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REVIEW

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Attention deficit hyperactivity disorder, tics and Tourette's syndrome: the relationship and treatment implications. A commentary

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Abstract Tourette's Syndrome (TS) is now recognised to be a common childhood onset neurodevelopmental disorder. Attention deficit hyperactivity disorder (ADHD) is also a common childhood disorder. There are many cases in which the two disorders are comorbid. The reasons for this are unclear, but the comorbidity does not necessarily point to one genetic cause. Sleep is also often disturbed in individuals with TS and ADHD. The treatment implications of ADHD in the setting of tics or TS are important. Clonidine is suggested as a first line treatment. It was once thought that stimulants were contraindicated in the treatment of ADHD in the setting of TS, whereas it is suggested that they may be safe, but should be used judiciously. In addition, it was once thought that the combination of stimulants and clonidine was contraindicated, but from a large study the combination does appear to be safe. A relatively new medication for ADHD is atomoxetine, and although not documented widely in the setting of tics and TS, it may prove useful in this setting; further research is required. This commentary briefly discusses the comorbidity between TS and ADHD and offers treatment suggestions.

Key words Tourette's syndrome – tics – attention deficit hyperactivity disorder – comorbidity treatment

Introduction

The second European Guidelines for the treatment of attention deficit hyperactivity disorder (ADHD) have recently been published in European Child and Adolescent Psychiatry [Taylor et al. 2004] and have prompted this communication. The present author wishes to make the case for the inclusion of a section on tics and Tourette's Syndrome (TS) in the Third Guidelines, or to give more emphasis to the treatment of the combination of disorders. In the interim period, this commentary may help with regard to information about the relationship between TS and ADHD, and offer some suggestions for treatment.

The first European Guidelines for the treatment of ADHD were published in 1998 [Taylor et al. 1998] and the second [Taylor et al. 2004], drawn up by a similar although slightly different set of authors, are welcome, thorough, practical and timely. They are likely to be the gold standard for years, and will be referred to and followed widely by clinicians throughout Europe. However, the present author is concerned that in the document tics and TS were only mentioned briefly. This is unfortunate, as, in individuals with ADHD, tics are common, and, in individuals with tics and TS, there is significant comorbidity with ADHD. In the latter, the ADHD is often the reason for referral to clinics, for schooling and interpersonal difficulties. ADHD has a major impact on social functioning and the comorbidity has major treatment implications.

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Commentary

TS is a childhood onset disorder characterised by the presence of multiple motor tics and one or more vocal tics, lasting longer than a year [APA 2000; WHO 1992]. For a full description of TS including clinical phenomenology, psychopathology and up-to-date discussions of treatment, the reader is referred to Robertson (2000) and Singer (2005).

TS, particularly in studies conducted on clinic populations, is often associated with other disorders including ADHD, obsessive compulsive behaviours (OCB) and/or disorder (OCD), depression, anxiety, oppositional defiant disorder, conduct disorder as well as personality disorders (for review, see Robertson 2000). Individuals with tics often also have associated behaviours.

In the context of this commentary, of all the co-morbid conditions encountered in people with tics and TS, ADHD is the most common, as evidenced by an enormous literature on the subject (Freeman 1997; Spencer et al. 1999). As early as 1973, it was accepted that a substantial proportion of children who have TS first manifest various behavioural disturbances often called minimal brain dysfunction (MBD), hyperkinetic disorder (HKD), hyperactivity or attention deficit disorder (Shapiro et al. 1973). Although early studies found ADHD in as few as 13 % of TS patients (Lieh Mak et al.), it is now evident that ADHD occurs in a substantial proportion of TS patients, ranging from 21–90% (Robertson and Eapen 1992) to 24–75 % of clinic populations (Walkup et al. 1999), and as high as 25 % of school-based studies (Walkup et al. 1999), clearly way in excess of the 4–19 % (Taylor et al. 1998) or 1–10 % (Swanson et al. 1998) of ADHD encountered in the general population. A PUBMED search in late June 2005, using the words Tourette and ADHD, gave rise to 340 hits and tics and ADHD gave rise to 435 hits.

In addition, attentional problems and difficulties with hyperactivity and impulse control frequently precede the emergence of tics, in that they appear at an earlier age than do the tics (Jagger et al. 1982; Singer et al. 1995). For a DSM-IV (APA 1994) diagnosis to be made, symptoms of ADHD must be present in two or more settings before age 7, while the TS and tic symptoms often begin later (Robertson 2000).

This ADHD comorbidity of tics and TS is not a North American phenomenon. A recent international investigation embracing 3500 patients in 22 countries including Austria, Belgium, Denmark, Germany, Hungary, Iceland, Italy, The Netherlands, Norway, Poland, Sweden, Turkey and the United Kingdom, demonstrated that 12 % of individuals with TS had no comorbidity. The most common comorbidity was ADHD, occurring in 60 % (Freeman et al. 2000). In many centres in clinical studies undertaken in Europe, documentations demonstrate that ADHD is common in TS. These include Italy (Saccomani et al. 1999; Zapella 2002), the Netherlands (Brand et al. 2002), Poland (Brynska et al. 2001), Spain (Garcia-Ribes et al. 2003), Turkey (Dimerkol et al. 1999; Toros et al. 2002), and the United Kingdom (Robertson et al. 2002; Eapen et al. 2004). In these case reports, cohorts and controlled studies, embracing over 400 patients, the comorbidity of TS and ADHD was significant.

The comorbidity of TS and ADHD is not, however, a phenomenon of clinic patients only, and, thus, may not only be due to referral bias. Thus, Apter et al. (1993) examined all recruits into the Israeli Defence Force, during one year, documenting that the rate of ADHD in people with TS was 8.3 %, compared with a population point prevalence of 3.9 % in individuals without TS at the time; this difference was highly significant.

In addition, several large epidemiological studies since 2000, specifically investigating the prevalence of tics and TS in school-aged children, have been published from the USA, Israel, Taiwan, mainland China, and at least four from Europe. A summary of these shows the prevalence of tics and/or TS; that of ADHD comorbidity and/or impaired school performance associated with tics/TS is shown in Table 1.

The "tic possible" (TPs) youngsters in the Hornsey et al. (2001) study were those youngsters who probably had tics, following three sets of responses to questionnaires: parents, teachers, and their own. Interviews were also undertaken to diagnose TS.

These studies have improved on their predecessors, although for practical reasons few are perfect. Many of these have employed direct observations. With regard to the direct observations, the more trained the observer/examiner, the better (e. g. doctors and psychologists as employed by some studies at various stages of the procedure) [Kadesjo and Gillberg 2000; Snider et al. 2002; Khalifa und von Knorring 2003].

Many have also used standardised questionnaires completed by children, parents and teachers, and the more specific the rating scales used for detecting ADHD and/or behavioural difficulties [e. g. Conners; Child Behaviour Checklist (CBCL)] [Snider et al. 2002; Kurlan et al. 2002]. Hornsey et al. (2001) employed Goodman's Strengths and Difficulties Questionnaire (SDQ). It is acknowledged that the SDQ is not a diagnostic instrument for ADHD, but, as a screening instrument for use in the community (Goodman et al. 2003; Mathai et al. 2004; Bourdon et al. 2005), it is reliable and valid and can be used as a brief measure of psychopathology of children and adolescents (Goodman 2001); it was used as such in the study.

In the majority of studies, the senior authors had a special interest in tics/TS. It is, therefore, suggested that a realistic figure for the prevalence of TS is between 0.43 % and 3.8 % of school children between the ages of 6 and 17, and a figure of 1 % is representative. The preva-

Table 1 Epidemiological studies on TD and TS, illustrating ADHD comorbidity

Authors	Country	Number studied	Age (years)	Methods/procedures	Prevalence tics/TS (%)	Prevalence of ADHD or school difficulties
Kadesjo and Gillberg 2000	Sweden	435 58	11	Clinical examination by a doctor	1.1 = TS	ADHD = 20 % ADHD = 64 %
Hornsey et al. 2001	UK	918	13–14	Children Q Parents' Q Teachers' Q + Two structured IVs by psychol + psych	4.6 % = TPs 0.76–1.85 = TS	↑ psychopath including ADHD
Kurlan et al. 2001	USA	1255 (RE) 341 (Sp ED)	8.5–17.5	Structured IVs (tech)	0.8 (3.8) = TS 18.5 = tics 1.5 (7.0) = TS 23.4 = tics	SpEd assoc with tics/TS
Kurlan et al. 2002	USA		9–17	IVs by tech + Std Qs (pupils) + Vocabulary test + CBCL + Q = (parents)		Children with tics ↑ psychopath including ADHD + ↑ CBCL scores TS = ↑ ADHD + CBCL scores
Gadow et al. 2002	USA	3006	3–18	Teacher = RS	3.4–22.3 = tics	Psychiatric symptoms more in those with ADHD
Snider et al. 2002	USA	553		Direct Obs by trained raters and psychol + Teachers' Q Conners' R + Parents Q = checklist	24.4 = tics	Obs = no significant ↑ in behaviour problems in pupils with tics of < 2 months' duration BP ↑ in those with persistent tics Teachers rated children with tics as having more BP (73 %)
Khalifa and von Knorring 2003	Sweden	4497	7–15	IVs + Q's = children and parents	6.6 = tics 0.6 = TS	Tics assoc. with social dysfunction
Wang and Kuo 2003	Taiwan	2000	6–12	FILL IN	0.56 = TS 4.9 = tics	ADHD = 36 %
Jin et al. 2004	China	9742	7–16	Not stated	0.43 = TS	Not stated
Lanzi et al. 2004	Italy	2347	6–11	Class Obs	24 = tics 0.68 = TS	Tics assoc with impaired school performance

After Robertson (2003); Lanzi et al. (2004)
TS Tourette Syndrome; *ADHD* attention deficit hyperactivity disorder; *IVs* interviews; *Psychol* psychologist; *Psych* psychiatrist; *assoc* associated; *Obs* observation; *Q* questionnaires; *R* Revised; *RE* regular/mainstream education; *SpEd* special education; *psychopath* psychopathology; *CBCL* Child Behaviour Checklist; *mot* motor; *BP* behaviour problems; *Std* standardised; *Tech* technician

lence of tics ranges from 3.4 % to 24.4 %. Of importance is that there is a consistency of findings in that children and individuals with persistent tics/TS have an increased prevalence of ADHD and/or hyperactivity, behaviour problems, and/or impaired school performance, with many cases requiring special education. Thus, ADHD is a significant comorbidity of tics/TS, even in epidemiological, community settings.

In order to place these studies and results in perspective, studies on youngsters with tics/TS conducted in

clinics will be examined briefly. Few to date have compared youngsters with TS + ADHD and ADHD alone. Spencer et al. (1998) compared patients with TS + ADHD and ADHD alone, and found that in TS patients there were increased rates of both OCD and ADHD. In contrast to the comorbidity with OCD, it was found that the other comorbidities (e. g. disruptive behaviours and mood disorders) were indistinguishable in comparison between children with TS + ADHD and children with ADHD alone. This suggests that some psychopathology (e. g. mood disorders) could be secondary to the comorbidity with ADHD, rather than the TS per se. In addition, it was shown that children with TS + ADHD had lower psychosocial functioning than children with ADHD alone.

Pierre et al. (1999) examined two groups of boys; ADHD + tics and ADHD alone. Standardised assessment schedules were employed. Boys with ADHD + tics received significantly higher scores for the Anxious/Depressed, Thought problems, and Attention Problem Scale of the Child Behaviour Checklist (CBCL) and also for Delinquent Behaviour, Thought Problems and Somatic Complaints on the TRF than did boys without tics. Children with mild tic disorder were more similar (CBCL) to ADHD boys without tics than they were to children with more severe tic disorder (TD). These data suggested, therefore, that it was not the presence per se, but the severity of TD which is associated with higher rates of emotional and behavioural disturbances.

Carter et al. (2000) examined 72 children (45 boys and 27 girls) between the ages of 8 and 14 years. They studied several groups of children including TS-only (n = 16), TS + ADHD (N = 33) and healthy unaffected controls (n = 23). Standardised assessment schedules were employed. Results indicated that youngsters with TS + ADHD evidenced more externalising and internalising behaviour problems and poorer social adaptation than children with TS alone or controls. Children with TS-only were not significantly different from controls on most measures of externalising behaviours and social adaptation, but had more internalising symptoms. Results demonstrated that much of the behavioural and social dysfunction in TS is ADHD-specific.

Sukhodolsky et al. (2003) conducted a similar study, including 207 children between the ages 7 and 18 years. The following were studied: TS-only (n = 42), TS + ADHD (n = 52), ADHD only (n = 52), unaffected controls (n = 61). Standardised instruments were employed. Results showed that TS-only children did not differ from unaffected controls on ratings of aggression, delinquent behaviours or conduct problems. By contrast, children with TS + ADHD were significantly above controls and similar to those with ADHD-only on indices of disruptive behaviours.

Cardona et al. (2004) studied 125 patients (108 males) with any tic disorder (TD), with a mean age of 9 who were attending clinic. They employed standardised scales such as the Yale Global Tic Severity Rating Scale (YGTSS), CBCL, and Children's Yale-Brown-Obsessive-Compulsive Scale (CYBOCS). Results indicated that 17 % of children had CBCL scores within the pathologic range, 9.6 % had scores on the Externalising subscale in the pathologic range, 31 % were in the pathologic range of the Attention subscale, and there was a linear correlation between the YGTSS scores and both the CBCL Total T and Externalising scores. Those with milder tics had no significant psychopathology.

Channon et al. (2004) studied social and non-social cognition in 15 patients with TS-only (i. e. with no comorbid psychopathology), and they were compared to 23 matched healthy controls using social measures (e. g. Advanced Theory of Mind Stories) and non-social executive measures [e. g. Inhibition (Hayling Test); Rule-Finding/Set Shifting (Wisconsin Card Sorting Test)]. Results showed that participants with TS-only made more errors than the controls on the inhibitory task, but they did not differ on other executive measures or on social cognition measures. This suggests that social cognition is intact in uncomplicated TS, at least on skills involved in empathy and theory of mind.

Hoekstra et al. (2004) studied 58 children aged 4–16 years, recruited children from the Netherlands Tourette Syndrome Association and their Child and Adolescent clinic. Children had TD or TS, with and without different forms of ADHD. Parents completed the CBCL and the Social Behaviour Questionnaire. Youngsters were also examined using the YGTSS, the CYBOCS and the Dutch translation of the Diagnostic Interview Schedule for Children. Patients with TD/TS with primarily hyperactive-impulsive ADHD had the highest scores on the relevant rating scales, and patients without ADHD had the lowest scores. The authors concluded that the presence and severity of ADHD were the main predictors of associated behavioural and social problems.

Another study examined quantitative and qualitative aspects of OCB in 41 children with ADHD compared with 38 with TD/TS and 42 healthy controls (Moll et al. 2000) using the CBCL, the abbreviated Conner's Scale, the Child Version of the Leyton Obsessional Inventory (LOI-CV) and the structured Mannheim Parent Interview. Results showed that youngsters with ADHD rather than TD had the highest OCB scores on the LOI-CV. Qualitatively, ADHD-related OCB included items such as "dirt and contamination", "repetition", "overconscientiousness" and "hoarding". Using the parent-rated CBCL, similar levels of OCB were reported for ADHD and TD patients. On expert interview only, youngsters with TD had clinically relevant OCB (Moll et al. 2000). None of the children with TD, TS or ADHD fulfilled diagnostic criteria for OCD.

In conclusion, when studies have compared children and individuals with TS-only ("Pure TS"), TS + ADHD

and controls, they have found that, in general, individuals with TS alone are no different from controls, particularly when referring to behaviour problems and social functioning, whereas the TS + ADHD group is the most disabled and disadvantaged. In addition, other comorbidities such as OCB/OCD may be present. In general, those individuals with TS alone appear to be different to those with TS + ADHD and this has major management and prognostic implications.

The relationship between ADHD and TS is complex and has stimulated debate. There are several possibilities as to the nature of the relationship between the two disorders. There have been suggestions that the two disorders are genetically related (e. g. Comings and Comings 1984; Knell and Comings 1993), although this has been disputed (e. g. Pauls et al. 1986, 1988; Eapen and Robertson 1996). The data from another study, however, suggested that there may be two types of individuals with TS and ADHD; those individuals in whom ADHD is independent of TS, and those in whom ADHD is secondary to TS (e. g. Pauls et al. 1993). A third possibility is that "pure" ADHD and TS + ADHD are different phenomenologically, but the exact relationship is unclear and few studies have been conducted (Spencer et al. 1998). A fourth possibility is consequent on the findings of Yordanova et al. (1997) who investigated the effect of the amplitude of the post imperative negative variation (PINV) (chosen as an indicator of frontal lobe functioning closely related to self-regulation of behaviour) in children with combined TD and hyperactivity symptoms (HA). They studied the PINVs of four groups of 43 children, made up of matched healthy controls, pure-TD, pure-ADHD and combined TD + ADHD children. PINVs were elicited in an auditory warned reaction task in three conditions [control, loss of control (LoCC), and lack of control (LaCC)] at midfrontal and midcentral leads of the scalp. Standardised measures such as the CBCL, Conners, LOI-CV, Tourette Syndrome Global Scale, Tourette Syndrome Severity Scale and Matching Familiar Figures Test were employed. Effects of TD and ADHD were revealed only in the noncontrol conditions, being independent in the LaCC, but interactive in the LoCC. Thus, the authors suggested that the additive model of comorbidity of TD and ADHD was only partially supported by the results. Another possibility is that suggested by Moll et al. (2001) who measured the motor system excitability in children with combined TS + ADHD. They found reduced intracortical inhibition, as well as a shortened cortical silent period in the comorbid children, which provides evidence for additive effects at the level of motor system excitability (Moll et al. 2001). The possibilities put forward need not be mutually exclusive and more research needs to be undertaken in the area.

Sleep often poses a problem in individuals with TS as well as those with ADHD and this has been studied for decades. Sleep in children with ADHD has been widely documented and it seems that although there are difficulties in sleep [increase of rapid eye movement (REM) latency and a proportional decrease of REM sleep in children with ADHD], in many instances parental reports were often not confirmed by objective sleep measures (Cohen-Zion and Ancoli-Israel 2004; Bullock and Schall 2005). Both reviews recommended that further research into sleep in children with ADHD is required, particularly the effects of stimulant medication. Sleep disturbances have also been reported in TS and have been reviewed by Rothenberger et al. (2001) and Kostanecka-Endress et al. (2003), noting that in patients with TS, about 20–50 % have sleep problems. The sleep disturbances complained about include separation anxiety in the evening, sleep walking, sleep talking, pavor nocturnus, unpleasant dreams, nightmares and difficulties in both falling and staying asleep (Rothenberger et al. 2001; Kostanecka-Endress et al. 2003). In contrast to the reports by patients and/or their relatives, the few polysomnographic studies available at the time had per se not found similar patterns of frequency, intensity and variability of sleep disturbances in TS (Rothenberger et al. 2001). It was noted that associated ADHD and migraine may also lead to an increase of sleep problems in patients with TS (Kostanecka-Endress et al.). The group undertook a polysomnographic study of 17 unmedicated TS children without comorbid ADHD, compared to 16 matched controls, and demonstrated that children with TS had longer sleep period time, longer sleep latency, reduced sleep efficiency and prolonged wakefulness after sleep onset. Their sleep profiles showed significantly more time awake and less sleep stage 11 (Kostanecka-Endress et al. 2003). REM sleep variables, slow-wave sleep and number of sleep stage changes were unaffected. Movement time was similar in both groups, but epochs with short arousal-related movements were increased in TS. The authors concluded that children with TS had disturbed sleep quality with increased arousal phenomena, and suggested that this may well be intrinsic to TS (and not only due to the comorbidity with ADHD) and might trigger tics and behavioural problems during the day (Kostanecka-Endress et al. 2003). This poor sleep in individuals with TS, and even more so if they also have comorbid ADHD, has treatment implications.

Treatment implications for ADHD in the setting of TS are important. There have been few studies in this context from Europe, but several investigations from the USA can give reasonable suggestions for use in Europe, particularly with regard to the use of stimulants.

The use of stimulants in ADHD is widely accepted and documented and has been successful for the last few decades (Santosh and Taylor 2000). The use of stimulants such as methylphenidate in children with TD/TS and ADHD, however, was controversial for some time

(for a review, see Robertson and Eapen 1992), as they were once thought to worsen the tics as evidenced by case reports (Denkla et al. 1976; Lowe et al. 1982), while improving the hyperactivity and concentration. Borcherding et al. (1990) reported abnormal movements (e. g. tics) and preservative/compulsive behaviours, or both, in 76 % of 45 eight-year-old boys with ADHD during a crossover Double Blind Trial (DBT) of methylphenidate and dexamphetamine. Chronic tics and TS had been exclusionary criteria for study entrance. All subjects had been medication-free for 3 weeks prior to the investigation. Adverse effects were often subtle and transient, and usually occurred only on one drug. The side-effects of tics necessitated discontinuation in only one case. Dexamphetamine tended to produce more compulsive behaviours, which were also more likely to resemble clinical OCD, than did methylphenidate. Abnormal movements and compulsive behaviours tended to co-occur on methylphenidate only.

Other studies examining stimulants in individuals with TS + ADHD are shown in Table 2. Sverd et al. (1989) reported the effects of methylphenidate in a single-blind (SB) trial in individuals who had TS + ADHD compared to placebo. Clinical ratings and playroom observations showed improvement in ADHD and no untoward effects on the tics. Gadow et al. (1992) studied prepubertal hyperactive boys with TD in a DBT comparing placebo and three doses of methylphenidate. Each boy was observed for approximately 20 h in the school setting. Results indicated that methylphenidate effectively suppressed hyperactive/disruptive behaviours and physical aggression. Methylphenidate also reduced the occurrence of vocal tics in two settings. None of the motor tic measures revealed drug effects. On an operationally defined minimal effective dose, only one boy experienced motor tic exacerbation. Gadow et al. (1995) subsequently conducted a DBT in prepubertal children with ADHD + TD comparing placebo and three doses of methylphenidate

Table 2 Summary of controlled studies using stimulants in tics and Tourette

Author	Year	Study design	Length of study (weeks)	Number of patients	Results
Sverd et al.	1989	SB	N/S	4	No ↑ tics
Gadow et al.	1992	DB	2	11	↓ motor tics
Gadow et al.	1995	DB		34	↑ motor tics, ↓ vocal tics
Castellanos et al.	1997	DB	9	20	↑ in tics
Tourette's Syndrome Study Group	2002	DB	16	136	No ↑ tics compared to clonidine or placebo
Total number				215	

SB Single Blind; *DB* Double Blind; *N/S* not stated

twice daily. Methylphenidate produced marked reductions of hyperactive, disruptive, and aggressive behaviours; there were no "nonresponders". The only observed changes in tics were a small, but statistically significant, increase in the frequency of motor tics and a tendency for fewer vocal tics. However, these changes in motor tic frequency were not perceived by care providers as a worsening in the severity of the child's TD. Most dose-response relationships were linear, and the mean minimal effective dose was 0.3 mg/kg. Castellanos et al. (1997) then compared methylphenidate and dexamphetamine on tic severity in boys with ADHD and TS. Fairly high doses of methylphenidate and dexamphetamine in the first cohort resulted in significant increases in tic severity, which was sustained on higher doses of dexamphetamine, but which attenuated on methylphenidate. Of 20 subjects, 14 continued stimulant treatment for 1 to 3 years, generally in combination with other psychotropic agents. Stimulant-associated adverse effects, including tic exacerbations, were reversible in all cases. The use of stimulants was felt at one time to represent an absolute contraindication, but recently cautious use of these agents in this context has been advocated (Freeman 1997) as evidenced by the studies discussed.

When giving methylphenidate, there is both the short acting form (e. g. Ritalin) and the once-a-day form (e. g. Concerta or Equasym). The latter may be easier to take for many individuals especially those attending school, as it requires one morning dose only. As multiple dosages of stimulants reduce compliance (Swanson 2003), and reduced dosage frequency may lead to increased compliance in medical conditions (e. g. Paes et al. 1997), the once-a-day preparations of methylphenidate such as Concerta may increase compliance (Pelham et al. 2001). To the best of the author's knowledge, there are no publications of the use of the once-a-day agents in TS + ADHD, but this is worth researching.

Clonidine has been used for some time with success in individuals with TS + ADHD (for a review, see Robertson 2000). It has also been suggested that, when treating ADHD with stimulants, the adjunctive use of clonidine can be helpful to extend stimulant effects and control the adverse effects. Pragmatically, doctors began using a combination of methylphenidate and clonidine, but the reports of three deaths halted the practice for many. Popper (1995) examined the evidence of these three deaths and concluded that the deaths were probably not due to the combination of stimulants and clonidine. The most convincing evidence for the safety and efficacy of the combination of stimulants and clonidine comes from a large multicentre, randomised DBT, in which 136 children with ADHD + TD were treated with clonidine alone (n = 34), methylphenidate alone (n = 37), clonidine and methylphenidate (n = 33), and placebo (n = 32) (TS Study Group; see Table 2). Each individual participated

for 16 weeks. Standardised schedules measured response. Compared to placebo, the greatest overall benefit in symptomatology was with the combination of clonidine and methylphenidate. Clonidine alone helped impulsivity and hyperactivity, while methylphenidate helped inattention. The proportion of subjects reporting a worsening of tics was no higher in those treated with methylphenidate (20 %) than those receiving clonidine (26 %) or placebo (22 %).

Clonidine has also been shown to effect sleep (Miyazaki et al. 2004) and is used successfully in the treatment of sleep difficulties (Efron et al. 2003), particularly in children with neurodevelopmental disorders (Ingrassia and Turk 2005). Thus, as it has been used for treating the tics in TS, for ADHD and for sleep, it may well be a useful agent for a child with TS + ADHD who may have sleeping problems, and it can be given as a night-time dose.

In conclusion, in the 215 individuals with tics or TS + ADHD studied under controlled conditions with stimulants, the stimulants appear to be safe and in many cases reduced the tics rather than increased them. However, the results must be interpreted with caution; as can be seen in Table 2, numbers are relatively small (just over 200) and also the duration of the studies was relatively short (weeks rather than months), and, thus, although results are encouraging, caution should be used when prescribing stimulants in the TS + ADHD population. While the most recent evidence indicates that stimulants are safe in the setting of TS + ADHD, it is suggested that more research be undertaken. In the context of this communication, it is also worth noting that stimulants can cause insomnia (Pliszka 2003).

A further difficulty in the treatment of individuals with TS + ADHD with stimulants is that, if the tics do increase, this may be coincidental as tics characteristically wax and wane. Nevertheless, it does appear from evidence-based studies that stimulants, if used judiciously in patients with TS or tics with ADHD, do not necessarily increase tics and may even reduce them. In addition, the combination of stimulants and clonidine appears to be safe. It is important to note that in the USA, but not in Europe, guanfacine is used in the treatment of ADHD and in TS (e. g. Chappell et al. 1995; Cummings et al. 2002).

Due to the difficulties of prescribing stimulants to patients with TS + ADHD, researchers have examined alternatives. Both reviews and studies have suggested successful use of deprenyl (Jankovic 1983), the tricyclic antidepressants desipramine (Hoge and Biederman 1986; Singer et al. 1995; Spencer et al. 2002), imipramine (Sandyk and Bamford 1988) and nortryptiline (Spencer et al. 1993). Other medications shown to be useful in ADHD include tacrine and donepezil (Banaschewski et al. 2004) and bupropion (Spencer et al. 2002); bupropion has, however, been shown to increase tics (Spencer et al. 1993). It may be worth mentioning that licensing laws are different in various countries and clinicians should be familiar with them when prescribing such medications in such circumstances.

More recently, atomoxetine, a new once-daily dosing and selective noradrenalin reuptake inhibitor with few side-effects (Banaschewski et al. 2004), an agent for the treatment of ADHD, first reported in adults by Spencer et al. (1998) and for which a PUBMED search using the words ADHD + atomoxetine revealed 102 hits. Atomoxetine has in both open studies (Buitelaar et al. 2004; Adler et al. 2005; Escobar et al. 2005) and DBTs (Michelson et al. 2001; Kaplan et al. 2004; Kelsey et al. 2004), and reviews (Banaschewski et al. 2004; Himpel et al. 2005) been shown to be effective in ADHD. Atomoxetine is licensed for ADHD in children and adults in the USA (Wernicke and Kratchovil 2002; Pliszka 2003) and is under consideration in Europe (Banaschewski et al. 2004). Sangal and Sangal (2005) demonstrated that cognitive evoked potential (P300) amplitude predicts treatment response to atomoxetine. Atomoxetine has also been suggested for use specifically in children with ADHD and TD and TS (Castellanos and Acosta 2004). Atomoxetine has been reported to increase tics in four cases (Lee et al. 2004) and be associated with the onset of tics in one case (Ledbetter 2005). Others (Feldman et al. 2005) showed no increase in tics in 4/76 (5.3 %) receiving atomoxetine vs. 2/72 (2.8 %) receiving placebo. There is no mention of tics in a comprehensive review (Wernicke and Kratchovil 2002). Another benefit of atomoxetine is that it is a once-daily dose, suggested to increase compliance (e. g. Paes et al. 1997). Thus, atomoxetine may be useful in patients with TS + ADHD, but further research is needed. There have recently been warnings from the USA Food and Drug Administration (FDA) and the Committee of Safety in Medicine (CSM) in the UK that in children and adolescents atomoxetine has been associated with suicidal thinking and behaviour. In addition, a case of overdose with oxcarbazepine, atomoxetine and quetiapine has been documented (Barker et al. 2004). The patient survived but these warnings and findings do illustrate how new medications must be carefully evaluated.

The sleep difficulties in the child with TD or TS and ADHD require special mention. Clonidine may be useful as it can help tics, ADHD and sleep. Another possible option for night-time medication may be melatonin. Melatonin is prescribed widely in children with insomnia (Owens et al. 2003) and has also been found to be useful in children with neurodevelopmental disorders and sleep difficulties (Phillips and Appleton 2004), including ADHD (Tjon Pian et al. 2003). At least one DBT of the melatonin agonist beta-methyl-6-chloromelatonin (BM6CM) in primary insomnia demonstrated that active agent was superior to placebo with regard to improved sleep latency and subjective measures of time to fall asleep. Adverse events were moderate and did not differ in frequency between BM6CM and placebo. Mela-

tonin secretion has been suggested to be relevant to the pathophysiology of TS (Sandyk and Kay 1991) and has been used successfully in a patient with TS and circadian rhythm sleep disorder, with risperidone (Ayalon et al. 2002). In the USA, melatonin is available over the counter and in the UK it is available for prescription on a named-patient basis. Other medications which have been used to treat the tics in TS and may help some aspects of sleep include tetrabenazine, risperidone and tiapride (Rothenberger et al. 2001). Clearly, this is an area which requires more research.

The present author suggests that, when a patient has TS + ADHD, the clinician should first assess which symptoms are the most problematic, and attempt to treat the target symptoms. It is important that a thorough assessment is conducted to ensure that the youngster has in fact both TS and ADHD. Because some youngsters with TS are so fidgety with their tics, and try to suppress them, they may appear to have poor concentration. Specific suggestions are made with regard to treatment options: (i) if the ADHD and tics pose equal difficulties, the first-line management suggested is clonidine, which may help tics, ADHD and sleep; (ii) if ADHD is the greatest problem, stimulants may be the preferred option; (iii) the next option would be to use stimulants in combination with clonidine, as the combination has been shown to be safe. Short-acting preparations should be used in the first instance. If these are successful, once-a-day formulations may be used as they may increase compliance; (iv) stimulants may also be given with neuroleptics, particularly if there is an increase in tics; some neuroleptics also help sleep; (v) atomoxetine may prove useful in treatment of the ADHD associated with TD or TS, although there have been reports suggesting a precipitation or increase in tics; and (vi) melatonin may be helpful, either alone, or in combination with other medications, if sleep disturbances persist. Finally, other medications may be necessary, but have not been well studied in the setting of ADHD and TD or TS.

Conclusion

In conclusion, ADHD or similar symptoms are common in people with TS, and it appears that they may even occur in mild TS cases that are identified in community epidemiological studies. It is unlikely, therefore, to be wholly due to referral bias. It is suggested for the Third European Guidelines that TD and TS are given more weight in the document, not only in terms of comorbidity, but also in terms of treatment guidelines. In the interim and prior to the Third European Guidelines, it is hoped that this communication will serve as a helpful reference point to the comorbidity between TD, TS and ADHD, offering suggestions for the treatment of ADHD in the setting of TD/TS.

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