

Gilles de la Tourette syndrome: the complexities of phenotype and treatment

Tourette syndrome is a chronic motor and vocal tic disorder, which is common (1%). The aetiology is complex (mostly genetic) and 90% of people have co-morbid psychiatric disorders and reduced quality of life. Management includes reassurance, education, behavioural treatments and medications for tics and psychopathology.

The Gilles de la Tourette syndrome is not a new disorder. The Marquise de Dampierre was described in the medical literature by Itard (1825) and then by Dr Georges Edouard Albert Brutus Gilles de la Tourette (1885), earning him eponymous fame.

How are individuals with Tourette syndrome and tics identified and classified?

Gilles de la Tourette syndrome is the most common cause of tics. Diagnostic criteria for Tourette syndrome include multiple motor tics and one or more vocal or phonic tics, lasting longer than a year (World Health Organization, 1992; American Psychiatric Association, 2000). Other tic disorders include transient tic disorder, chronic motor tic disorder and chronic vocal tic disorder. Transient tic disorder includes both motor and vocal tics with a duration of under a year, while the latter two include motor or vocal tics, but not both, for over a year (American Psychiatric Association, 2000).

Tics are relatively brief, rapid, intermittent, purposeless, involuntary, movements (motor tics) or sounds (vocal or phonic tics). Most tics are abrupt in onset and duration (clonic tics), but may be slow and sustained, either dystonic (associated with a twisting type of movement), or tonic (if the muscle contractions are isometric and not associated with any movement, e.g. arm or abdominal tensing). Tics may be simple (isolated, involving only one group of muscles, single or repetitive, e.g. blinking) or complex (coordinated, sequential movements resembling normal motor acts or gestures but which are inappropriately intense and timed (e.g. touching) and may be repetitive (stereotypic)). Tics fluctuate (wax/wane), are suppressible, suggestible and persist during sleep (Jankovic, 1997).

The age at onset of Tourette syndrome ranges from 2–21 years, with a mean of 5–7 years being common. The onset of vocal tics is usually later (11 years). Premonitory sensations occur in 80% of patients (children are often less able to describe them); they may be localized (around the area of the tic, like the uneasiness before a sneeze) or generalized (covering a wide area of

the body). Simple vocalizations include sniffing and throat clearing, while complex vocal or phonic tics include barking and animal noises. Other symptoms include echolalia (copying what others say), echopraxia (copying what others do) and palilalia (repeating one's last word or part of sentence). Coprolalia (inappropriate, involuntary swearing) is uncommon, occurring in about 10–15% of patients and often starting at 15 years of age, i.e. later than other tics; it differs from 'social swearing'. Many doctors are under the misapprehension that coprolalia must be present for the diagnosis. Instead of the whole swear word, many say only parts of the word (e.g. fu fi shi cu), and disguise it by coughing. For reviews of the clinical phenomenology, see Leckman and Riddle (2000), Leckman (2002, 2003a), Robertson (1989, 1994, 2000).

The clinical characteristics of Tourette syndrome are similar irrespective of the country of origin, highlighting the biological nature of Tourette syndrome. In some instances it seems that, within families, the affected males have tic symptoms whereas the females have obsessive compulsive behaviour.

What is the underlying aetiology?

Although originally suggested to be psychological, Tourette syndrome is now recognized as a biological disorder and the majority of cases have a positive family history suggesting a genetic background, which at face value looked as if it were autosomal dominant. Soon bilineality (positive family history on both maternal and paternal sides) was described. Supporting autosomal dominant transmission followed several complex segregation analyses. However, much of the genome was excluded and it was realized that the genetic basis of Tourette syndrome was much more complex (O'Rourke et al, 2009). Exciting findings were links to the SLITRK1 gene and then the positive findings on chromosome 2p23.2 (Tourette Syndrome Association International Consortium for Genetics, 2007), which remain the most promising (O'Rourke et al, 2009).

It seems there are other aetiological factors including an autoimmune hypothesis (Martino et al, 2009). Swedo et al (1998) first documented a group of 50 youngsters with obsessive compulsive disorder and tic disorders, with paediatric autoimmune neuropsychiatric disorder

Professor Mary M Robertson is Emeritus Professor of Neuropsychiatry, University College London and Visiting Professor and Honorary Consultant, Department of Neurology, St Georges Hospital and Medical School, London SW17 0QT

associated with streptococcus (PANDAS), specifically group A beta-haemolytic streptococcal infections; diagnostic criteria included obsessive compulsive disorder and/or a tic disorder, pre-pubertal symptom onset (usually acute, dramatic), association with group A beta-haemolytic streptococcal infections, episodic course of symptom severity and association with neurological abnormalities, relapsing, remitting course and significant psychopathology.

The disorder just referred to is PANDAS, which was a group of 50 paediatric cases originally documented by Swedo et al (1998): the disorder is very specific in terms of symptomatology and dramatic commencement after the streptococcal infection, and in this author's opinion is relatively rare. PANDAS syndrome remains under some debate, and the relationship between PANDAS and Tourette syndrome is controversial. Several centres have found laboratory evidence of group A beta-haemolytic streptococcal infections in some patients with Tourette syndrome and/or documented that some Tourette syndrome patients have increased antibasal ganglia antibodies (Church et al, 2003; Rizzo et al, 2006), while the finding is disputed by others (Morris et al, 2009).

The only controlled study to demonstrate that patients with Tourette syndrome did indeed have significantly more streptococcal infections than a comparison control group in a community setting was that of Mell et al (2005), while another similar study gave negative results (Schrage et al, 2009): the latter study's negative results may have been the result of under-diagnosis of Tourette syndrome as the patients were taken from a general practice UK database. More recently, Kawikova et al (2010) have published a preliminary report giving laboratory evidence that some patients with Tourette syndrome have significantly lower immunoglobulin A compared with control subjects, suggesting that some patients with Tourette syndrome have immunoglobulin A dysgamma-globulinaemia. Further, Murphy et al (2010) have pointed out an overlap both clinically and neuroanatomically between PANDAS and Tourette syndrome.

Taking all the evidence into account, there seems no doubt that a sub-group of patients with Tourette syndrome have an increased susceptibility to group A beta-haemolytic streptococcal infections, and evidence suggests that this may well be the result of immune deficiency which renders the patients more prone to upper respiratory infections. The relationship between the sub-group and the PANDAS syndrome remains unclear in the author's opinion.

Leckman (2003b) summarizes the pre- and perinatal difficulties implicated in the possible aetiology of Tourette syndrome. One controlled study (Burd et al, 1999) showed that people with Tourette syndrome had increased pre- and perinatal difficulties compared to healthy controls. These difficulties include low birth weight, severity of maternal life stress during pregnancy,

severe nausea and/or vomiting during the first trimester, prematurity, low Apgar scores, frequent maternal prenatal visits (Leckman, 2003b) and maternal smoking (Mathews et al, 2006).

Thus the aetiology of Tourette syndrome is much more complex than previously recognized, with complex genetic mechanisms, some infections and pre- and perinatal difficulties all affecting the phenotype.

What is the prevalence of Tourette syndrome?

Tourette syndrome was once considered to be uncommon, but studies have suggested a prevalence of 1% of youngsters between the ages of 5 and 18 years (Robertson, 2008a,b). These studies were worldwide, and were conducted in mainstream schools, using similar multi-staged methods, with both observations and questionnaires about pupils, as well as obtaining information from parents, teachers or both. They were also conducted by clinicians with a special interest in Tourette syndrome. The majority of the Tourette syndrome 'cases' identified were undiagnosed and mild, without distress, impairment or coprolalia (Robertson, 2008a,b). The prevalence of Tourette syndrome in special educational populations, such as those with emotional and behavioural and/or learning difficulties or autistic spectrum disorders, is higher (Robertson, 2008a,b). Robertson (2008a,b) suggests that although less obvious or severe, the prevalence in adults is also 1%. Tourette syndrome is more prevalent in boys than girls (3–4:1) (Robertson, 1989).

How do you diagnose Tourette syndrome?

Individuals with Tourette syndrome are assessed in a variety of ways. The main key to diagnosing Tourette syndrome is taking detailed, thorough and relevant personal and family histories, conducting a mental state examination, and performing physical and neurological examinations. There are no blood tests which can be used to diagnose Tourette syndrome and any investigations are only useful to exclude other disorders (e.g. copper, caeruloplasmin to exclude Wilson's disease, or electroencephalogram to exclude epilepsy). Many specialized clinics use standardized schedules (*Table 1* – this can be accessed, along with the supporting references, from www.bjhm.co.uk). These rate the severity of Tourette syndrome and presence of various symptoms in the patient and family members.

Key difficulties for people with Tourette syndrome

People with Tourette syndrome may experience specific difficulties in life (*Table 2*), and their parents have increased caregiver burden and also psychopathology. Several groups have investigated quality of life in adults and young patients with Tourette syndrome (*Table 3*). Cavanna et al (2008) developed the Tourette Specific Health Related Quality of Life Scale (GTS-QOL). This

includes 27 items with four sub-scales (psychological, physical, obsessional, cognitive). The GTS-QOL demonstrated satisfactory scaling assumptions and acceptability, internal consistency, reliability and test-retest reliability to be valid (Cavanna et al, 2008).

Table 2. Key areas of difficulty for individuals with Tourette syndrome

At home	Having motor tics and making noises – which may disturb other members of the family. Some people with Tourette syndrome spit as a tic and this can be difficult when the family sit down to a meal, especially if strangers are present. If another family member has tics (even mildly), the young person may copy and then repeat them with increased severity
At school	The motor and vocal tics may disturb other children. If the young person has unusual tics, e.g. spitting, laughing as a tic, swearing or making obscene gestures, he/she may get into trouble for doing them. Vomiting as a tic may result in many unnecessary medical investigations
At work	Some adults with Tourette syndrome find interviews and the workplace difficult because of their tics
Common associated difficulties:	Attention deficit hyperactivity disorder – poor attention, concentration, hyperactivity and impulsivity
	Obsessive compulsive behaviour – need for symmetry, getting things ‘just right’, counting, ordering, ego-syntonic
	Obsessive compulsive disorder – such as checking, washing, ego-dystonic and takes more than an hour a day
	Depression – may further lower self esteem, important to treat
	Low self esteem, difficulty in making and maintaining friendships, potentially associated with lack of opportunity and practice

Individuals with Tourette syndrome have lower quality of life than the healthy population, but better quality of life than people with intractable epilepsy and psychiatric patients. So, if of moderate or more severity or associated with psychopathology or co-morbid conditions, youngsters with Tourette syndrome and their parents have disadvantages which merit correct diagnosis and management.

In addition people with Tourette syndrome also have a wide but specific variety of co-morbid conditions or psychopathology associated with their tic disorder. In clinic populations about 90% of patients with Tourette syndrome have co-morbid conditions or psychopathology: this is possibly best argued by a worldwide international collaboration involving 3500 clinic patients of all ages, in which 88% of individuals had reported co-morbidity. The most common was attention deficit hyperactivity disorder, followed by obsessive compulsive behaviours and obsessive compulsive disorder. Anger control problems, sleep difficulties, coprolalia and self-injurious behaviours only reached high levels in individuals with co-morbidity. Males were more likely than females to have co-morbid disorders (Freeman et al, 2000). Even in community studies, about 90% of individuals identified as having Tourette syndrome have co-morbid conditions (Khalifa and von Knorring, 2003, 2005; Mol Debes et al, 2008).

One question is whether this psychopathology is general or specific. The suggested relationships between psychopathology and Tourette syndrome are complex; Robertson (2003) summarized them as follows:

Table 3. Studies of the effects of Tourette syndrome on the patient (quality of life) and the family (caregiver burden) in individuals with Tourette syndrome

Reference	Country	Population	Schedule/ questionnaire	Results	Domains affected
Elstner et al (2001)	UK	103 adults	SF36 QOLAS	Patients with Tourette syndrome rated their quality of life as worse compared with the general population in the UK, but better than that of people with epilepsy	Employment, tic severity, obsessive compulsive behaviours, anxiety, depression
Müller-Vahl et al (2010)	Germany	200 adults	EQ-5D	Patients with Tourette syndrome felt that they had a worse quality of life than the general population in Germany	Anxiety and depression= 57.1%; pain and discomfort= 46.5%; usual activities= 38.4%; mobility =14%; self care = 6.6% Main independent factors for determining health-related quality of life were depression, severity of symptoms and age
Storch et al (2007)	USA	59 youngsters	Self-report Parents report	Tourette syndrome = reduced compared with healthy controls Tourette syndrome = higher compared with psychiatric controls	Tic severity
Bernard et al (2009)	USA	58 youngsters	TACQOL	Attention deficit hyperactivity disorder (inattentive type) and obsessive compulsive disorders symptoms were associated with reduced quality of life	Attention deficit hyperactivity disorder (inattention), not tics
Cutler et al (2009)	UK	57 youngsters	Self report	Youngsters with Tourette syndrome had significantly lower quality of life than the UK general population norms	Tic severity, attention deficit hyperactivity disorder, obsessive compulsive behaviours
Cooper et al (2003)	UK	29 youngsters with Tourette syndrome vs asthma	GHQ Caregiver burden	Parents of youngsters with Tourette syndrome had worse caregiver burden and increased psychopathology	

GHQ = General Health Questionnaire

1. Generally suggested as an integral part of and genetically related to Tourette syndrome – obsessive compulsive behaviours or obsessive compulsive disorder
2. Common in Tourette syndrome and not genetically linked – attention deficit hyperactivity disorder
3. Multifactorial – depression
4. Bipolar affective disorder – possibly caused by comorbidity with obsessive compulsive disorder and attention deficit hyperactivity disorder, rather than by Tourette syndrome per se
5. Adult psychopathology as a result of childhood comorbid psychopathology (attention deficit hyperactivity disorder) rather than Tourette syndrome per se, e.g. personality disorder
6. Secondary to medication – dysphoria, anxiety, cognitive impairment, school phobia
7. Relationship is unknown and more research is needed – autistic spectrum disorder, rage attacks, learning disability, mental retardation
8. No relationship or uncommon, the association is by chance – e.g. schizophrenia, Huntington's disease, Parkinson's disease, Wilson's disease.

One of the most important concepts to understand about Tourette syndrome is the range of both severity and comorbidity, which varies from very mild to severe. Those who are very mildly affected (e.g. merely excessive blinking, shoulder shrugging, tossing of the head, repetitive sniffing and throat clearing) with no co-morbidity are by and large unnoticed, living full lives in the community. At the other end of the severity spectrum, the patient may have very noticeable facial grimacing, gnashing of the jaws, intrusive loud vocal tics, coprolalia, self-injurious behaviours plus obsessive compulsive disorder, attention deficit hyperactivity disorder and depression. These individuals will have lower quality of life, may not be able to sustain a relationship, achieve any formal educational qualifications or have a job.

These clinical observations are mirrored by uncontrolled (Robertson et al, 1988, 1989, 2006; Eapen et al, 2004) and controlled studies showing that Tourette syndrome patients have self-injurious behaviours and significantly more depressive, anxious and obsessional symptomatology and, in adults, also personality disorders, than matched control subjects (Pauls et al, 1994; Robertson et al, 1993, 1997, 2002; Carter et al, 2000; Rickards and Robertson, 2003). For reviews of mood and psychopathology in Tourette syndrome see Robertson (2003, 2006a).

Is Tourette syndrome a single syndrome?

Ever since the disorder was first described, 'maladie de tics' or Tourette syndrome has been considered to be a single syndrome. This has been perpetuated by both the *Diagnostic and Statistical Manual* (American Psychiatric Association, 2000) and *International Classification of Diseases* criteria (World Health Organization, 1992) suggesting, and stipulating, that Tourette syndrome is a single condition. Many studies have challenged this.

Studies comparing children with Tourette syndrome-only to those with Tourette syndrome and attention deficit hyperactivity disorder, attention deficit hyperactivity disorder-only, and unaffected controls (Spencer et al, 1998; Carter et al, 2000; Sukhodolsky et al, 2003) have shown that Tourette syndrome-only patients did not differ from unaffected controls on many ratings, apart from more internalizing symptoms. In contrast, children with Tourette syndrome and attention deficit hyperactivity disorder had higher ratings on disruptive behaviours, internalizing behaviour problems and poorer social adaptation than children with Tourette syndrome-only or controls.

Similarly in adults, Haddad et al (2009) compared adults with Tourette syndrome-only with those with Tourette syndrome and attention deficit hyperactivity disorder. The latter had significantly more depression, anxiety, obsessive compulsive behaviours, and maladaptive behaviours (e.g. aggression to property, attacking other people, having had forensic encounters, alcohol or drug abuse). The Tourette syndrome and attention deficit hyperactivity disorder patients were significantly more likely to have copro- and echo- phenomena and reported significantly more relatives with a history of attention deficit hyperactivity disorder than the Tourette syndrome-only group. These findings suggest that many of the maladaptive behaviours encountered are the result of the attention deficit hyperactivity disorder co-morbidity and not Tourette syndrome per se. They also suggest that individuals with Tourette syndrome-only are different from those with Tourette syndrome and attention deficit hyperactivity disorder.

Studies using hierarchical cluster analysis, principal component factor analysis and latent class analysis have documented that Tourette syndrome is not a unitary condition, with many factor/cluster/class/types (types) (2–5) being reported. There has been some similarity in the types in that all have included a simple tic type, while others have included aggressivity, compulsive behaviours, socially inappropriate behaviours, complex vocal tics, complex motor tics, touching self, and the three classes:

1. Tourette syndrome and obsessive compulsive symptoms
2. Tourette syndrome and obsessive compulsive disorder
3. Tourette syndrome and obsessive compulsive disorder and attention deficit hyperactivity disorder.

A couple of isolated factors have included tapping and no grunting (Robertson et al, 2008).

This may look confusing at first glance, but although not directly comparable, all the studies using hierarchical cluster analysis, principal component factor analysis or latent class analysis have shown two or more types, in terms of both tics and psychopathology, and in all one type has included simple motor and phonic or vocal tics. These studies add to the growing body of evidence that Tourette syndrome is not a single or unitary condition and can be disaggregated into more homogeneous symptom components.

Of importance is that one of the types (pure tics only) seems to support the clinical data of Freeman et al (2000)

and community data of Khalifa and von Knorring (2003, 2005), which suggested that about 10% of Tourette syndrome individuals have tics only.

Whichever way one looks at the data (i.e. epidemiological, clinical or statistical), about 10% of people with Tourette syndrome have simple pure tics only, while 90% have co-morbid conditions and associated psychopathology. Thus the Tourette syndrome phenotype is heterogeneous and not unitary as previously suggested (Robertson, 2008a,b; Robertson et al, 2008).

Robertson (2008a,b) suggested a nomenclature change for Tourette syndrome to types 1 (pure simple motor and vocal/phonic tics only) and more; pending further research, other subtypes may follow. It is likely that these will mirror the clusters and factors mentioned earlier, e.g. Tourette syndrome and obsessive compulsive disorder, or Tourette syndrome and attention deficit hyperactivity disorder, or Tourette syndrome and obsessive compulsive disorder and attention deficit hyperactivity disorder.

Impact and prognosis of Tourette syndrome

It was always thought that Tourette syndrome was a life-long disorder, as the Marquise de Dampierre, described by both Itard (1825) and Gilles de la Tourette (1885), lived to be an old woman. Since then several groups have shown that tics begin between 5 and 7 years, are at their worst between 10 and 12 years, and improve with age (Erenberg et al, 1987; Bruun and Budman, 1997; Leckman et al, 1998; Peterson et al, 2001; Coffey et al, 2000, 2004; Bloch et al, 2006). Pappert et al (2003) demonstrated via video recordings that although Tourette syndrome symptoms improve with age, the distress lessens and need for medication reduces, the symptoms remain even if the individuals consider they no longer have them.

Tourette syndrome may interfere with the life of both the patient and the family (Tables 2 and 3), and youngsters may require special help with education. Therefore it is imperative that Tourette syndrome is correctly diagnosed and managed as early as possible.

The author suggests that adults with Tourette syndrome, even though they have had a childhood onset disorder, are clinically different to youngsters with the disorder. Eapen et al (2002) reported differences between childhood and adult onset patients with tic disorders, suggesting that adult onset tic disorders and Tourette syndrome do not have the same aetiology, phenomenology, treatment and prognosis.

Thus, although the prognosis of Tourette syndrome in the majority of individuals, as far as impairment goes, is better than originally thought, early diagnosis and treatment is important.

What do we know about intervention and management?

There are several thorough review articles on the complexities of treatment of Tourette syndrome and associated co-morbid conditions (e.g. Peterson and Cohen,

1998; Robertson, 2000, 2006b; Robertson and Stern, 2000; Sandor, 2003; Scahill et al, 2006). This article summarizes these articles, adds new data and offers treatment suggestions.

Reassurance, explanation, supportive psychotherapy and psychoeducation are mandatory for the patient and family and, in mild cases, may be all the intervention required. Ideally, treatment should be multidisciplinary, but this is often difficult to achieve. Behavioural methods may be useful alone or in combination with medications for many aspects of Tourette syndrome (Robertson, 2004). Habit reversal training is significantly better than other methods such as supportive psychotherapy and being on a waiting list.

Table 4 shows the double-blind medication trials, large cohort studies, systematic Cochrane reviews and meta-analyses conducted on the treatment of tics in Tourette syndrome. It also has a column devoted to the most prescribed medications in the UK. Using all this data as a basis, the medications are ranked A–D to suggest evidence for efficacy and prescribing. It can be accessed, along with the supporting references, from www.bjhm.co.uk.

In many instances, medication is required for the treatment of the tics and psychopathologies in patients with Tourette syndrome. Neuroleptics have been most commonly used and in double-blind trials haloperidol, pimozide, risperidone, sulpiride and tiapride are all superior to placebo (Table 4). The dose given for Tourette syndrome is small compared to the dose given for schizophrenia or mania. For instance, a dose of haloperidol 0.5–3mg daily may be sufficient in Tourette syndrome patients, whereas 30 mg may be required in severe mania or schizophrenia in adult patients.

Few negative studies are published but one non-response to risperidone (Robertson et al, 1996). Sulpiride is not available in the USA or Canada but has been popular in Europe for some time. Robertson (2000) describes 16 side effects of typical neuroleptics, including sedation, cognitive difficulties, dysphoria, depression, dystonia and social phobias. Electrocardiogram changes with haloperidol and pimozide have been documented (Fulop et al, 1987; Welch and Chue, 2000). In the literature and the author's experience, patients treated with neuroleptics can have raised prolactin levels, which in some cases requires discontinuation of the drugs.

The 'atypical' antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) are useful in treating patients with Tourette syndrome but often have different side-effect profiles, including serious weight gain (Czobor et al, 2002), hyperlipidaemia (Meyer, 2001, 2002), glucose abnormalities (Budman and Gayer, 2001; Meyer, 2002) and new onset diabetes (Wirshing et al, 1998). In patients receiving these it may be worth checking the fasting glucose, especially if the patient has put on weight. In the author's opinion the response to individu-

al neuroleptics is idiosyncratic: an individual may respond to one particular neuroleptic but not another (Robertson, 2000, 2002).

Aripiprazole (DeLeon et al, 2004) (*Table 5* – available from www.bjhm.co.uk) is now widely prescribed, with 24 papers of 222 successfully treated Tourette syndrome patients documented, but there are no double-blind trials to date. Aripiprazole works well and has few and transient side effects (nausea, tiredness); the dose begins at 1 mg and we rarely use as much as 15–20 mg, although such doses have been reported. In the literature a few patients have experienced extrapyramidal side effects which have disappeared on discontinuation (e.g. Fountoulakis et al, 2006; Lyon et al, 2010 and in the author's clinic). One report describes how aripiprazole monotherapy was ineffective in treating a patient with Tourette syndrome: however, the patient also had bipolar affective disorder and both the tics and mania responded to the combination of risperidone and lithium (Wang et al, 2009).

Lesser used, but successful treatment can be botulinum toxin injections to affected areas (e.g. vocal cords if loud distressing vocal tics and coprolalia). Tetrabenazine can be effective, prescribed mainly by neurologists: depression is a side effect. Nicotine (shown to potentiate haloperidol) tablets or transdermal patches and meclizine have both been used successfully in Tourette syndrome, although the majority of reports and studies of nicotine and meclizine have been from one centre.

Antidepressants, especially the selective serotonin-reuptake inhibitors, are useful for depression (using the standard dose, e.g. fluoxetine 20 mg), whereas the dose for obsessive compulsive behaviours or obsessive compulsive disorder is higher (e.g. fluoxetine 40–60 mg). Clomipramine (a tricyclic antidepressant) may also be useful in obsessive compulsive behaviours or obsessive compulsive disorder, but usually has more side effects than the selective serotonin-reuptake inhibitors and is dangerous in overdose. In the UK one must be aware of National Institute for Health and Clinical Excellence guidance when prescribing selective serotonin-reuptake inhibitors to young people. In the obsessive compulsive behaviours or obsessive compulsive disorder associated with Tourette syndrome, a small dose of neuroleptic is useful as an augmentation agent.

Robertson (2006b) reviewed the relationships between Tourette syndrome and attention deficit hyperactivity disorder, particularly as far as treatment is concerned: the use of stimulants does not necessarily increase tics significantly or from a clinical point of view and may be used judiciously in treating attention deficit hyperactivity disorder symptoms in youngsters with Tourette syndrome. Both the short-acting form (e.g. Ritalin) and the long-acting or sustained release forms (e.g. Concerta, Equasym, Medikinet XL) of methylphenidate are used.

Clonidine can be given for the tics, impulse control, attention deficit hyperactivity disorder and can help ini-

tial insomnia. If used, baseline electrocardiogram and regular monitoring of pulse and blood pressure are advisable. One can commence at a dose of clonidine 25 µg and go up to 150 µg daily. Clonidine must not be stopped suddenly as there may be rebound hypertension. Good evidence for the safety and efficacy of the combination of stimulants and clonidine comes from a large randomized double-blind trial in children who had attention deficit hyperactivity disorder and a tic disorder. They were treated with clonidine alone, methylphenidate alone, clonidine and methylphenidate, and placebo (Tourette's Syndrome Study Group, 2002). Compared to placebo, the greatest benefit was with the combination of clonidine and methylphenidate and there was no increase in tics with methylphenidate.

Atomoxetine is a relatively new agent for the treatment of attention deficit hyperactivity disorder and may prove useful in the treatment of Tourette syndrome and attention deficit hyperactivity disorder.

Although seemingly unconventional and alternative, electroconvulsive therapy can be used in severe medication-resistant Tourette syndrome patients and has been documented in eight patients: in one patient the authors reported a 5-year long full remission following continuously applied maintenance electroconvulsive therapy in a patient with Tourette syndrome (Dehning et al, 2010).

Deep brain stimulation is useful in adult Tourette syndrome patients who have severe refractory symptoms which reduce the patient's quality of life. It has been used relatively frequently, given the lifetime of the treatment within medicine. Approximately 55 patients have received deep brain stimulation in 19 centres worldwide and nine targets have been stimulated. Deep brain stimulation should only be conducted by experienced functional neurosurgeons operating in centres which also have a dedicated Tourette syndrome clinic. It is as yet experimental (Hariz and Robertson, 2010).

Future direction and challenges

During the 30 years the author has been working and researching in a Tourette syndrome clinic, the knowledge about the disorder has mushroomed. The challenges remain higher awareness (particularly among GPs and teachers), improved treatment regimens, better description of the phenotypes and also better knowledge about the causes of Tourette syndrome.

In addition, despite the increased knowledge, particularly about the phenotype, the treatment of Tourette syndrome often remains complex and challenging.

In the UK, as in many other countries in the past few years, there has been increased awareness of Tourette syndrome by parents and clinicians. This is partly the result of the now worldwide Tourette Syndrome associations (e.g. www.tourettes-action.org.uk) and the media. This has also resulted in increased demand on the available services. **BJHM**

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Comment on method: While the author has attempted to be comprehensive using PubMed, articles and cross-references, she regrets any possible omissions. Table 4 has been composed taking some suggestions from the Bandolier Index (www.medicine.ox.ac.uk/bandolier/band6/b6-5.html) for assessing efficacy of medications and updated and modified from Scabill et al (2006).

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KEY POINTS

- Tourette syndrome consists of multiple motor and one or more vocal tics for more than a year.
- Tourette syndrome is common (seen in 1% of youngsters).
- The aetiology of Tourette syndrome is predominantly biological, but complex. The majority of cases have a genetic cause, but autoimmune mechanisms and immune deficiency are possible.
- People with Tourette syndrome have a reduced quality of life and co-morbid conditions or psychopathology occur in 90% of cases.
- Tourette syndrome is not a unitary or single syndrome and symptoms usually improve with age.
- Treatment and management includes reassurance, explanation and support; behaviour therapy and medications (e.g. neuroleptics and clonidine).
- Medications used for co-morbid conditions include antidepressants (for depression and obsessive compulsive disorder) and stimulants (for attention deficit hyperactivity disorder).

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Gilles de la Tourette syndrome: the complexities of phenotype and treatment – further information

This document contains three additional tables (Tables 1, 4 and 5) and their references for the article Robertson MM (2011) Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *Br J Hosp Med* 72(2): 100–7

The author conducted a survey among UK Tourette specialists asking which drugs they prescribed for Tourette syndrome patients: the author ranked the replies (indicating which was commonly prescribed and how many ‘points’ each drug scored in the ranking). Results were as follows: aripiprazole (53 points) was the most commonly prescribed by far, followed by clonidine (41 points), then risperidone (39 points), haloperidol (23 points), amisulpiride (10 points), pimozide (6 points), tetrabenazine (4 points) and finally clonazepam (1 point). This

information is highlighted in a column in *Table 4*. A large unpublished survey in Europe undertaken on behalf of the European Society for the Study of Tourette Syndrome also demonstrated that aripiprazole is by far the most commonly prescribed medication for the tics.

Haloperidol is the only drug licensed worldwide for Tourette syndrome, but few use it as first line in USA, UK and Western Europe because of its many unacceptable side effects. It is also worth noting national differences. For example, tiapride is available in all Europe apart from the UK, while sulpiride is available in only the UK and neither drug is available in the USA: the author knows of several American or Canadian practitioners who import sulpiride for use in their (private) practices. Tiapride is the most prescribed medication in Russia. [BJHM](#)

Table 1. Standardized schedules and rating scales used to assess aspects of Tourette syndrome

Scale (abbreviation)	Reference	Comments
Yale Global Tic Severity Scale (YGTSS)	Leckman et al (1989)	Clinician-rated severity scale gold standard
MOVES (MOVES)	Gaffney et al (1994)	Self-report, not useful in young children
Hopkins Motor and Vocal Tic Severity Scale (Hopkins Scale)	Walkup et al (1992)	Clinician-rated severity scale
Premonitory Urges Scale (PUTS)	Woods et al (2005)	Self-report – giving information about premonitory sensations
Tourette syndrome-specific health related-quality of life scale (GTS-QOL)	Cavanna et al (2008)	Self-report Tourette syndrome-specific quality of life scale (adults only)
Diagnostic Confidence Index (DCI)	Robertson et al (1999)	Clinician-rated, gives lifetime probability of diagnosis
National Hospital Interview Schedule (NHIS)	Robertson and Eapen (1996)	Standardized interview to obtain family history and to diagnose Tourette syndrome, attention deficit hyperactivity disorder, obsessive compulsive behaviours, obsessive compulsive disorder, oppositional defiant disorder, conduct disorder
Tourette syndrome Videotaped Scale (Rush Video)	Goetz et al (1987)	Mainly used in research as standardized videos are used
Obsessive–Compulsive Inventory – revised (O-C Inventory (R))	Foa et al (2002)	Self-report inventory to measure obsessive compulsive symptoms
Social and communication disorders checklist	Skuse et al (2008)	Useful screening scale for presence of social communication disorders
Beck Depression Rating scale (BDRS)	Beck et al (1961)	Self-report adult depression scale
Birleson Child Depression Rating scale (Birleson)	Birleson (1981)	Self-report young person’s depression scale

Table 4. Management of the motor and vocal/phonic tics of Tourette syndrome

Treatment modality	Level of empirical support*	References	Rank order (no of points scored) for UK prescription†	Comments	
Antipsychotics	Haloperidol	A	Ross and Moldofsky (1978) Shapiro et al (1989) Sallee et al (1997)	4 (23) Used worldwide and in many countries, Only drug licensed for Tourette syndrome Many adverse side effects	
	Risperidone	A	Dion et al (2001), Gaffney et al (2002) Bruggeman et al (2001) Scahill et al (2003)	3 (39) Randomized controlled trials in both adults and children Subsequently reports of serious adverse effects = increase in weight and glucose abnormalities (diabetes)	
	Pimozide	A	Ross and Moldofsky (1978) Sallee et al (1997)	6 (6)	Pimozide and haloperidol = efficacy Pimozide less adverse side effects than haloperidol Some reports of prolonged QTC interval with pimozide (difficult with polypharmacy)
			Regeur et al (1986) (LC)		Series of 65 cases
			Pringsheim and Marras		Cochrane Review says effective, but more studies with better methods suggested. Author suggests not an appropriate choice of treatment
	Sulpiride	B	George et al (1993) (DBT)	3 (39)	Case series on 60 patients Case series on 189 patients, sulpiride improved motor and vocal tics and significantly reduced the Yale Global Tic Severity Scale: few side effects (sedation = 16%)
			Yvonneau and Bezard (1970) (SCS)		
			Robertson et al (1990) (LC)		
			Ho et al (2009) (LC)		
	Tiapride	C	Eggers et al (1988) (DBT)		10 patients
	Ziprasidone	C	Sallee et al (2000) (DBT)		Some deaths reported subsequently
	Aripiprazole	C	See Table 5	1† (53)	Becoming first-line treatment in many dedicated Tourette syndrome clinics in UK and Europe (222 patients successfully documented to date)
	Metaclopramide	C	Nicolson et al (2005) (DBT)		Small study
Ondansetron	C	Toren et al (2005) (DBT)		Small study	
Fluphenazine	D	Goetz et al (1984)		16/21 patients, intolerant of previous haloperidol, responded well and/or had fewer side effects when taking fluphenazine	
Olanzapine	D	Stephens et al (2004)		Single blind	
		McCracken et al (2008), Van den Eynde et al (2005), Margolese et al (2002) Meyer (2002), Lucas Taracena et al (2002), Budman et al (2001), Onofrij et al (2000), Stamenkovic et al (2000)		In total less than 50 Tourette syndrome patients have been treated with olanzapine and published	
Quetiapine	D	De Jonge et al (2007), Neves Ramos et al (2007), Copur et al (2007), Mukaddes and Abali (2003), Schaller and Behar (2002), Párraga et al (2001), Matur and Uçok (2003)		All open label or small case series In total about 40 patients with Tourette syndrome have been successfully treated with quetiapine and published	
Amisulpiride	D	Trillet et al (1990) Fountoulakis et al (2004)	5 (10)	Only small case series	

* A=good (two or three double blind trials), B = adequate (one double blind trial and other evidence, e.g. series total > 150 patients), C = fair (one double blind trial only, or open label or series, case reports (< 150 patients)), D = minimal (only case reports; small series). † for full explanation, see text on p. S1. CR = Cochrane review; DBT = double-blind trials; LC = large cohort; MA = meta-analysis; SCS = small case series. Updated and modified from Scahill et al (2006)

Table 4. Management of the motor and vocal/phonic tics of Tourette syndrome (continued)

Treatment modality	Level of empirical support *	References	Rank order (no of points scored) for UK prescription†	Comments		
Other medications	Clonidine	Goetz et al (1987) (DBT) TS Study Group (2002) (DBT) Gaffney et al (2002) (DBT) Hedderick et al (2009) (DBT)	2 (41)	Tablets		
		Du et al (2008) (DBT) Kang et al (2009) (DBT)		Transdermal patch		
		Bloch et al (2009) (MA)				
	Botulinum toxin	B	Marras et al (2001) (DBT)		Decreased tics, decreased urges, patients not satisfied	
			Awaad (1999) (LC)		450 patients (many responded well)	
		Porta et al (2004) (LC) Scott et al (1996) Salloway et al (1996) (SCS) Trimble et al (1998) (SCS) Kwak et al (2000) (SCS) Vincent (2008) (SCS)		30 patients – open label – decreased tics, decreased urges, increased quality of life; hypophonia in 80%		
		Atomoxetine	B	Allen et al (2005) Spencer et al (2008)		Double blind trials (attention deficit hyperactivity disorder and tics reduced but attention deficit hyperactivity disorder more so)
				Topiramate	C	Jankovic et al (2010) (DBT)
	Nicotine	C	Silver et al (2001a) (DBT) Dursun et al (1994) (SCS)			
	Mecylamine	C	Silver et al (2001b) (DBT) Silver et al (2000) (SCS)			
	Baclofen	C	Singer et al (2001) (DBT)		Only 10 patients	
			Awaad (1999)		250/264 improved with baclofen	
Guanfacine	C	Scahill et al (2001) (DBT)				
		Chappell et al (1995) (SCS)				
Pergolide	C	Gilbert et al (2000) (DBT)		24 youngsters		
		Lipinski et al (1997)		Small open-label trial		
Naltrexone	C	Kurlan et al (1991) (DBT)		Naltrexone significantly reduced tics		
Levetiracetam	D	Smith-Hicks et al (2007) (DBT)		n=22 – not useful		
		Hedderick et al (2009) (DBT)		n=12 – not useful		
		Fernandez-Jaen et al (2009)		Open-label study; n=29		
		Awaad et al (2005)		n=60 – useful		
		Oulis et al (2008)		n=1		
		Seijo-Martinez et al (2008)		n=1		
Tetrabenazine	D	Jankovic et al (1984)	7	n=9		
		Porta et al (2008) (LC)		n= 77		
Clonazepam	D	Merikangas et al (1985)	8 (1)	Single-blind		
		Gonce and Barbeau (1987)		Add on		

* A=good (two or three double blind trials), B = adequate (one double blind trial and other evidence, e.g. series total > 150 patients), C = fair (one double blind trial only, or open label or series, case reports (< 150 patients)), D = minimal (only case reports; small series). † for full explanation, see text on p. S1. CR = Cochrane review; DBT = double-blind trials; LC = large cohort; MA = meta-analysis; SCS = small case series. Updated and modified from Scahill et al (2006)

Table 4. Management of the motor and vocal/phonic tics of Tourette syndrome (continued)

Treatment modality	Level of empirical support*	References	Rank order (no of points scored) for UK prescription†	Comments
Other treatments	Cannabinoids	D	Müller-Vahl et al (2001), Müller-Vahl (2003), Curtis et al (2009) (CR)	Reduced tics and did not produce cognitive impairment Systematic review showed it was not useful
	Transcranial magnetic stimulation	D	Mantovani et al (2006)	First study to show some benefit
Psychological treatments	Habit reversal training	A	Azrin and Peterson (1990) (DBT) O'Connor et al (2001) (DBT) Wilhelm et al (2003) Verdellen et al (2004) Deckersbach et al (2006)	Double blind and randomized controlled trials indicated that habit reversal training was better than psychotherapy and the waiting list
Neurosurgery	Ablative	E		No trials – few cases
	Deep brain stimulation	C or D	Maciunas et al (2007) (DBT) Welter et al (2008) (DBT) Hariz and Robertson (2010) (review)	Two small double blind trials 50–55 cases, 19 centres, 9 targets, targets as yet under debate; ideally research based only at present

* A=good (two or three double blind trials), B = adequate (one double blind trial and other evidence, e.g. series total > 150 patients), C = fair (one double blind trial only, or open label or series, case reports (< 150 patients)), D = minimal (only case reports; small series). † for full explanation, see text on p. S1. CR = Cochrane review; DBT = double-blind trials; LC = large cohort; MA = meta-analysis; SCS = small case series. Updated and modified from Scahill et al (2006)

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Table 5. Aripiprazole in Tourette syndrome (2004–2010)

Reference	No. of patients	Country
Cui et al (2010)	72	China
Frolich et al (2010)	7	Germany
Lyon et al (2010)	11	USA
Ikenouchi-Sugita et al (2009)	1	Japan
Kawohl et al (2009)	10	Switzerland and Germany
Ben Djebara et al (2008)	1	France
Budman et al (2008)	35	USA
Seo et al (2008)	15	Korea
Stenstrom and Sindo (2008)	1	Denmark
Su et al (2008)	1	Taiwan
Winter et al (2008)	1	Germany
Miranda and Castiglioni (2007)	10	Chile
Bubl et al (2006)	2	Germany
Constant et al (2006)	1	Belgium
Davies et al (2006)	11	UK
Duane (2006)	15	USA
Fountoulakis et al (2006)	1	Greece
Murphy et al (2006)	6	USA
Yoo et al (2006)	14	Korea
Dehning et al (2005)	1	Germany
Kastrup et al (2005)	2	Germany
Padala et al (2005)	2	USA
Hood et al (2004)	1	USA
Hounie et al (2004)	1	Brazil
Total	222	

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