

## Olanzapine in Gilles de la Tourette syndrome : beyond tics

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### Summary

*Although there only have been a limited number of double-blind, placebo controlled trials, antipsychotics are considered to be effective drugs for the treatment of tics in Gilles de la Tourette syndrome (GTS). Evidence concerning the efficacy of olanzapine and other atypical antipsychotics in the treatment of tics in GTS is growing, but still limited. Little is known about the use of olanzapine in adult GTS patients and about its effect on comorbid behavioural problems.*

*We report on the use of olanzapine in a 25-year old male GTS patient with comorbid obsessive-compulsive behaviours, who was treated with olanzapine.*

*Tic severity was rated using the Yale Global Tic Severity Scale (Y-GTSS). Comorbid obsessive-compulsive symptoms were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Both scales were performed at admission and after 4 weeks of treatment with olanzapine.*

*Treatment with olanzapine (20 mg) resulted not only in a fast reduction of tic severity and frequency, but also in a reduction of obsessive-compulsive behaviours.*

*Conclusions : This case report further supports the available literature on the use of olanzapine as a therapeutic strategy for tics in GTS and draws attention to its possible use for comorbid behavioural disorders. Further research of antipsychotics in GTS should include measurements of comorbid behavioural symptom clusters.*

**Keywords :** Gilles de la Tourette syndrome ; olanzapine ; tics ; obsessive-compulsive behaviour ; antipsychotics.

### Introduction

Gilles de la Tourette syndrome (GTS) was initially thought to be rare, but currently GTS is estimated to occur in about 1% of school children between the ages of 6 and 17 years (Robertson *et al.*, 2003). GTS is characterized by the presence of waxing and waning multiple motor tics and at least one vocal tic, which start before adulthood and last at least for one year (The Tourette Syndrome Classification Study Group, 1993 ; American Psychiatric Association, 2000 ; World Health Organization, 2000).

In addition to tics, patients with GTS often demonstrate behavioural symptoms similar to an attention-deficit and hyperactivity disorder (ADHD) or an obsessive-compulsive disorder (OCD) (Robertson, 2000 ; Jankovic, 2001). Furthermore, poor impulse control, inability to control anger, self-injury and other behavioural disturbances may also occur (Robertson, 2000 ; Jankovic, 2001). These associated disorders should be treated as well since they have a negative influence on the patient's professional, social and emotional outcome (Jankovic 2001 ; Leckman, 2002). These wide manifestations of GTS urge an individualized and tailored therapy, in which the most prominent symptom cluster should be treated first (Jankovic 2001 ; Leckman, 2002).

Pharmacological treatment of tics is recommended when there's interference with daily life functioning (Jankovic, 2001 ; Jiménez-Jiménez and Garcí-Ruiz, 2001). Haloperidol and pimozide, two antidopaminergic drugs, and the  $\alpha_2$ -adrenergic agonist, clonidine, are approved by the Food and Drug Administration (FDA) for the treatment of tics. Recently, there is a growing literature on the use of atypical antipsychotic drugs on tics in GTS (Sandor, 2003). Most reports are on the use of risperidone (Van der Linden *et al.*, 1994 ; Lombroso *et al.*, 1995 ; Shuman *et al.*, 1995 ; Bruun and Budman, 1996 ; Bruggeman *et al.*, 2001 ; Dion *et al.*, 2002 ; Scahill *et al.*, 2003 ; Gilbert *et al.*, 2004) and olanzapine (Bhadrinath, 1998 ; Krishnamoorthy and King, 1998 ; Karem-Hage and Ghaziuddin, 2000 ; Bengi Semerci, 2000 ; Stamenkovic *et al.*, 2000 ; Onofroj *et al.* 2000 ; Budman *et al.*, 2002 ; Taracena and Rada, 2002 ; Stephens *et al.*, 2004), but there are also reports on the use of clozapine (Schmider and Hoff, 1998), quetiapine (Párraga and Woodward, 2001 ; Párraga *et al.*, 2001 ; Mukkades and Abali, 2003) amisulpiride (Trillet *et al.*, 2001 ; Foutoulakis *et al.*, 2004), sulpiride (Robertson *et al.*, 1990) and ziprasidone (Sallee *et al.*, 2000 ; Meisel *et al.*, 2004).

Drug treatment of obsessive-compulsive behaviours in GTS patients includes clomipramine and

selective serotonin reuptake inhibitors (SSRIs) (Jankovic, 2001 ; Jiménez-Jiménez and Garcí-Ruiz, 2001 ; Leckman, 2002 ; Miguel *et al.*, 2003). However, it has been suggested that the presence of tics might be associated with worse treatment response to SSRIs, and that the addition of an antipsychotic in this condition should be considered (Miguel *et al.*, 2003). In this context, evidence is available that olanzapine and other atypical antipsychotics, such as risperidone and quetiapine, have an effect on OCD-symptoms when they are used as augmentation agents in treatment refractory OCD (Denys *et al.*, 2004 ; Sareen *et al.*, 2004). Psychostimulants are the best choice for the management of the ADHD-like behaviour (Kurlan, 2003).

We report on a GTS patient for whom treatment with olanzapine resulted in a significant and fast reduction of tic severity and frequency, but, importantly, also in a reduction of obsessive-compulsive behaviours.

### Case report

A 25-year old male, diagnosed with GTS at the age of 13, was referred to our department from prison, where he had been into custody for one month. His index offence had been rather severe and included repeated verbal aggression toward and threatening of police officers. Because of the alleged relationship of this behaviour and the diagnosis of GTS, he was referred to our department.

Previously, he had been admitted at the age of 13 for investigation of a conduct disorder. The diagnosis of GTS with tics, ADHD and an impulse control disorder was made at that moment. The diagnosis of GTS was originally based on the diagnostic criteria of DSM-III and was confirmed based on the criteria of DSM-IV-TR (American Psychiatric Association, 2000).

During adolescence and early adulthood, he was treated with antipsychotic drugs (haloperidol, 8 mg daily dose ; pimozide, 4mg daily dose ; pipamperon, 120 mg daily dose ; risperidone, 4 mg daily dose ; clotiapine, 80 mg daily dose), SSRIs (sertraline, 50 mg daily dose ; paroxetine, 20 mg daily dose) and betalytics (propranololhydrochloride, 80 mg daily dose). Before admission, he had not been able to maintain any treatment regimen for more than six months. All drugs had very limited success, at least to some extent due to poor compliance.

His phonic tics consisted of bilabial thuds, snoring, blowing, and sniffing, whereas his motor tics consisted of blepharospasms, bilateral facial grimaces and abrupt head and neck movements. The latter were less prominent than the phonic tics. His speech was not fluent and rather stammered. Coprolalia, echolalia or palilalia could not be observed, although they had been reported in the

past. Impulse control and frustration tolerance appeared to be impaired.

He demonstrated a number of obsessive-compulsive behaviours ; his obsessions concentrated around neatness and symmetry, he had compulsions about doing obscene gestures and shouting inappropriate words, he was constantly touching things, and he repeatedly was arranging and rearranging things. The patient mentioned that these symptoms also as disturbing and invalidating.

At first assessment, he obtained a score of 90 on the Y-GTSS (Leckman *et al.*, 2003) (maximum possible score of 100) and of 22 on the Y-BOCS (Goodman *et al.*, 1989 ; Goodman *et al.*, 1989) (maximum possible score of 40). Both the patient and the treating team noted the severe impairment in global functioning. The initial daily dose of olanzapine was 10 mg and was increased to 20 mg after one week. We clinically noted an improvement in the number, frequency and intensity of tics after three weeks of olanzapine treatment and the patient confirmed this. At week four of olanzapine treatment, he had a score of 19 on the Y-GTSS ; on the Y-BOCS he had a score of 14. Clinically, a stabilisation of the effect was observed after 8 weeks of treatment. This was in accordance with the patient's subjective experience.

Compliance was not a problem, although mild sedation was initially reported as a side effect. This became less disturbing when olanzapine was administered in the evening. This did not affect the treatment efficacy. The patient had a weight gain of 4 kg over a two months period. Routine laboratory measures, including fasting glucose, remained normal during treatment with olanzapine.

Despite sufficient efforts, the patient was not willing to engage in cognitive behavioural therapy.

Written informed consent was obtained from the patient.

### Discussion

In this patient with GTS, a daily dose of 20 mg olanzapine resulted in a considerable improvement of tic severity and tic frequency, and a reduction of obsessive-compulsive behaviours.

The efficacy of olanzapine has been established in different psychiatric disorders, mainly schizophrenia (Lieberman *et al.*, 2003) and bipolar disorder (Tohen *et al.*, 2004). We only found a limited number of case reports and clinical trials of olanzapine in the treatment of tics in GTS using olanzapine. Especially, data on its application in adult patients and on its possible effect on comorbid behavioural symptom clusters are scarce. The available data suggest that olanzapine is a safe and efficient drug treatment in GTS and that it might serve as a valuable alternative for typical antipsychotics in the future.

Bhadrinath *et al.* (1998) reported on a case of a 16-year old girl with GTS with a history of unsuccessfully treatment with haloperidol, pimozide and risperidone. Olanzapine in a dosage of 10 mg daily yielded a substantial tic reduction over a period of nine weeks. In another case report, Karam-Hage *et al.* (2000) demonstrated the efficacy of treatment with olanzapine in an adolescent with GTS. Other case reports on the efficacy of olanzapine in reducing tic severity in children and adolescents with GTS, were presented by Bengi Semerci *et al.* (2000) and by Krishnamoorthy and King (1998).

In their 6 week open-label study of olanzapine in GTS, Stamenkovic *et al.* (2000) reported a significant reduction of Y-GTSS scores in 14 adult patients (seven drug naïve and seven non-responsive to or discontinued from other antipsychotics). The starting daily dose was 10 mg, and was increased to a maximum of 20 mg (mean daily dose 15 mg). In another open-label study, Budman *et al.* (2001) investigated 10 adult GTS patients who were treated with a mean daily dose of 10.9 mg olanzapine. The patients were evaluated at baseline and at weekly intervals for 8 weeks with the Y-GTSS and the Y-BOCS. Eight subjects completed the trial – two dropped out due to sedative side effects – and they showed a significant reduction of the Y-GTSS score from baseline to week 4 and even further by week 8. Budman *et al.* (2001) found no significant changes, either improvement or worsening, in Y-BOCS scores. It is unclear whether individual cases within their study might have had a substantial reduction in obsessive-compulsive behaviours. Maybe the small sample size prohibited the finding of a statistically significant change in Y-BOCS score.

Onofroj *et al.* (2000) described four adult GTS patients, who took part in a 52-week double-blind cross-over study with olanzapine (5 and 10 mg) and a low dose of pimozide (2 and 4mg). The patients were assigned to two groups. The first two weeks of treatment consisted of 2 mg/day pimozide or 5 mg/day olanzapine. The following 2 weeks the doses were doubled in both groups. The evaluation of drug efficacy was performed after 4 months of treatment. After 8 weeks of drug withdrawal the two groups were switched to the other drug treatment. They reported a significant reduction in scores on tic rating scales in the patients who were treated with olanzapine. The results were highly significant for 10 mg olanzapine vs. basal conditions and vs. 2 mg pimozide ; significant for 10 mg olanzapine vs. 4 mg pimozide ; and significant for 5 mg olanzapine vs. basal conditions and vs. 2 mg pimozide. Stephens *et al.* (2004) performed the first double-blind study of olanzapine in GTS. They studied the effects of olanzapine on aggressive behaviour and tic severity in 10 children with GTS. The patients were treated in a single-blind,

2-week placebo run-in, 8- week treatment phase trial. The initial dose of olanzapine was 1,25 to 2,5 mg/day and was titrated every two weeks, as tolerated. The mean daily dose at the end of the trial was 14,5 mg. In the olanzapine group, significant reductions of both aggression and tic severity scores were observed. These data on children support the idea that olanzapine may be an effective treatment for tics in GTS, but weight gain remains the main adverse event.

In our patient, olanzapine seemed to exhibit a certain effect not only on tics but also on associated obsessive-compulsive behaviours. To our knowledge, this is the first report on the beneficial effect of olanzapine on obsessive-compulsive behaviours in an adult GTS patient. Although there's a growing body of evidence on the addition of antipsychotics as an augmentation strategy in OCD, especially in those cases with comorbid tics (Hollander *et al.* 2002 ; Sareen *et al.*, 2004), treatment with clomipramine or SSRIs remains the golden standard for treatment of OCD and is indicated in cases of GTS in which these symptoms are prominent (Miguel *et al.*, 2003). The efficacy of olanzapine in reducing obsessive-compulsive symptoms has been reported in case reports (Weiss *et al.*, 1999), open-label studies (Baker *et al.* 1996 ; Bogetto *et al.* 2000 ; Koran *et al.*, 2000 ; Franco-bandiera, 2001 ; Sasson *et al.* 2001 ; Crocq *et al.* 2002 ; D'Amico *et al.* 2003 ; Marazziti *et al.*, 2005) and one placebo-controlled double-blind study (Bystritsky *et al.*, 2001). However, in another double-blind placebo-controlled study, Shapira *et al.* (2004) found no additional advantage of adding olanzapine for 6 weeks to patients who have had no satisfactory response to fluoxetine for 8 weeks. Double-blind studies have demonstrated that risperidone (McDougle *et al.* 2000 ; Hollander *et al.* 2003 ; Li *et al.* 2005) and quetiapine (Denys *et al.* 2004 ; Bogan *et al.* 2005) are also effective as augmentation strategy in antidepressant-treatment resistant OCD. Others (Carey *et al.* 2005) found no additional effect of quetiapine.

Compliance in our patient was very good, perhaps due to the administration of olanzapine in a soluble form, making control easier. Other important reasons for his good compliance were the marked improvement in symptoms and the tolerability of the drug with only a mild degree of side effects (weight gain, mild sedation). Failure of earlier pharmacological treatments in our patient may have been due to low compliance, lack of efficacy or a combination of these factors. ADHD-like behaviours were much less prominent at this episode, but may have played a role in failure of previous treatments. Although olanzapine was well tolerated, a weight gain of 4 kg over a 2-month period was noted. Furthermore our patient reported a mild sedation. The presence of weight gain and mild sedation as side effects is in accordance with

findings of other authors (Stamenkovic *et al.*, 2000 ; Onofroj *et al.*, 2000 ; Stephens *et al.*, 2004).

Taking account of the currently available evidence, it would be premature to advocate atypical neuroleptics or olanzapine as the gold standard of treatment of GTS. However, our case report adds further support to the rather small body of literature on this topic, especially in adults. Additionally, we underline the possible beneficial effect on the comorbid obsessive-compulsive behaviours. Given the often severe nature of tics and associated behavioural disorders, there is an urgent need to further investigate the use of olanzapine and other second generation antipsychotics in GTS. Special interest should be given to their effect on associated obsessive-compulsive behaviours.

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