

A case series of patients with Tourette's Syndrome in the United Kingdom treated with aripiprazole

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Objective These cases illustrate that a new neuroleptic, aripiprazole, may be an effective treatment for the motor and vocal tics of Tourette Syndrome (TS), even in younger people.

Method A case series of 11 consecutive patients with TS (age range 7–50 years; M=7) who were felt to require neuroleptic medication, were treated with aripiprazole, the majority of whom had been refractory to treatment with other neuroleptics, and in one case, Habit Reversal Training as well.

Results Ten out of the 11 patients who were treated with aripiprazole improved, although to differing degrees. The only individual who showed no response was treated for only 1 month with a low dose (5 mg). Eight of the patients had been treated with many typical and atypical neuroleptics without success, and which had also given unacceptable side effects, resulting in them being unable to function at times. One was also unresponsive to previous Habit Reversal Training. The response to aripiprazole was dramatic and quick in five patients; in the rest (5/10) the response was less dramatic. In the majority of patients, response was sustained. The successful aripiprazole doses were between 10–20 mg daily. Side effects were mild and transient. This, to the best of our knowledge, is the first case series of patients with TS successfully treated with aripiprazole in the United Kingdom, and one of the few to date in the English Scientific literature. Our patients are also the first cases reported, in which the patients were assessed and whose improvement was monitored using standardised schedules and rating scales, such as the Yale Global Tic Severity Rating Scale and MOVES. Aripiprazole was licensed for use in patients with schizophrenia in the European Union in June 2004. We discuss possible reasons for these dramatic and idiosyncratic responses to aripiprazole.

Conclusion We suggest that aripiprazole may well be useful for individuals with TS as response to it is often quick, dramatic, sustained and with few generally mild and transient side effects. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — Tourette Syndrome; treatment; aripiprazole

INTRODUCTION

Tourette Syndrome (TS) is characterised by multiple motor and one or more vocal tics and lasting longer than a year (World Health Organization, 1992; American Psychiatric Association, 2000). The age at onset of motor tics is usually around the 5–7 years, with vocal tics starting somewhat later. Tics may be simple or complex. Apart from the motor and vocal (phonic) tics, patients may have echolalia (copying what other people say), palilalia (repeating what the

individual him/her self has just said), coprolalia (inappropriate and involuntary use of swear words) and self-injurious behaviours (SIB). In addition, many patients have additional co-morbid disorders and psychopathology including attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), obsessive-compulsive behaviours (OCB) and depression. TS is now recognised to be more common than was previously reported with prevalence figures of between 0.4% and 1.76% of youngsters between the ages of 5 and 18 years. The prognosis is better than was once thought, with many individuals improving substantially by the age of 18 years. The aetiopathology includes genetic influences, pre- and peri-natal difficulties, and proposed more recently, an association with some infections (e.g. streptococcus)

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via neuroimmunological mechanisms and molecular mimicry. Management includes reassurance, explanation, psycho-education, and more recently, behavioural methods such as Habit Reversal Training (HRT) and medications. Treatment of the motor and vocal tics is more complex than once thought, but even today, the typical and atypical neuroleptics form the mainstay of treatment of motor and vocal tics in adults. Double-blind trials have demonstrated that the typical neuroleptics including haloperidol pimozone, sulphiride and tiapride are better than placebo. Atypical neuroleptics, which have been used successfully, include risperidone, olanzapine and quetiapine. Many other medications have been used including clonidine and botulinum toxin for vocal tics (Robertson, 2000, 2004).

Aripiprazole acts predominantly as a partial agonist at dopamine D2 and Serotonin 5-HT-1A receptors and an antagonist at Serotonin 5-HT-2A receptors (De Leon *et al.*, 2004). It is available in oral tablets, is well absorbed, and elimination is primarily through hepatic metabolism. It became licensed for use in patients with schizophrenia in the European Union in June 2004. Aripiprazole has been widely used in the treatment of patients with schizophrenia in the United States of America, Mexico, Australia, Brazil and Korea. It is well tolerated and side effects greater than placebo in double-blind trials include insomnia, tremor, nausea, vomiting and akathisia, usually mild to moderate and transient. No specific blood monitoring is required with aripiprazole (Travis *et al.*, 2005).

Only a few cases of the successful use of aripiprazole in patients with TS have been documented in the literature. We report the first in the United Kingdom, and also the first two patients whose improvement was monitored using standardised rating scales, to the best of our knowledge. After our success with these two patients, we treated nine others who presented at our dedicated TS clinic and who were thought to require neuroleptics (children who have TS and ADHD are usually given clonidine initially (Robertson, 2006).

METHODS

Two initial cases were treated with aripiprazole and responded dramatically and well (see case reports, and in the Table 1, no. 1,2). We therefore decided to treat nine other patients who presented consecutively to the clinic, who (7/9) had been refractory to other treatments (see Table 1) and in whom we thought that a neuroleptic was the treatment of choice. The age

range of the nine patients was 7–50 years and seven were male. All 11 patients were initially assessed, and histories obtained, using a semi-structured interview, the National Hospital Interview Schedule for Gilles de la Tourette Syndrome (NHIS; Robertson and Eapen, 1996) and current initial tic severity was measured using both the physician rated Yale Global Tic Severity Rating Scale [YGTSS], Leckman *et al.*, 1989) and the self-rated MOVES Scale (Gaffney *et al.*, 1994), the latter both before and after treatment with aripiprazole. The lifetime severity symptom scale, rated by a physician, the Diagnostic Confidence Index ([DCI], Robertson *et al.*, 1999), was also employed. All patients gave written consent for the publication.

CASE REPORTS AND RESULTS

Case 1

The first patient, Ms A (no. 1 on Table 1) was referred to us for expert management. She is 33 years old, right handed and a night care assistant looking after elderly people with dementia, having been in the same post for 13 years.

The first symptoms were vocal tics (a sound similar to hiccupping/grunting), at the age of 5. At about 7 years of age she had bad arm tics, which lasted about 2 weeks but was then relatively well until the age of 16 years. She had obsessionality from the age of 7, which on DSM criteria, seems to have progressed from OCB to OCD over the years. At the age of 16 years, she started to develop further tics and involuntary noises and was diagnosed as having TS at the age of 25, having suffered substantially up until that point. Over the last 13 years she has not improved, and if anything, was better off about 8 years ago compared to the present time when she first consulted us. Her tics are present on a daily basis, worsened by stress, and improved with alcohol. Her tics are briefly suppressible and suggestible, and she has premonitory sensations. The most noticeable feature is a very frequent loud hiccupping/'grunting' tic. There are no echo-phenomenon, palilalia nor copropraxia, but she does have some mild coprolalia (muttering of swear words under her breath). In addition, she was noted to talk in two different personae. During her two pregnancies, the tics recovered significantly despite no medication.

Ms A's birth was complicated as her mother had to be induced because of mild maternal hypertension and the infant had shoulder dystosia, but she was born a normal vaginal delivery, weighing 8 pounds. She was breast fed for 8 months. Her milestones were normal;

Table 1. Details of 11 patients with Tourette's Syndrome treated with aripiprazole

CASE NR	Sex	DCI %	Age (years)	Diagnoses	Previous treatments	Current treatment	Time on Aripiprazole	Dosage	Side effects	Subjective improvement	MOVES score
1	F	81	33	TS, OCD ADHD Dyslexia Depression	Haloperidol, Sulpiride, Amisulpiride, Risperidone	Aripiprazole Citalopram,	10 months	15 mg	Nausea, blurred vision	"Dramatic"	17 > 14 > 13 > 11
2	F	88	12	TS	Sulpiride Clonidine Risperidone	Aripiprazole Diazepam	10 months	15 mg	Anorexia nausea palpitations Chest pain, sedation	"Dramatic", but not sustained 20%	16 > 7 > 18
3	M	59	50	TS	Pimozide, Sulpiride, Risperidone, Haloperidol, Olanzapine	Aripiprazole Olanzapine	10 months	10 mg			18 > 31
4	M	66	8	TS ADHD SIB Mild OCB	Clonidine, Sulpiride, Risperidone	Aripiprazole	9 months	20 mg	mild nausea, headache, sedation	80% improvement	18 > 11
5	M	60	43	TS OCD Anxiety Disorder	Clomipramine, Ativan, Diazepam antidepressants, Axon, Sulpiride, Fluoxetine, Alvorstatin, Propranolol Vivalan	Aripiprazole Haloperidol Sertraline Thyroxine, Alvorstatin, Propranolol Aripiprazole	5 months	10 mg	Sedation	Slight	21 only score)
6	M	51	48	TS	Nil	Aripiprazole	4 months	10 mg	Akathisia, sedation	60-70%	6 > 11
7	M	40	7	TS	Nil	Aripiprazole	3 months	15 mg	chest pains, severe headaches, sedation, dizziness	Yes	9 > 7
8	F	70	23	TS OCD- borderline ADHD depression	Sulpiride, Risperidone Haloperidol	Aripiprazole	3 months	15 mg	sedation, dizziness nausea, vomiting, sedation, ?akathisia, withdrawn headache	80% -TS 40-50% OCD "fantastic" (patient)	40 > 34
9	F	63	20	TS	Clonidine	Aripiprazole Clonidine	2 months	15 mg	Sedation, headache	70-80% "dramatic" especially vocal tics 50%	10 > 3
10	M	61	32	TS OCB Catalandral ability	Haloperidol, Sulpiride	Aripiprazole	1 month	15 mg	mild sedation		21 > 16 > 12
11	M	83	18	TS Depression	Clonidine, Sulpiride, Risperidone, Haloperidol, Pimozide, Quetiapine	Aripiprazole Mirtazapine	1 month	20 mg	tiredness	None	17 (only score)

TS = Tourette Syndrome; ADHD = Attention Deficit Hyperactivity Disorder; OCD = Obsessive Compulsive Disorder; OCB = Obsessive Compulsive Behaviours; Mg = milligram; MOVES (Gaffney *et al.*, 1994) treatment post with aripiprazole; DCI = Diagnostic Confidence Index Score.

she was described as a 'clingy baby'. She stopped attending a nursery school because of an ear infection and after starting school, became 'mute' for a month. She suffered with dyslexia. She initially went to a private school, afterwards attending a mainstream state school, but required extra help with English. She hated school and left with no examinations at the age of 16 years. As a youngster she had temper tantrums. She had various unskilled jobs but latterly has been a care assistant in the same post for 13 years. There is no forensic history. She takes no illicit drugs and drinks about 14 units a week. She smokes one packet of tobacco a week and it helps her TS symptoms. She tried the nicotine patch, but it did not help, and she missed the enjoyment of smoking.

Ms A's symptoms began getting steadily worse from the age of 20 years. Ms A was previously well treated for her TS symptoms with haloperidol, sulpiride, amisulpiride, risperidone, olanzapine, nicotine patch and possibly tetrabenazine. None of these medications helped her symptoms, and gave her unacceptable side effects such as sedation and excessive sleep. Sulpiride made her so withdrawn and doxy that she was unable to go to work. At the age of 24 years she received HRT from a psychologist without success. She has two children, B, a boy of 3, and C, a girl of 6 who are in good health with no neuropsychiatric disorders or symptoms.

The only medical history of note was that she had repetitive throat infections as a youngster and thus at the age of 11 years, had a tonsillectomy. In addition we diagnosed childhood OCB and ADHD (inattentive type), and dyslexia. She also had two depressive illnesses in the past. She was given citalopram and improved, but relapsed after non-compliance, and was compliant for 6 years. There was never ever any evidence of an eating disorder (despite her buying food excessively as part of her compulsive spending sprees). As a child there had been no evidence of oppositional defiant disorder (ODD) or conduct disorder (CD).

The family history is as follows: Ms A's parents were separated when the patient was 24. Her father died at 72 of Barrett's disease. Mother, has epilepsy ('petit mal with grand mal tendencies') which has been treated successfully with phenobarbitone for many years; she also had a 'nervous breakdown' 6 weeks after the birth of one of her children and was treated with sodium amytal, which she has remained on ever since. We diagnosed her as having OCB with arithmomania (fascination with numbers) and touching things twice. She also has spending sprees with a compulsive flavour, similar to her daughter. Maternal grandmother also probably had OCB. Our patient has

several siblings: a sister has epilepsy, a brother has speech difficulties, a brother is reported to have several diagnoses including TS, possible psychosis, alcoholism, drug abuse and aggression. Maternal grandmother possibly overspent as well.

Ms A's mental state and neurological examinations were normal apart from her tics. The following motor tics were observed at interview: scalp movements, frowning, eyebrow raising, blinking, a nasal twitch, head nodding, shoulder shrugging, and a whole body jump. Vocalisations, which were heard at interview included throat clearing and very frequent, almost constant hiccupping/grunting. Ms A muttered under her breath, but there was no actual coprolalia heard. Ms A's MOVES score was 17/60, the YGTSS was 94%, and the Diagnostic Confidence Index was 81%. She was moderately to severely affected at the time of the consultation. We also diagnosed OCD so recommended that she continue with the citalopram 40 mgm daily which she was taking. We also recommended cognitive behavioural therapy (CBT). We suggested that she stop the olanzapine she had been taking, as this was of minimal benefit for her tic symptomatology. As she had been on many medications and also had had no success with HRT, she was keen to try further medication, particularly wanting to try something new which she had not used before, we chose aripiprazole and prescribed 15 mg a day.

We saw her again 3 months later and her tics had dramatically improved, after 2–3 weeks of her having taken aripiprazole, especially her noises and whole body jerking. She had mild transient nausea and blurred vision as the only side effects. In addition, her scores on the MOVES reduced from 17/60 to 13/60, and her YGTSS went from 94% to 10%. She ascribed her dramatic improvement to aripiprazole. She remained on citalopram. The main problem with Ms A at her second visit was the compulsive spending, which had become significant. We thus recommended that her citalopram be increased from 40 mg up to 50 mg for a couple of weeks, before increasing it further to 60 mg. We also re-referred her for CBT as this had not materialised. We saw her a third time. She was briefly non-compliant during a holiday, her symptoms worsened, but they improved again after restarting aripiprazole and remained improved after 16 weeks' follow-up, with no side effects at present (MOVES score = 11/60).

Case 2

The second case is Ms B, a 12 year old girl (no. 2 on Table 1) who was referred to us for expert management,

particularly as she had been refractory to many traditional medications and had had prolonged periods off school because of her severe tic symptomatology.

Her tics started at the age of 7 years. Her first tics were eye blinking and staring, and since then she has had a wide variety of typical TS tics, which have waxed and waned over time. She had been treated unsuccessfully with adequate doses of pimozide, sulpiride, risperidone, clonidine and ziprasidone. She and her parents did not feel any of these medications helped her tics, and there had always been a problem with side effects, or, in the case of ziprasidone, the risk of potential side effects (the possible effects of QT prolongation). She had not been taking any medication for 2 months prior to the first visit to us. While she was taking risperidone she was said to have had a Transient Ischaemic Attack (TIA), during which she became weak down her right side, with slurred speech for approximately 3 days: the risperidone had been recently increased to 4 mg. She was investigated, with results showing normal MRI neuroimaging and echocardiogram.

We diagnosed coprolalia in that she made a 'fuh' sound involuntarily. There was no neither copropraxia nor echo-phenomenon nor palilalia. She did, however, have SIB and slapped herself. She also had a compulsion to slap her younger brother, as well as touch the cooker and had burnt herself by doing this. She had also broken a glass on her head and on her teeth in the past. Her tics could be suppressed, but with subsequent rebound, and they tend to be worse with stress. She suffered both a lot of pain in her back and soreness of her skin around the neck, as a result of the tics, and therefore regularly took many analgesics for this every day. In the past she has also suffered tongue ulcers as a result of her tics.

Ms B was born weighing well over 9 lbs, 10 days post-mature, but with no other associated problems. She walked and talked by around her first birthday. The major problem with her at our first interview was that she had severe tics and in the last 4 years she had consequently missed approximately two and a half years of schooling because of her TS symptoms. There was no evidence of any comorbidity such as OCD, ADHD, CD or ODD.

She has four male siblings aged 14, 8, 6 and 2. Her 6-year old brother had mild TS and possible ADHD. Her mother exhibited mild tics around the mouth and eyes and also describes arithmomania. She also had had some panic attacks approximately 15 or 16 years before. Her mother's sister was diagnosed as having OCD. She had two maternal cousins, one with Asperger's syndrome and one with autism. A maternal uncle had epilepsy.

Examination of her mental state was normal apart from severe TS with an area of excoriation on the left side of her neck from severe tics and she complained of poor sleep because of tics. Neurological and physical examinations were normal except for mild 'disco-ordination'. Eleven tics were seen at interview, although she had a total of at least 52. Those at interview included eyebrow raising, blinking, eyes looking down, eyes looking sideways, mouth to the side, smiling, facial grimacing, hair out of the eyes flick, shoulder shrugging, arm extension, hand flicking and an orchestrated sequence of smiling, shoulder shrug, arm extension and hand movements. We heard throat clearing and sniffing but she had 11 other vocal tics in total. She gave a clear history of self-injurious behaviours (slapping) but this could well be a complex tic. Of note is that she had a history of frequent throat infections although none confirmed streptococcal growth. The MOVES score at her initial assessment was 16/60, the Diagnostic Confidence Index was 85% and the YGTSS was 84%.

We suggested aripiprazole 5 mg initially, followed by 10 mg daily and when seen again 5 months later for follow-up, she and her family were delighted with her dramatic response to aripiprazole. She commenced aripiprazole at 5 mg and had a minimally good response. However, 4 days after her first 10 mg dose she made a dramatic response. She had attended school almost every day for the last 3 months since her commencement of the aripiprazole. She was coping at school and enjoying it. She had experienced a few minor side effects (nausea, tiredness, some shortness of breath), but as she had responded so well to the medication, these posed no great problems to her. Her MOVES score reduced from 16/60 at her first visit to 7/60 at follow-up. Apart from a few minor tics, her mental state examination was normal.

Case series results

The details of the other nine TS patients (age 7–50 years) treated with aripiprazole (for between 1 and 10 months) are presented in the Table 1. All but one responded to aripiprazole, though to varying degrees. Five had dramatic responses (cases nos. 1, 2, 4, 8, 9); four had a response of 20% or less. One patient (no. 8) not only responded with regards to their tics (80%), but her OCD reduced by half. One (no. 11) did not respond. This was likely, as he had only been taking 5 mg for 1 month. In all patients, side effects were minimal and transient, but occurred in all patients; sedation and tiredness were the most common side effects. The chest pain of Patient Number 3 was

investigated with a full cardio-vascular work-up and no abnormalities were found. In addition, this patient had his medication discontinued with the pain and only recently restarted aripiprazole after the investigations were completed, which may account for his MOVES score ($18 > 31$). In addition Patient number 6 discontinued his medication (because of excessive OCD and misattributing ongoing anxiety symptoms to the aripiprazole) and thus his MOVES score increased ($6 > 11$). After reassurance, he recommenced the medication.

DISCUSSION

We report 10/11 patients with TS of whom 9/11 had been refractory to other treatments and who responded well and often dramatically to aripiprazole 10–20 mg daily.

We report in detail our first case, a 33-year old woman with TS who was refractory to treatment with many neuroleptics and HRT, and who finally improved dramatically with aripiprazole 15 mg daily. We also report in detail our second case, a 12-year old girl refractory to treatment with many neuroleptics and who, because of her TS symptoms had missed an enormous amount of school. She improved dramatically on aripiprazole 10 mg daily. We also report on nine other patients with TS who were treated with aripiprazole (10–20 mg daily) for 1 to 10 months.

These are the first communication of the use of aripiprazole in individuals with TS in the United Kingdom. These are also the first cases whose dramatic response to aripiprazole was assessed using standardised measures such as the YGTSS in the first two patients and the MOVES at follow-up. In some instances (2/10) the MOVES scores did not go down (indicative of improvement) as expected, and indeed increased, despite subjective improvement; in both instances the patients' medication had been discontinued and restarted. This may also however, illustrate the possible difficulties in using only a self-rated scale to assess improvement. In addition, it may be worth noting that Patients 3 and 6 in our series received more than usual counseling about the new medication and in particular the possible side-effects; this may be important when new medications are used as the Internet, BNF and other consultation resources, will not yet be informative about newer drugs.

To the best of our knowledge there have been only five published single case reports of the successful use of aripiprazole in patients with tics or TS to date. A case series of six youths was published in late 2005 from the United States of America.

One of the first reports was that of Hounie *et al.* (2004) in Brazil who reported, in Portuguese, the case of a 20 year old man with TS who had previously been treated with haloperidol, pimozide, trifluoperazine, sulpiride, olanzapine, quetiapine, ziprasidone, clonidine, botulinum toxin, pergolide, nicotine, clonazepam and reserpine. With the addition of aripiprazole 15 mg daily to his regime of sertraline and olanzapine, he improved markedly.

Hood *et al.* (2004) reported the successful treatment of severe SIB in the context of TS and OCD in a 16-year old adolescent girl. She had been treated with many agents including clonidine, olanzapine, quetiapine and paroxetine, and in the Emergency Department yet others including lorazepam, morphine, benzotropine, diphenhydramine, chlorpromazine and clomipramine. As an in-patient she received citalopram, clomipramine, clonazepam and risperidone. Risperidone was discontinued because of galactorrhoea and aripiprazole 10 mgm added. Without risperidone the OCD symptoms worsened and so it was recommenced. Psychological treatment was also instituted. On that regime she improved.

Dehnig *et al.*, 2005 documented the case of a 19-year old woman with TS who had had symptoms since the age of 6 years. She also had marked SIB. She had been treated with tiapride, sulpiride, amisulpiride, pimozide and ziprasidone, but was vulnerable to side effects with all of these. She was therefore treated with aripiprazole 10 mg daily and after 2 weeks was nearly tic free for the first time in 13 years, and experienced no side effects. She was so well that she began working as a waiter for the first time.

Kastrup *et al.* (2005) documented two cases with TS successfully treated with aripiprazole 15 mg daily. Neither experienced serious side effects. The first was a 33 year old male who had been treated unsuccessfully with pimozide, tiapride and haloperidol, which had to be discontinued because of side effects. Within 2 weeks of commencing aripiprazole, his symptoms had almost disappeared and he was stable at 16 weeks follow-up. The second patient was a 48-year old man who had TS with complex SIB who refused to take medications because of the risk of side effects. Within 2 weeks of taking aripiprazole his motor tics almost completely disappeared and he remained stable at 16 weeks follow-up.

Murphy *et al.* (2005) then reported the successful use of aripiprazole in six youths with TS and OCD who were treated for 12 weeks.

Thus, in these 22 cases with TS (11 from the literature and our 11), who have received aripiprazole, there was in general a dramatic and long-lasting relief from tics, in

many cases bringing tic relief for the first time in years. Side effects were common, but mild and transient. The optimal dose was between 10 and 20 mg.

CONCLUSIONS

In conclusion, we suggest that our patients add to the literature suggesting that aripiprazole may well be a useful medication for treating patients with TS as it is well tolerated and only has mild transient side effects. It is well known that individuals with TS respond idiosyncratically to neuroleptics, and that these responses can change over time. It has been speculated that TS, or suppression of its symptoms, may be mediated both through dopaminergic and other systems, including serotonin. It is intriguing to posit that the mixed characteristics of aripiprazole as an atypical agent may be particularly effective in some cases, and may include an action at pre-synaptic D2 receptors as has been suggested for low-dose conventional agonists. Clearly, further cases should be treated and if possible a double blind trial against placebo or a head to head double blind trial against established neuroleptics such as haloperidol or sulpiride.

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