).

Marijuana. An early study by Consroe and colleagues suggested that cannabidiol may be useful in dystonic movement disorders (Consroe *et al.*, 1986). Sandyk and Awerbach then described three TS patients who had incomplete responses to conventional anti-TS medications and who then reported a significant reduction in both motor and vocal tics following recreational use of marijuana; the authors, however, note that the patients may have used marijuana to reduce the stress and anxiety that occurred secondary to TS, as all three reported reduced anxiety when using marijuana (Sandyk and Awerbach, 1988). Moss and colleagues then suggested that cannabinoids may increase the effectiveness of neuroleptics in TS (Moss *et al.*, 1989). Hemming and Yellowlees reported a 36-year-old man who failed to respond to either haloperidol or pimozide, but who, several years later, found that his nightly intake of marijuana rendered him absolutely symptom free (Hemming and Yellowlees, 1993). In the author's clinical experience several patients have reported a reduction in symptoms with the recreational use of marijuana. It has also been documented, however, that cannabis has no effect on tics and increases the individuals inner tension (Meuldijk and Colon, 1992). A recent study evaluated the effect of marijuana smoking in 47 TS patients; of the 13 patients taking marijuana, 11 (85%) reported a marked tic reduction (Muller-Vahl *et al.*, 1997).

Melatonin. Children with TS and ADHD often have sleep problems, especially in initiating sleep. Certain drugs may be helpful in reducing the next-day effects of sleep deprivation such as melatonin. A preliminary study using melatonin in multidisabled children and early results in TS and ADHD are promising, with no significant side-effects (Freeman, 1997).

Combination/augmentation therapies. Several combination strategies have been used in TS including nicotine and haloperidol (Silver and Sanberg, 1993), and nicotine and sulpiride (Dursun and Reveley, 1996); recently, the safe use of pergolide and both stimulants and clonidine has been reported (Lipinski *et al.*, 1997). Safe use of a combination of tiapride, haloperidol and clonazepam has been reported (Müller, 1992). Successful use of SSRIs plus risperidone has also been described for treatment of TS (Stein *et al.*, 1997).

Kurlan, however, cautions that an acute parkinsonistic syndrome may be induced by the combination of a SSRI and a neuroleptic in adult TS patients (Kurlan, 1998).

Uncommon treatments for TS

Immunomodulatory, antibiotic and antiviral therapy. As has been discussed, several authors have suggested that certain group A β -haemolytic streptococcal infections and some viral

infections may precipitate or exacerbate some cases of TS (e.g. PANDAS).

Following on from these suggestions, youngsters with TS/OCD aged 10–14 years, who all had evidence of recent group A β -haemolytic streptococcal or viral infection, were treated with plasmapheresis ($n = 2$), intravenous immunoglobulin ($n = 1$), prednisolone (Allen *et al.*, 1995) and penicillin (Swedo and Kiessling, 1994) with good results.

Budman and colleagues have reported the successful use of the antiviral agent acyclovir (Budman *et al.*, 1997), while Riedel and colleagues have used the antibiotic ceftriaxone in patients with TS symptomatology (Riedel *et al.*, 1998).

These suggested medications have only been used in a small number of patients with very specific indications; results are still to be replicated in other laboratories and the treatments assessed in controlled studies in larger samples of patients.

Hormonal therapy. Based on evidence implicating abnormal gonadotrophic functioning in TS, Sandyk and colleagues studied luteinizing hormone, follicle stimulating hormone, luteinizing hormone releasing hormone and testosterone; abnormalities suggested a hypothalamic-mediated luteinizing hormone releasing hormone deficiency. The antioestrogenic agent clomiphene citrate (Clomid) was successful in treating TS symptoms (Sandyk *et al.*, 1987).

Peterson and colleagues reported the first use in TS of the non-steroidal androgen receptor blocking agent flutamide (Eulexin, Fugerel). One male and one female underwent open trials of the drug and a second male participated in a placebo-controlled crossover DBT. Improvement in tic symptoms ranged from 45 to 60%. The improvement was sustained in the woman during daily flutamide ingestion and in one of the men during intermittent use. The symptoms of one of the men became refractory to treatment after 5 weeks of flutamide and the woman became depressed and had protracted diarrhoea during her treatment (Peterson *et al.*, 1994).

Laser therapy of TS. One of the most novel recent treatments of TS has been laser therapy in Russia. Bondarenko and colleagues reported successful low-intensity infrared laser irradiation of blood, used to correct the antioxidative system in TS. Index patients (receiving laser therapy) received lower doses of neuroleptics in contrast to controls (no laser therapy) who required higher neuroleptic doses (Bondarenko *et al.*, 1997). This of course is interesting, but must be viewed as experimental at this stage and is not used or advocated by experts, including the author.

Acupuncture. Wu and colleagues treated 156 TS patients with acupuncture in China. The success rate was 92.3%. The cure rate in children aged 11–15 years was markedly higher than in children aged 6–10 years. Among the 84 cases with an abnormal EEG, the pathological waves in 54 (64%) disappeared or improved after acupuncture treatment (Wu *et al.*, 1996). Although fascinating, once again this is a single report and experts in the field, including the author, do not use this method.

Psychosurgery. In a few TS cases which are severe, have severe OCS/OCB and usually SIB as well, psychosurgery has been used successfully, including in the author's clinic (Robertson *et al.*, 1990a). However, as there have been <40 such operations ever performed in TS patients, a more formalized approach has been suggested, with a rigorous and standardized protocol (Rauch *et al.*, 1995).

General prescribing habits. Jankovic and Rohaidy documented their experience with 112 TS patients. Most patients required a trial of more than one medication before a satisfactory improvement was reached. Thirty-four out of 112 (30%) received haloperidol, of whom 30 (88%) responded well; 24 out of 28 (86%) responded well on fluphenazine; 18 out of 27 (67%) responded to clonidine; 12 out of 15 (80%) responded to tetrabenazine; 10 out of 13 (77%) responded to clonazepam; and seven out of nine (78%) responded to pimozide. In summary, clonazepam and clonidine were tolerated relatively well, but only one-third had an excellent response. Pimozide, fluphenazine and tetrabenazine seemed most effective but were associated with more adverse reactions. Haloperidol had the highest incidence of side-effects. There were no ECG abnormalities attributable to pimozide (Jankovic and Rohaidy, 1987).

Fulton and colleagues surveyed 210 TS subjects who replied to a mailed questionnaire. Almost 60% took medication for symptom relief. The most commonly prescribed medications were reported to be haloperidol, pimozide, clonidine and benzotropine (Cogentin) which was taken in conjunction with other medications. Carbamazepine was reported to be effective in <1% of patients, while no patients found clonazepam or prolixin useful (Fulton *et al.*, 1988).

Conclusions

TS is probably a heterogeneous condition, from an aetiopathological, genetic, clinical phenomenological and psychopathological point of view.

To summarize, and in the author's opinion (taking into account the literature and personal experience), there is no doubt that ADHD is very common in TS, even in mild cases. It is thought that, in time, it will be clear that there is a specific type of ADHD which is peculiar to TS, which is phenomenologically different from that in pure ADHD, but it is unclear as to whether or not this has treatment implications. There is no doubt at all, as evidenced by the literature, that OCS/OCB are integral to TS; they are common in TS and genetically related, but are different from pure OCD and different clinically from the egodystonicity point of view; this does have treatment implications (neuroleptics are used in addition to SSRIs). SIB is also common in TS, and in the author's opinion may well prove to be integral to TS; it can occur in mild TS individuals, is related to OCS/OCB and is often difficult to treat. In the author's opinion, the depression in TS is highly likely to be multifactorial in aetiology, highlighting the importance of a full psychiatric history

and mental state examination in each patient. The anxiety, personality disorders and other behavioural problems are often seen in TS clinics and may be due either to the comorbidity with ADHD or to referral bias. Certainly, the majority of the patients in the author's clinic usually have multiple pathology, although it is recognized that as it is a specialist clinic, it probably attracts patients who are more difficult to manage.

Many neurotransmitters have been implicated as malfunctioning in TS. As can be seen, the medications used to treat the various TS symptoms differ in their receptor affinity profile and indeed their efficacy. The most tried and tested medications for the motor and vocal tics remain the dopamine antagonists, with haloperidol, pimozide, sulpiride and tiapride receiving most attention. The new atypical neuroleptics such as risperidone and olanzapine have appeal and deserve further research; more DBTs are certainly needed.

Clonidine (which affects the noradrenergic system) is also used widely and has been noted to improve tics, ADHD symptoms and behaviour problems.

In addition, with the comorbid depression and OCS/OCB (or even OCD) so often found in TS, and serotonin also being implicated in the pathophysiology of TS, the SSRIs and clomipramine are being increasingly investigated and used successfully.

New and novel treatments as diverse as immunomodulatory therapy, plasmapheresis, antibiotics, antiviral agents, melatonin, psychosurgery and even laser therapy and acupuncture, have all been reported to be successful in treating TS. These, however, have only been tried on a few patients and must be given only with the strictest of indications (e.g. antibiotics after specific infections in which there is a positive culture or raised antistreptolysin titre). The author has no personal experience with any of these and would not recommend anyone (other than experienced clinicians very well acquainted with TS) to use them.

In the author's clinic, the most commonly prescribed medications to adults are sulpiride in approximately one-third of patients, followed by fluoxetine and haloperidol, and then pimozide. The most commonly prescribed medications to children and adolescents are clonidine in around one-third, followed by sulpiride, haloperidol and fluoxetine. Many patients with milder symptoms require no medication, but reassurance and psycho-education (M. M. Robertson, R. Gibbons, M. Dimitrakos, J. Black and M. R. Trimble, unpublished data). Many patients require polytherapy and thus the author prefers not to use agents such as pimozide in these instances. In addition, the author is somewhat cautious, as in the UK at least, most of the agents are neither recommended for children, nor licensed for use in TS.

TS is a truly fascinating disorder. Each patient presents the clinician with something well known and well recognized, as well as something new or unusual, which stimulates further research. Although the phenomenology of TS is becoming clearer, what is included in the 'TS spectrum' remains under debate. Only when the putative gene(s) or genetic mechanisms

are well defined, will some of these issues be resolved, such as the precise phenotype(s). Further medication trials in better defined subgroups may then lead to improved treatments.

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