



# Tourette syndrome in children and adolescents: aetiology, presentation and treatment<sup>†</sup>

ARTICLE

**Mary May Robertson****SUMMARY**

Tourette syndrome is a complex neuropsychiatric disorder of juvenile onset, characterised by motor and phonic tics. It is associated with a number of comorbid psychiatric conditions and a reduced quality of life in the young person and with parenting stress, caregiver burden and psychopathology in the parents. The global prevalence (about 1%) is higher than previously thought, with a strong male preponderance. Evidence is emerging that Tourette syndrome is not a unified disorder; rather, it encompasses a number of subtypes, characterised by complexity of tics and the simultaneous presence of other behaviours or disorders. This article discusses the aetiology of the syndrome, and examines its clinical features and comorbid psychiatric conditions and psychopathologies. Assessment and diagnosis are also discussed. Psychoeducation is a cornerstone of management, augmented with behavioural and/or pharmacological treatments. Newer therapies, such as deep brain stimulation, offer tantalising possibilities, but further research is still needed.

**LEARNING OBJECTIVES**

- Understand the varied clinical presentations of Tourette syndrome, recognising that it is not a unitary disorder, but has complex manifestations with frequent comorbidities
- Appreciate the evolving understanding of the aetiological processes that contribute to Tourette syndrome, especially the complex gene-environment interactions
- Acquire a working knowledge of current treatments for Tourette syndrome in a range of modalities, including promising experimental therapies

**DECLARATION OF INTEREST**

None

The impact of this disorder is significant and a plethora of studies by several groups have examined the quality of life (QoL) of young people who are affected by Tourette syndrome (see Table DS1 in the online data supplement). Despite different schedules, the results have been remarkably consistent, and also concordant with adult data, showing that people with Tourette syndrome have a reduced QoL compared with healthy individuals.

A Tourette-specific quality of life scale has now been validated (the Gilles de la Tourette Syndrome-Quality of Life scale (GTS-QOL; Cavanna 2008) and a version for children and adolescents has been published in Italian (C&A-GTS-QOL; Cavanna 2013). For a full discussion of QoL in people with Tourette syndrome see Robertson (2014a).

Studies have shown considerable parenting stress, caregiver burden and psychopathology in the parents of youngsters with Tourette syndrome (Cooper 2003; Lee 2007) and this is a fruitful area for further research.

**Epidemiology and prevalence**

Tourette syndrome has now been described almost worldwide. Males are more commonly affected, the male/female ratio being 3 or 4 to 1. Clinical characteristics 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 tics whereas the females have obsessive-compulsive behaviours.

Tourette syndrome was once considered to be rare in the general population, but a comprehensive review shows that at least eight studies with similar multistaged methods documented remarkably consistent findings and suggests a global prevalence of between 0.4 and 3.8% for youngsters between the ages of 5 and 18 years, with a calculated prevalence (from raw data) of 1% worldwide, apart from Sub-Saharan Africa (Robertson 2008a,b). A more recent review of my work over 35 years, as well as that of others, suggests an updated figure of 0.85% (Robertson

**Mary May Robertson** is Emeritus Professor of Neuropsychiatry at University College London, UK and an Honorary Professor in the Department of Psychiatry and Mental Health at the University of Cape Town, South Africa. She also acts as Visiting Professor and Honorary Consultant to the Tourette Clinic at St George's Hospital, London and to St George's, University of London, UK. **Correspondence** Professor Mary Robertson, Tourette Clinic, Department of Neurology, Atkinson Morley Wing, St George's Hospital, Blackshaw Rd, London SW17 0QT, UK. Email: rejummr@ucl.ac.uk

<sup>†</sup>This is a condensed and updated version of a chapter published in Hulme-Dickens S (ed) (2014) *Clinical Topics in Child and Adolescent Psychiatry*. RCPsych Publications.

A complex neuropsychiatric disorder with onset in childhood, Tourette syndrome is characterised by multiple motor tics and one or more vocal/phonic tics, lasting longer than a year (World Health Organization, 1992; American Psychiatric Association 2013).

2014b): in any event, the important fact is that Tourette syndrome is more common than was previously thought. The prevalence in special educational populations, such as individuals with intellectual disabilities and emotional and behavioural disorders, is much higher, and in the case of autism spectrum disorders (ASD) it is as high as 6–11% (for individual references see Robertson 2008a,b).

### Aetiological theories

Aetiological suggestions for Tourette syndrome include genetic factors and environmental influences. The latter might be infections and neuroimmunological effects, pre- and/or perinatal difficulties, psychosocial stressors and/or androgen influences. The idea that the aetiology of Tourette syndrome is psychological has now been discredited.

#### *Genetic theories*

No single gene has been identified to date, and although the scientific community has been enthused by the ‘discovery’ of various genes (e.g. *SLTRK1*), it is likely that more than one gene is responsible. For full reviews of the genetics of Tourette syndrome see O’Rourke *et al* (2009) and Deng *et al* (2012). Recent genetic data implicate a genetic variant of *HTR2C*, a rare functional mutation in the *HDC* gene encoding L-histidine decarboxylase, and the *DLGAP3* gene. Another study conducted a genome-wide linkage analysis in a large high-risk Utah pedigree examining a qualitative trait (a diagnosis of Tourette syndrome) and a quantitative phenotype based on tic severity. Two regions of interest were found: chromosome 3p for the Tourette syndrome phenotype and chromosome 1p for tic severity (Knight 2010). These results are all exciting, but emphasise the need for studies on large numbers of individuals using rare variants, sib-pair analysis, extended pedigrees or large cohorts. At least two international collaborative efforts are in place. Of importance is the fact that in the vast majority of individuals with Tourette syndrome the chromosomes are normal (Robertson 1993).

#### *Neuroimmunological theories*

Perhaps stimulated by the fact that no gene(s) have been positively implicated in Tourette syndrome, neuroimmunological theories have been a focus of interest. These include hypotheses of (a) autoimmunity and (b) lowered immunity. These theories began when Swedo *et al* (1998) described a group of 50 children with obsessive-compulsive disorder (OCD) and tic disorders, designated as paediatric

autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The diagnostic criteria included: presence of OCD and/or a tic disorder, prepubertal symptom onset (usually acute and dramatic), association with group A beta-haemolytic streptococcal (GABHS) infections, episodic course of symptom severity and association with neurological abnormalities. The relapsing, remitting course was associated with significant psychopathology, including emotional lability, separation anxiety, night-time fears, bedtime rituals, cognitive deficits, oppositional behaviours and hyperactivity. It must be emphasised that PANDAS and Tourette syndrome are not the same entity.

Recently, researchers have found laboratory evidence of GABHS infections in some patients with Tourette syndrome, and/or documented in several controlled studies that some individuals with Tourette syndrome have increased anti-basal ganglia antibodies (ABGAs). One suggestion in this context is that people with Tourette syndrome have a predisposition to autoimmune responses, as indicated by the reduced frequency of regulatory T-cells that induce tolerance towards self-antigens. Another is that there may be a general lowered immunity, as evidenced by an immunoglobulin A (IgA) dysgammaglobulinaemia. Low levels of IgA may then lead to increased risk of upper respiratory tract infections (see Robertson 2012).

#### *Pre- and perinatal difficulties and androgen influences*

Leckman (2003) has suggested that the mothers of children with tics are 1.5 times as likely to have experienced a complication during pregnancy than the mothers of children who did not have tics. Among monozygotic twins discordant for Tourette syndrome, the index twins with Tourette syndrome have had lower birth weight than their unaffected twins. It has also been demonstrated that the severity of maternal life stress during pregnancy, and severe nausea and/or vomiting during the first trimester, are risk factors for tic disorders in offspring. Other studies have shown that prematurity, low birth-weight, low Apgar scores and more frequent maternal prenatal visits were associated with Tourette syndrome (see Leckman 2003). One controlled study (Burd 1999) demonstrated that people who developed Tourette syndrome had had more pre- and perinatal difficulties than a control group. Maternal smoking during pregnancy has been associated with: (a) a diagnosis of Tourette syndrome (Motlagh 2010; Zhang 2012); (b) increased tic severity (Mathews 2006); and (c) an increased likelihood of comorbid

attention-deficit hyperactivity disorder (ADHD) in Tourette syndrome (Pringsheim 2009; Cui 2010; Motlagh 2010). Finally, Leckman and his group have suggested that androgen exposure ('prenatal masculinisation of the brain') may also be important in the aetiopathogenesis of Tourette syndrome and tic-related disorders.

Thus, the aetiopathology of Tourette syndrome is much more complex than previously recognised, with complicated genetic mechanisms, some infections, pre- and perinatal difficulties, maternal smoking, life stressors and androgens affecting the phenotype (Leckman 2003; Robertson 2012, 2014a).

## Clinical features

### *Onset and characteristic features*

The age at onset of Tourette syndrome ranges from 2 to 21 years, with a mean of 7 years commonly reported. The onset of vocal tics is usually some months to years later, many studies reporting a delay of around 11 years. Tics usually begin in the head and face, and eye blinking is often the first (and one of the most common) tics. Tics can be simple (e.g. blinking, eye rolling) or complex (e.g. touching, hopping). Simple vocal tics include sniffing, throat clearing, gulping, snorting and coughing. Complex vocal tics include barking, making animal noises and uttering strings of words. Tics characteristically wax and wane, are usually preceded by premonitory sensations, diminish during goal-directed behaviour and increase with emotional excitement and fatigue.

Other important and characteristic features include echolalia (copying what others say), echopraxia (copying what others do), palipraxia (repeating one's action) and palilalia (repeating the last word or part of one's sentences). Non-obscene socially inappropriate behaviour and self-injurious behaviour are both common and difficult to treat.

### *Echo phenomena*

Echo phenomena have long been understood to be part of Tourette syndrome, described by Gilles de la Tourette himself in 1885. In one study, echo phenomena were significantly associated with the longer duration and severity of Tourette syndrome, as well as measures of obsessiveness, depression and anxiety (Robertson 1988). Echo phenomena are healthy in children up to 36 months of age, but in older children clinicians should investigate for neuropsychiatric pathology. Echo phenomena are a feature of Tourette syndrome, with patients echoing both healthy movements and tics, although, as expected, echoes were predominantly part of the tic repertoire (Ganos 2012a).

### *Coprolalia and copropraxia*

Coprolalia has been widely misunderstood as a pathognomonic feature. It denotes inappropriate, involuntary, out-of-context swearing, often disguised by the patient and without offensive intent. Instead of the whole swear word, many individuals say only part of the word (e.g. 'fu fi') and disguise it, for example, by coughing. It occurs in about 20–30% of patients of Tourette syndrome clinics and begins within 5 years of tic onset. It seldom occurs in community samples. The Tourette Syndrome Association in the USA suggests that as few as 10–15% of all people with Tourette syndrome have this feature.

Many physicians are still under the misapprehension that coprolalia must be present for the diagnosis to be made. Coprolalia is often used in the media as a symptom of Tourette syndrome, probably because its sensational effect increases viewing numbers.

It has been suggested that copropraxia (the inappropriate making of obscene gestures) occurs in about 6–18% of clinic patients (Robertson 1988; Freeman 2009). Those authors have also documented that coprophenomena are associated with tic severity, repetitive behaviours, the amount of comorbid psychiatric disorders and the number of anti-tic medications taken.

### *Peak of severity and premonitory sensations*

The peak of tic severity is around 10–12 years of age. Symptoms usually begin with transient bouts of tics, but by 10 years, most children notice nearly irresistible urges that precede the tics. These premonitory sensations appear to be in the child's conscious awareness and are likely to reflect a defect in sensorimotor gating because they intrude and become a source of distraction. Premonitory sensations are common, occur with the majority of tics and may be either localised (around the area of the tic) or generalised (covering a wide area of the body). They have been likened to the 'urge' or 'tight' sensation before a sneeze and, as with the sneeze in healthy people, they are usually relieved by the tics (Kwak 2003). It has been understood that most people can suppress tics, and that this is in part due to the premonitory sensations. In a recent study, however, it was demonstrated that there was no correlation between the perceived strength of premonitory sensations and the ability to suppress tics: in other words, the urges and tic inhibition are not directly related (Ganos 2012b).

Over the course of hours, tics occur in bouts, with a regular inter-tic interval (Leckman 2006). It has been suggested that there may be a fractal, deterministic and possibly chaotic process in the

tic time series (short-term bouts, and longer-term waxing and waning) (Peterson 1998).

### Comorbidity with Tourette syndrome

The comorbid psychiatric disorders most commonly seen in Tourette syndrome include ADHD, obsessive-compulsive behaviours, OCD and ASD. The relationships between these and Tourette syndrome are complex and are summarised in Table 1.

An investigation embracing 3500 clinic patients with Tourette syndrome worldwide demonstrated that at all ages, 88% of individuals had reported comorbidity/psychopathology. The most common was ADHD, followed by obsessive-compulsive

behaviours and OCD. Anger control problems, sleep difficulties, coprolalia and self-injurious behaviours reached high levels only in patients with comorbid disorders. Males were more likely than females to have comorbid disorders (Freeman 2000). This has also been shown to be true in community studies, with around 90% of people with Tourette syndrome having attracted other diagnoses (for studies, see Robertson 2012). Thus, both in clinic populations and in the community, only about 10% of people with just Tourette syndrome ('Tourette syndrome alone') have tics and 90% have comorbid psychiatric diagnoses.

### *Attention-deficit hyperactivity disorder*

Relatively recently, research groups have separated individuals with Tourette syndrome into subgroups on the basis of clinical symptoms, specifically separating those with and without ADHD. Thus, they have examined children with Tourette syndrome alone, and compared them with groups such as Tourette syndrome plus ADHD, ADHD alone, and unaffected controls. Youngsters with Tourette syndrome alone did not differ from unaffected controls on many ratings, including aggression, delinquency and conduct difficulties. By contrast, children with Tourette syndrome plus ADHD were significantly above unaffected controls, and similar to those with ADHD alone, on the indices of disruptive behaviours. Studies further showed that youngsters with Tourette syndrome plus ADHD demonstrated more internalising and behaviour problems and poorer social adaptation than children with Tourette syndrome alone or controls. Of importance is that youngsters with Tourette syndrome alone were not significantly different from unaffected controls on most measures of externalising behaviours and social adaptation, but had more internalising symptoms.

In summary, individuals with Tourette syndrome alone appear to be similar to healthy controls and, except for the internalising problems, significantly different from those with Tourette syndrome plus ADHD, and this clearly has major management and prognostic implications (Robertson 2006a).

### *Obsessive-compulsive disorder and obsessive-compulsive behaviour*

In other controlled studies, young people with Tourette syndrome have been shown to have more obsessional symptoms than control participants. Importantly, the obsessive-compulsive behaviours encountered in Tourette syndrome are statistically and clinically different from those behaviours in OCD (for a review, see Robertson 2000, 2003). The obsessive-compulsive behaviours in people with

**TABLE 1** Comorbid disorders and coexistent psychopathology in young people with Tourette syndrome<sup>a</sup>

	Incidence	Aetiology/possible associations
<b>Comorbid disorders</b>		
ADHD	Most common: 21–90%; mean: 60%	Genetic in a subgroup
OCB/OCD	Common: 27–32% in clinics	Integral part of Tourette's; share genetic influences
ASD	6–11%	Genetic in a subgroup; also probably non-specific and there may be general neurodevelopmental problems
Self-injurious behaviour	30%	Difficult to treat
Non-obscene socially inappropriate behaviour	Common (30–60%)	Possibly related to impulsivity, ADHD or conduct disorder; not related to OCB/OCD
<b>Coexistent psychopathology</b>		
Depression	13–76%	Multifactorial; not genetic
Anxiety	Common (range 19–80%)	Secondary to having Tourette's; some suggest anxiety pre-dates tics
Personality disorders	Common (64%)	Probably related to childhood ADHD, ODD, conduct disorder
Dysphoria	Fairly common with almost all antipsychotics	Side-effect of anti-Tourette's medication
School phobia/separation anxiety	Not common, but noted	May be side-effect of anti-Tourette's medication
Rage or explosive outbursts	20%	Associated with ADHD, tic severity, lower age at tic onset, prenatal exposure to tobacco
Sleep problems	Very common: 75%	Night terrors, insomnia, nightmares, sleep-walking, sleep-talking/walking, nocturnal enuresis, bruxism
Cognitive dulling/drowsiness	32% (some studies)	Side-effect of anti-Tourette's medication
Dyslexia, dyspraxia, reading difficulties	6%	
Schizophrenia	Very rare	Co-occurs by chance
Total comorbidity and/or psychopathology	88–90%	Mixed

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorders; OCB, obsessive-compulsive behaviour; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder.

a. For a more detailed version of this table, including study references, see online Table DS2.

Tourette syndrome include thoughts (obsessions) of violence, sex and aggression, and actions (compulsions) concerning touching of the self and/or others, symmetry and ordering. This differs from many people with OCD, who are often more preoccupied with dirt, germs and contamination. It is also clear that there is a genetic link between Tourette syndrome and obsessive-compulsive behaviours (Eapen 1993).

### **Autism spectrum disorder**

It has long been documented that Tourette syndrome and ASD have clinical similarities and share many symptoms. Evidence has been emerging from phenomenological, epidemiological and pathogenetic perspectives (State 2010) that Tourette syndrome and ASD overlap. It has been suggested that shared molecular pathways affect the development of both disorders: examples include disruption of the *NRXN1*, *NLGN4X* and *CNTNAP2* genes (Clarke 2012; Eapen 2012).

It seems likely that the disorders discussed in this section are comorbid with Tourette syndrome because they have neurodevelopmental similarities, clinical similarities and in some cases are probably genetically related.

### **Coexistent psychopathology**

The most common coexistent psychopathologies found in Tourette syndrome include depressive illness, depressive symptoms, anxiety, phobias, intellectual disability and, in adolescents and adults, personality disorder. These appear to be coexisting rather than comorbid, as they are unlikely to share a genetic underpinning. The psychoses, such as bipolar affective disorder, are probably related to other disorders such as OCD and ADHD, whereas schizophrenia is rare and the two disorders co-occur only by chance (Robertson 2003, 2012). The relationships between Tourette syndrome, comorbid disorders and coexistent psychopathology are summarised in Table 1.

There is some exciting evidence emerging that specific aspects of the aetiology, phenotype and indeed endophenotype (e.g. specific brain changes related to a particular clinical type) may be found in Tourette syndrome and this is a worthwhile direction for future research (Robertson 2013).

### **Aggression and behavioural difficulties**

It has been suggested that aggressive behaviours are probably influenced by both genetic (e.g. the *MAOA* gene) and epigenetic (e.g. risk to the fetus, pre- and perinatal difficulties) factors (Liu 2011a). For example, violence or aggression to women during pregnancy can result in obstetric problems

and altered personality in offspring if the child has an individual vulnerability. Environmental effects such as early-life stressors may also play a part (Verhoeven 2012). There are, of course, also cultural theories of aggression, for example that it is related to the male dominance in society or that children learn it from their early role models such as parents.

As already mentioned, one of the most common comorbidities in youngsters with Tourette syndrome is ADHD (Robertson 2012). Compared with unaffected peers, adults with Tourette syndrome are more likely to have personality disorders (e.g. Robertson 1997). In youngsters with both Tourette syndrome and ADHD (compared with Tourette syndrome alone) there are significantly more disruptive behaviours (Robertson 2006a), and adults with Tourette syndrome have additional problems with substance misuse, aggression and forensic encounters (Haddad 2009). Some of the explanations may be integral to Tourette syndrome, whereas others may well be generic, as outlined above.

It appears that Tourette syndrome and conduct disorder are not intimately (i.e. aetiologically, genetically) connected. In a person with Tourette syndrome and conduct disorder, the latter is associated with ADHD in the proband and a family history of violence, aggression and forensic encounters (Robertson 2015).

### **Types of Tourette syndrome**

There have been many studies indicating that Tourette syndrome is not a unitary condition as suggested, indeed stipulated, by both American Psychiatric Association (DSM-5) and World Health Organization (ICD-10) diagnostic criteria. An early study of 90 people with Tourette syndrome found a high incidence of obsessiveness, depression and hostility (Robertson 1988). Importantly, depression was not related to medication. Aggression, hostility and obsessiveness were significantly associated with some core features of Tourette syndrome, including copro- and echo-phenomena and a family history of the syndrome.

The first study to formally investigate the phenotype was that of Alsobrook & Pauls (2002), who used hierarchical cluster analysis (HCA) and principal component factor analysis (PCFA) and reported four significant factors, which accounted for 61% of the variance. These were:

- aggressive phenomena (e.g. kicking, temper fits and argumentativeness)
- motor and vocal/phonic tics only
- compulsive phenomena
- tapping and absence of grunting.

Since then there have been many other analytical studies conducted on clinical cohorts (see Robertson 2014d), and all have reported more than one type or phenotype. A large multiply affected pedigree living in the community was submitted to HCA and PCFA and again four types (phenotypes) were found (Robertson 2007). Moreover, in all studies that examined for it, one type was 'pure Tourette syndrome', i.e. motor and vocal tics only. This is in agreement with the clinical data of Freeman *et al* (2000) and community data of Khalifa & von Knorring (2003, 2005), who found that only about 10% of all individuals with Tourette syndrome have only motor and vocal tics. Although not directly comparable, all studies using HCA, PCA or latent class analysis (LCA) have shown two or more factors, in terms of both tics and psychopathology. Further studies have used similar methods, and although their results give different slants, they agree that there is more than one phenotype (Robertson 2014d). Robertson (2014b) highlights the neurological heterogeneity as well as other clinical differences (other than comorbidity and psychopathology) encountered in Tourette syndrome.

All these studies add to the growing body of evidence that Tourette syndrome is not a unitary condition. Thus, one is able to conclude that the Tourette syndrome phenotype is heterogeneous and not unitary as previously suggested and shown in DSM and ICD. In conclusion, whether using complex statistical methods (e.g. HCA, PCA, LCA) or material derived from clinical or community settings, one type (phenotype) or clinical presentation of Tourette syndrome consists of 'pure simple motor and vocal tics only', whereas other phenotypes include complex tics and the comorbid disorders, various coexistent psychopathologies and complex behaviours.

### Assessment

The assessment of patients with Tourette syndrome requires a thorough personal and family history, as well as full mental state and neurological examinations. Several standardised schedules may be useful for accurately diagnosing Tourette syndrome, assessing the response to medication and in research (Box 1). The physician-rated Diagnostic Confidence Index and the self-rated MOVES in particular are useful for the practising clinician, as they will ensure that the main symptoms for diagnosis (Diagnostic Confidence Index) and severity (MOVES) are assessed. The Diagnostic Confidence Index highlights the phenomenological characteristics of tics, including the presence of coprolalia, echolalia and palilalia,

### BOX 1 Some instruments for diagnosing Tourette syndrome, assessing medication response, and research

- National Hospital Interview Schedule
- Yale Global Tic Severity Scale
- Premonitory Urge for Tics Scale (self-rated)
- Motor tic, Obsessions and compulsions, Vocal tic Evaluation Survey (MOVES)
- Hopkins Motor and Vocal Tic Severity Scale
- Rush Video-Based Tic Rating Scale
- Diagnostic Confidence Index

For reviews of these scales see Robertson & Cavanna (2008c) and Robertson (2011)

complex tics, premonitory urges/sensations, relief after tics, suppressibility, rebound, suggestibility, variability of tics, and the waxing and waning course (Robertson 1999).

Familiarity with Tourette syndrome, as well as training by an expert, are important for implementing most of these scales. However, a good clinician, given time, will be able to elicit symptoms, make a diagnosis and give correct treatment and management.

Many clinicians would suggest blood sampling for copper and ceruloplasmin (to exclude Wilson's disease) and acanthocytes (to exclude neuroacanthosis) as good practice, but genetic testing for Huntington's disease would only be undertaken exceptionally. Neuroimaging in research studies shows differences between patients with Tourette syndrome and controls, and endophenotypes (brain changes specific to Tourette syndrome) have been suggested (Robertson 2013): in routine practice, however, computed tomography, electroencephalograms (EEGs) and electrocardiograms (ECGs) are usually non-contributory. These investigations are usually only warranted to exclude any other diagnosis, such as myoclonic (jerking) or petit mal (blinking) epilepsy or chorea with rheumatic fever.

### Management and treatment

The treatment for all individuals with Tourette syndrome includes psychoeducation, reassurance and explanation. In many mild cases and young people this may in fact suffice. Medication is the mainstay for the majority of symptoms of Tourette syndrome and many of the comorbid conditions and coexistent psychopathologies. New strategies include the successful and side-effect-free habit reversal training and comprehensive behavioural

intervention for tics. Injection of botulinum toxin into the periorbital tissues and vocal cords has yet to be fully evaluated, and deep brain stimulation for severe and refractory tics in adults also needs further study (see Robertson 2011, 2012, 2014a).

Table 2 includes the main management strategies and medications for Tourette syndrome currently available and used by many clinicians. Empirical evidence of efficacy, ranked A to D ('good' to 'minimal'), has been collated from double-blind trials (best evidence), large series (some evidence) and case reports (minimal or anecdotal evidence) and also personal experience, which, although anecdotal, covers many patients and is representative of clinic populations.

### **Behavioural interventions**

Behavioural methods for adult and child patients may be useful alone or in combination with medications for many aspects of Tourette syndrome. Habit reversal training has been shown to be significantly better than or equal to supportive psychotherapy and better than the waiting list for adults with Tourette syndrome. Comprehensive behavioural intervention for tics was found to be helpful for young people (Piacentini 2010). Exposure and response prevention has also proved very successful in the treatment of tics, and a novel non-pharmacological treatment using self-hypnosis was successful in 26 (almost 80%) of 33 children (see Robertson 2012). In recent

**TABLE 2** Main strategies of the management of the motor and vocal/phonic tics of Tourette syndrome in young people, showing the quality of the current evidence<sup>a</sup>

Treatment	Empirical evidence <sup>b</sup>	Comments
Haloperidol (antipsychotic)	A: good	Three DBTs show haloperidol better than placebo Has many adverse side-effects; used worldwide: in many countries is the only drug licensed for Tourette syndrome
Risperidone (antipsychotic)	A: good	Four RCTs in both adults and children Subsequent reports of serious adverse effects: increase in weight and glucose abnormalities (diabetes); in common use worldwide
Pimozide (antipsychotic)	A: good	Four DBTs show that pimozide and haloperidol have equal efficacy, and pimozide fewer adverse side-effects than haloperidol Some reports of prolonged QTc interval with pimozide; widely used
Sulpiride (antipsychotic)	B: adequate	One DBT showed that sulpiride was superior to placebo; one small case series and two large case series (249 patients) showed that sulpiride improved motor and vocal tics and had few side-effects Widely used in UK; unavailable in USA and Canada
Tiapride (antipsychotic)	B: adequate	One DBT v. placebo (number of patients not given) and one DBT (10 patients) showed tiapride superior to placebo Widely used in Europe (most common in Russia and Germany); unavailable in UK, USA, Canada
Aripiprazole (antipsychotic)	B: adequate	Positive successful reports in 222 patients; pilot study in China showed aripiprazole to be effective and safe, with transient minimal side-effects; treated 20 adults for 56 months successfully; series of 100 patients treated successfully; multicentre controlled study in China showed it as effective as tiapride Becoming first-line treatment in many dedicated Tourette's clinics in UK and Europe
Clonidine	A: good	Six DBTs showed clonidine (tablets and transdermal patches) superior to placebo
Botulinum toxin	B: adequate	One DBT showed decreased tics, decreased urges; one series of 30 in open label study showed decreased tics, decreased urges, improved QoL hypophonia in 80% of the 30; other case series and reports showed positive results
Atomoxetine	B: adequate	Two DBTs showed reduced tics and ADHD
Tetrabenazine	D: minimal	Two studies (86 patients) report success; no DBTs; depression is common side-effect Used mainly by neurologists
Habit reversal training	A: good	RCTs show it to be better than psychotherapy, and waiting list to be as effective as other behavioural methods
Exposure and response prevention	A: good	More evidence for habit reversal training than for exposure and response prevention
Comprehensive behavioural intervention for tics	A: good	Good improvement
Deep brain stimulation	Not indicated for young people	Just over 100 patients with Tourette syndrome have had DBS for severe refractory symptoms with good effect At present only recommended in research centres with strict protocols

ADHD, attention-deficit hyperactivity disorder; DBT, double-blind trial; QoL, quality of life; RCT, randomised controlled trial.

a. For a more detailed version of this table, including study references, see Robertson 2014b: Table 17.3.

b. A, good, 2–3 DBTs; B, adequate, 1 DBT, >150 patients; C, fair, 1 DBT only, or open label trial or case series/case reports, <150 patients; D, minimal, only case reports, small series.

European guidelines, behavioural therapies are recommended as a first-line treatment of Tourette syndrome, albeit on the basis of evidence less strong than for habit reversal training (Verdellen 2011).

### *Pharmacological interventions*

Medication is often required for the treatment of moderate to severe tics and psychopathologies in patients with Tourette syndrome. Double-blind trials have demonstrated that many medications (Table 2) are superior to placebo. Importantly, the dose given for Tourette syndrome is small compared with the dose for schizophrenia or mania. Thus, a daily dose of 0.5–3 mg of haloperidol may be sufficient in Tourette syndrome, whereas 30 mg may be required in severe mania or schizophrenia in adults. Tetrabenazine can also be effective and is prescribed mainly by neurologists: a side-effect can be depression. Clonidine (or guanfacine in the USA) can be given for tics, impulse control and ADHD (and it may also help with insomnia). A baseline ECG is advisable, as is regular monitoring of pulse and blood pressure. One can commence at a dose of 25 µg, increasing gradually to 150 µg daily. It is advisable to take blood for a baseline prolactin, as many antipsychotic medications result in hyperprolactinaemia, which can have endocrinological repercussions (Robertson 2000, 2012).

Antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), are useful for depression (e.g. fluoxetine at a standard dose of 20 mg/day) and obsessive-compulsive behaviours or OCD (e.g. fluoxetine at 40–60 mg/day). Clomipramine (a tricyclic antidepressant) may also be useful in obsessive-compulsive behaviours or OCD, but it usually has more side-effects than the SSRIs and is dangerous in overdose. In the obsessive-compulsive behaviours and OCD associated with Tourette syndrome, a small dose of an antipsychotic is useful as an augmentation agent. It is important to know that the response to individual antipsychotics is idiosyncratic; a patient may respond to one but not another and, unfortunately, not to a second trial of an original medication, if discontinued.

Recently, the newer atypical (second-generation) antipsychotics have been shown to be useful in treating Tourette syndrome. The main side-effects are weight increase and, in some individuals, precipitation of diabetes or metabolic syndrome. It is therefore advisable to check fasting glucose levels in patients receiving the atypicals, especially if they have put on weight. Atypical antipsychotics used successfully in treating Tourette syndrome include risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. In both the literature

and my clinical experience, patients treated with antipsychotics can have raised prolactin levels, which in some cases requires discontinuation of the drugs (Robertson 2012). Rickards *et al* (2012) have reported findings from a survey of European prescribing practices in Tourette syndrome which showed that, in the management of various symptom clusters, risperidone was most frequently prescribed for tics, sertraline for obsessive-compulsive behaviours and methylphenidate for ADHD. The use of aripiprazole has gained momentum in Europe, the UK and the USA, and one controlled trial in China showed it to be as effective as tiapride (Liu 2011b). Aripiprazole is therefore rated B in Table 2.

As stated earlier, clonidine has been used in the treatment of Tourette syndrome and of ADHD, and thus it may well be a useful treatment for individuals with both disorders. Good evidence for the safety and efficacy of the combination of stimulants and clonidine comes from a large randomised double-blind trial including over 130 children who had ADHD and a tic disorder and were treated with clonidine alone, methylphenidate alone, clonidine and methylphenidate, or placebo (Tourette's Syndrome Study Group 2002). Compared with placebo, the greatest benefit was with the combination of clonidine and methylphenidate. Of importance was that the proportion of participants reporting a worsening of tics was no higher in those treated with methylphenidate than in those receiving clonidine or placebo.

Thus, it does appear from evidence-based studies that stimulants, if used judiciously in patients with Tourette syndrome or tics and comorbid ADHD, do not necessarily increase tics. In addition, the combination of stimulants and clonidine appears to be safe. Atomoxetine is a relatively new agent for the treatment of ADHD and it may prove useful in the treatment of Tourette syndrome plus ADHD – further research is needed.

A less used but successful treatment is botulinum toxin injected into affected areas (e.g. the vocal cords for loud distressing vocal tics and coprolalia); treatment is usually carried out by a neurologist with special expertise, in expert clinics.

Deep brain stimulation is used worldwide for Parkinson's disease, tremor and dystonia, and even for depression, OCD and Tourette syndrome (e.g. Hariz 2010). It has been used in over 100 people with Tourette syndrome, but only those with severe refractory illness. It is unlikely that it would be used in youngsters under the age of 20.

## Continuity into adult life

It was initially thought that Tourette syndrome was lifelong. Several studies have now reported that tic severity reduces during adolescence and it seems that by the age of 18, tics decrease in many patients. Only greater tic severity in childhood has been associated with increased tic severity at follow-up. Although the prognosis for Tourette syndrome is better than originally thought concerning tic symptomatology (for a review, see Robertson 2008a,b), the comorbidity often changes with age (Rizzo 2012) and the psychopathology (e.g. depression) worsens with age (e.g. Robertson 2006b).

In an elegant study, Pappert *et al* (2003) followed up a group of 56 individuals with Tourette syndrome who had been videotaped according to a strict protocol between 1978 and 1991, when they were 8- to 14-year-olds. Thirty-one of the original cohort, now aged over 20, were contacted and included in a follow-up video study. A rater assessed the 62 tapes and rated five tic domains: the two videotapes for each participant were compared for each tic domain, as well as a composite tic disability score. Results showed that 90% of the adults still had tics. Many patients who had suggested that they were tic free were not, as no less than 50% had objective evidence of tics. The mean tic disability score reduced significantly with age. All tic domains improved with age and there were significant improvements for motor tics. The improvements in tic disability were not related to medication, as only 13% of the adults were receiving medication for tics, compared with 81% of the children. The authors concluded that although tics improve with time, most adults have persistent tics.

Rizzo *et al* (2012) investigated 100 people with Tourette syndrome who were assessed at onset and at follow-up 10 years later to evaluate the severity of the tics and the presence of comorbid disorders and coexistent psychopathologies. Impairment was also evaluated. At 10-year follow-up, 58% of the 38 individuals with 'pure' Tourette syndrome (i.e. no comorbidity) persisted with the same 'pure' clinical phenotype, whereas 42% had changed to a 'Tourette plus OCD' phenotype. In the Tourette plus OCD subgroup, 55% required medication and fared better than those with initial comorbidities, who also had a significantly reduced quality of life.

## Conclusions

Tourette syndrome is now recognised to be common, affecting about 1% of the population almost worldwide. The aetiology is more complex

than was once thought, and is widely accepted to be genetic in most individuals, although no single gene has been identified. Other behaviours, however, such as obsessive-compulsive behaviours and OCD, are widely recognised phenotypes of the putative gene(s). Newer evidence is that some cases of ADHD and ASD also share some genetic underpinning. Other aetiopathological suggestions include environmental influences, such as infections, neuroimmunological effects, pre- and/or perinatal difficulties, psychosocial stressors and/or androgen influences. The old idea that Tourette syndrome is psychological and to be treated with psychoanalysis has now been discredited.

Exciting evidence is emerging that specific aspects of the aetiology, phenotype and endophenotype (e.g. brain changes related to a particular clinical type) may be identified in Tourette syndrome and this is a worthwhile direction for future research.

A wide variety of comorbid psychiatric disorders and/or psychopathology are common, and it seems that the presentation may change over time. Unexpectedly, it appears that uncomplicated Tourette syndrome (without comorbid disorders) may not have the best prognosis. Some comorbidities are common and integral (e.g. OCD, obsessive-compulsive behaviours, ADHD, ASD), whereas some coexistent psychopathologies (e.g. depression) are common but multifactorial in origin, and others (such as personality disorder in adults and bipolar affective disorder) may be due to comorbid conditions (e.g. ADHD, OCD) rather than Tourette syndrome itself.

Treatment should be symptom targeted and, ideally, should also be holistic. This is important as it not only alleviates the suffering but may also improve the outlook in terms of tics, psychopathology and psychosocial functioning. Habit reversal training, exposure response prevention and comprehensive behavioural intervention are gaining momentum in the treatment of tics in Tourette syndrome. Deep brain stimulation is currently the 'quantum leap' in many of our professional lives, but remains a research tool.

## References

- Alsobrook JP 2nd, Pauls DL (2002) A factor analysis of tic symptoms in Gilles de la Tourette's syndrome. *American Journal of Psychiatry*, **159**: 291–6.
- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders (5th edn) (DSM-5)*. APA.
- Burd L, Severud R, Klug MG, et al (1999) Prenatal and perinatal risk factors for Tourette disorder. *Journal of Perinatal Medicine*, **27**: 295–302.
- Cavanna AE, Schrag A, Morley D, et al (2008) The Gilles de la Tourette Syndrome – Quality of Life scale (GTS-QOL): development and validation. *Neurology*, **71**: 1410–6.

**MCQ answers****1 d    2 d    3 c    4 d    5 a**

- Cavanna AE, Luoni C, Selvini C, et al (2013) The Gilles de la Tourette Syndrome – Quality of Life Scale for children and adolescents (C&A-GTS-QOL): development and validation of the Italian version. *Behavioural Neurology*, **27**: 95–103.
- Clarke RA, Lee S, Eapen V (2012) Pathogenetic model for Tourette syndrome delineates overlap with related neurodevelopmental disorders including autism. *Translational Psychiatry*, **2**: e158.
- Cooper C, Robertson MM, Livingston G (2003) Psychological morbidity and caregiver burden in parents of children with Tourette's disorder and psychiatric comorbidity. *Journal of the American Academy of Child & Adolescent Psychiatry*, **42**: 1370–5.
- Cui YH, Zheng Y, Yang YP, et al (2010) Effectiveness and tolerability of aripiprazole in children and adolescents with Tourette's disorder: a pilot study in China. *Journal of Child and Adolescent Psychopharmacology*, **20**: 291–8.
- Deng H, Gao K, Jankovic J (2012) The genetics of Tourette syndrome. *Nature Reviews (Neurology)*, **8**: 203–13.
- Eapen V, Pauls DL, Robertson MM (1993) Evidence for autosomal dominant transmission in Tourette's syndrome: United Kingdom cohort study. *British Journal of Psychiatry*, **162**: 593–6.
- Eapen V (2012) Neurodevelopmental genes have not read the DSM criteria: Or, have they? *Frontiers in Psychiatry*, **3**: 75.
- Freeman RD, Fast DK, Burd L, et al (2000) An international perspective on Tourette syndrome: selected findings from 3,500 individuals in 22 countries. *Developmental Medicine and Child Neurology*, **42**: 436–47.
- Freeman RD, Zinner SH, Muller Vahl KR, et al (2009) Coprophenomena in Tourette syndrome. *Developmental Medicine and Child Neurology*, **51**: 218–27.
- Ganos C, Ogrzal T, Schnitzler A, et al (2012a) The pathophysiology of echopraxia/echolalia: relevance to Gilles de la Tourette syndrome. *Movement Disorders*, **27**: 1222–9.
- Ganos C, Kahl U, Schunke O, et al (2012b) Are premonitory urges a prerequisite of tic inhibition in Gilles de la Tourette syndrome? *Journal of Neurology, Neurosurgery and Psychiatry*, **83**: 975–8.
- Haddad ADM, Umoh G, Bhatia, V, et al (2009) Adults with Tourette's syndrome with and without attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica*, **120**: 299–307.
- Hariz MI, Robertson MM (2010) Deep brain stimulation and the Gilles de la Tourette syndrome. *European Journal of Neuroscience*, **32**: 1128–34.
- Khalifa N, von Knorring AL (2003) Prevalence of tic disorders and Tourette syndrome in a Swedish school population. *Developmental Medicine and Child Neurology*, **45**: 315–9.
- Khalifa N, von Knorring AL (2005) Tourette syndrome and other tic disorders in a total population of children: clinical assessment and background. *Acta Paediatrica*, **94**: 1608–14.
- Knight S, Coon H, Johnson M, et al (2010) Linkage analysis of Tourette syndrome in a large Utah pedigree. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics*, **153B**: 656–62.
- Kwak C, Dat Vuong K, Jankovic J (2003) Premonitory sensory phenomena in Tourette's syndrome. *Movement Disorders*, **18**: 1530–3.
- Leckman JF (2003) In search of the pathophysiology of Tourette syndrome. In *Mental and Behavioral Dysfunction in Movement Disorders* (eds MA Bedard, Y Agid, S Chouinard, et al): 467–76. Humana Press.
- Leckman JF, Bloch MH, Scamill L, et al (2006) Tourette syndrome: the self under siege. *Journal of Child Neurology*, **21**: 642–9.
- Lee MY, Chen YC, Wang HS, et al (2007) Parenting stress and related factors in parents of children with Tourette syndrome. *Journal of Nursing Research*, **15**: 165–74.
- Liu J (2011a) Early health risk factors for violence: conceptualization, review of the evidence and implications. *Aggression and Violent Behavior*, **16**: 63–73.
- Liu ZS, Chen YH, Zhong YQ, et al (2011b) A multicenter controlled study on aripiprazole treatment for children with Tourette syndrome in China [article in Chinese]. *Chinese Journal of Pediatrics*, **49**: 572–6.
- Mathews CA, Bimson B, Lowe TL, et al (2006) Association between maternal smoking and increased symptom severity in Tourette's syndrome. *American Journal of Psychiatry*, **163**: 1066–73.
- Motlagh MG, Katsovich L, Thompson N, et al (2010) Severe psychosocial stress and heavy cigarette smoking during pregnancy: an examination of the pre- and perinatal risk factors associated with ADHD and Tourette syndrome. *European Child & Adolescent Psychiatry*, **19**: 755–64.
- O'Rourke JA, Scharf JM, Yu D, et al (2009) The genetics of Tourette syndrome: a review. *Journal of Psychosomatic Research*, **67**: 533–45.
- Pappert EJ, Goetz CJ, Loius ED, et al (2003) Objective assessments of longitudinal outcome in Gilles de la Tourette's syndrome. *Neurology*, **61**: 936–40.
- Peterson BS, Leckman JF (1998) The temporal dynamics of tics in Gilles de la Tourette syndrome. *Biological Psychiatry*, **44**: 1337–48.
- Piacentini J, Woods DW, Scamill L, et al (2010) Behaviour therapy for children with Tourette disorder: a randomized controlled trial. *JAMA*, **303**: 1929–37.
- Pringsheim T, Sandor P, Lang A, et al (2009) Prenatal and perinatal morbidity in children with Tourette syndrome and attention-deficit hyperactivity disorder. *Journal of Developmental and Behavioral Pediatrics*, **30**: 115–21.
- Rickards H, Cavanna AE, Worral R (2012) Treatment practices in Tourette syndrome: the European perspective. *European Journal of Paediatric Neurology*, **16**: 361–4.
- Rizzo R, Gulisano M, Cali PV, et al (2012) Long term clinical course of Tourette syndrome. *Brain Development*, **34**: 667–73.
- Robertson MM, Trimble MR, Lees AJ (1988) The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. *British Journal of Psychiatry*, **152**: 383–90.
- Robertson MM, Trimble MR (1993) Normal chromosomal findings in Gilles de la Tourette syndrome. *Psychiatric Genetics*, **3**: 95–9.
- Robertson MM, Banerjee S, Fox Hiley PJ, et al (1997) Personality disorder and psychopathology in Tourette's syndrome: a controlled study. *British Journal of Psychiatry*, **171**: 283–6.
- Robertson MM, Banerjee S, Kurlan R, et al (1999) The Tourette Diagnostic Confidence Index: development and clinical associations. *Neurology*, **53**: 2108–12.
- Robertson MM (2000) Tourette syndrome, associated conditions and the complexities of treatment. *Brain*, **123**: 425–62.
- Robertson MM (2003) The heterogeneous psychopathology of Tourette syndrome. In *Mental and Behavioral Dysfunction in Movement Disorders* (eds MA Bedard, Y Agid, S Chouinard, et al): 443–66. Humana Press.
- Robertson MM (2006a) Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications. A commentary. *European Child and Adolescent Psychiatry*, **15**: 1–11.
- Robertson MM (2006b) Tourette syndrome and affective disorders: an update. *Journal of Psychosomatic Research*, **61**: 349–58.
- Robertson M, Cavanna A (2007) The Gilles de la Tourette syndrome: a principal component factor analytic study of a large pedigree. *Psychiatric Genetics*, **17**: 143–52.
- Robertson MM (2008a) The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 1: the epidemiological and prevalence studies. *Journal of Psychosomatic Research*, **65**: 461–72.
- Robertson MM (2008b) The prevalence and epidemiology of Gilles de la Tourette syndrome. Part 2: tentative explanations for differing prevalence figures in GTS, including the possible effects of psychopathology, aetiology, cultural differences, and differing phenotypes. *Journal of Psychosomatic Research*, **65**: 473–86.

- Robertson M, Cavanna A (2008c) *Tourette Syndrome: The Facts* (2nd edn). Oxford University Press.
- Robertson MM (2011) Gilles de la Tourette syndrome: the complexities of phenotype and treatment. *British Journal of Hospital Medicine*, **72**: 100–7.
- Robertson MM (2012) The Gilles de la Tourette syndrome: the current status. *Archives of Disease in Childhood: Education & Practice*, **97** (5): 166–75.
- Robertson MM, Eapen V (2013) Whither the relationship between etiology and phenotype in Tourette syndrome? In *Tourette Syndrome* (eds D Martino, JF Leckman): 361–94. Oxford University Press.
- Robertson MM (2014a) A personal 35 year perspective on Gilles de la Tourette syndrome: assessment, investigations and management. *Lancet Psychiatry*, **2**: 88–104.
- Robertson MM (2014b) A personal 35 year perspective on Gilles de la Tourette syndrome: prevalence, phenomenology, comorbidities and coexistent psychopathologies. *Lancet Psychiatry*, **2**: 68–87.
- Robertson M (2014c) Tourette syndrome. In *Clinical Topics in Child and Adolescent Psychiatry* (ed S Hulme-Dickens): 262–86. RCPsych Publications.
- Robertson MM (2014d) Movement disorders: Tourette syndrome – beyond swearing and sex? *Nature Reviews Neurology*, **10**: 6–8.
- Robertson MM, Cavanna AE, Eapen V (2015) Gilles de la Tourette syndrome and disruptive behavior disorders: prevalence, associations and explanation of the relationships. *Journal of Neuropsychiatry and Clinical Neurosciences*, **27** (1): 33–41.
- State MW (2010) The genetics of child psychiatric disorders: focus on autism and Tourette syndrome. *Neuron*, **68**: 254–69.
- Swedo SE, Leonard HL, Garvey M, et al (1998) Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *American Journal of Psychiatry*, **155**: 264–71.
- Tourette's Syndrome Study Group (2002) Treatment of ADHD in children with tics: a randomized controlled trial. *Neurology*, **58**: 527–36.
- Verdellen C, van de Grient J, Hartmann A, et al (2011) European Clinical Guidelines for Tourette Syndrome and other tic disorders. Part III: behavioural and psychosocial interventions. *European Child & Adolescent Psychiatry*, **20**: 197–207.
- Verhoeven FE, Booij L, Kruyt AW, et al (2012) The effects of MAOA genotype, childhood trauma, and sex, on trait and state-dependent aggression. *Brain and Behavior*, **2**: 806–13.
- World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. WHO.
- Zhang HY, Liu CY, Wang YQ (2012) Risk factors for Tourette syndrome [article in Chinese]. *Chinese Journal of Contemporary Pediatrics*, **14**: 426–30.

**MCQs**

Select the single best option for each question stem

**1 Which of the following has not been shown to adversely affect quality of life in Tourette syndrome?**

- a tic severity
- b ADHD
- c OCD
- d enlarged ventricles on neuroimaging
- e employment status.

**2 The prevalence of Tourette syndrome worldwide has been estimated as about:**

- a 0.05%
- b 0.2%
- c 0.5%
- d 1%
- e 3%.

**3 The mean age at onset of Tourette syndrome is:**

- a 3 years
- b 5 years
- c 7 years
- d 9 years
- e 11 years.

**4 Which of the following is not thought to be a putative factor in the aetiology of Tourette syndrome?**

- a prenatal androgen exposure
- b autoimmunity
- c maternal smoking during pregnancy
- d pathological psychodynamic defence mechanisms
- e genetics.

**5 Which of the following behavioural treatments has been shown to be effective in the treatments of tics associated with Tourette syndrome?**

- a exposure and response prevention
- b flooding
- c debriefing
- d mindfulness-based meditation
- e behavioural activation.