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Research report

Tardive dyskinesia from atypical antipsychotic agents in patients with mood disorders in a clinical setting

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ABSTRACT

Background: There is a paucity of information on the risks and clinical characteristics of tardive dyskinesia with atypical antipsychotic agents in patients with mood and anxiety disorders in clinical practice.

Methods: The authors retrospectively screened the charts of 268 patients with a mood or anxiety disorder treated with atypical antipsychotic agents from a psychiatric practice. Fifteen patients who developed tardive dyskinesia were identified and further data was collected on these patients.

Results: Tardive dyskinesia occurred in 5.9% of patients after exposure to an atypical antipsychotic agent for a mean of 28.7 months (range: 1–83). The average dosage of the offending agent in chlorpromazine equivalents was 350 mg/day (range: 67–969). All patients experienced oral-buccal-lingual stereotypy, which was frequently severe in nature, but completely resolved in all but one patient. Most patients (90.9%) who consented to a second trial of an atypical antipsychotic did not experience a relapse of TD.

Limitations: All patients were treated in a clinical practice setting by a single psychiatrist, which may limit the generalizability of the findings.

Conclusions: The observed rate of TD represents a real world estimate of the risk of TD with atypical antipsychotic agents in patients with mood disorders. Fortunately, with early recognition symptoms appear to be reversible and further treatment with another atypical antipsychotic does not necessarily lead to relapse.

1. Introduction

Second-generation or atypical antipsychotic agents have emerged as an important part of the psychopharmacologic repertoire for the treatment of mood disorders. Although once limited mainly to the treatment of psychotic illness, nearly all atypical antipsychotics are currently FDA-approved for the treatment of bipolar disorder and three are approved for treatment-resistant unipolar depression (olanzapine, quetiapine and aripiprazole). With the prescription of these agents to an expanding segment of the population comes the obligation for clinicians and researchers to be fully aware of their safety profile.

Metabolic syndrome is perhaps the most significant safety concern with several atypical antipsychotics, but this risk is thought to be offset by the relative freedom from extrapyramidal side effects. Many randomized, controlled trials concluded that these drugs, with their atypical receptor-binding profile, carry minimal or even placebo rate of extrapyramidal side effects (Nasrallah et al., 2006), but it is important to remember that the primary outcome of these studies was efficacy and most studies of this kind lack power to detect meaningful differences in side effects. With respect to tardive dyskinesia (TD), the delayed onset of symptoms results in great underestimation of risk in short-term, randomized, controlled trials (Gentile, 2007). A systematic review of long-term studies conducted between 2004–2008 found an annualized incidence of TD of 3.9% for atypical antipsychotics and 5.5% for typical antipsychotics in patients with schizophrenia, which represents an increase in incidence of TD for atypical antipsychotics since the authors' last review in 2004 (Correll and Schenk (2008)). Furthermore, a recent epidemiologic study found that the risk of TD with atypical antipsychotics in a general population of psychiatric outpatients is about two-thirds that of typical antipsychotics. This is in stark contrast to previous studies where the risk of TD with atypical antipsychotics was deemed one-quarter that of typical antipsychotics (Woods et al., 2010). We are not aware of any long-term studies that assess the risk of TD

Abbreviations: ADHD, Attention-deficit hyperactivity disorder; AIMS, Abnormal Involuntary Movement Scale; GAD, Generalized anxiety disorder; MDD, Major depressive disorder; MPH, Methylphenidate; MS, Multiple sclerosis; OCD, Obsessive-compulsive disorder; PTSD, Post-traumatic stress disorder; TRD, Treatment-resistant depression

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with atypical antipsychotics in patients with mood disorders; however, based on older studies with typical antipsychotic agents, patients with mood disorders appear to have a greater risk than patients with schizophrenia (Keck et al., 2000). Clearly, more research is critically needed to further delineate the risk of this disfiguring and potentially irreversible extrapyramidal syndrome in patients with mood disorders. The aim of this study is to retrospectively describe the clinical characteristics of TD from atypical antipsychotic agents in patients with mood and anxiety disorders in the clinical setting.

2. Methods

We conducted this retrospective study with patients treated by one of the authors (JDC) in an outpatient setting. Chart reviews were performed at SUNY Downstate Medical Center in the Department of Psychiatry and the study was approved by the Institutional Review Board.

We first performed a screening review of over 598 charts of patients evaluated for the possibility of having received a typical and/or atypical antipsychotic medication during the course of treatment from 1994 to 2009. Out of 598 patients, 506 were treated for symptoms of a DSM-IV-TR mood or anxiety disorder and were available for follow-up. Charts of patients with schizophrenia and schizoaffective disorder were excluded. Among the 506 patients, 238 were not treated with an atypical antipsychotic agent while 268 (53%) patients were treated with atypical antipsychotic agents. Data was collected from 15 of those 268 patients who developed TD to further evaluate the characteristics of dyskinesia in the affected individuals. None of these patients experienced abnormal involuntary movements prior to treatment with the index atypical antipsychotic agent.

The treating psychiatrist screened for abnormal movements during each office visit and when present, an Abnormal Involuntary Movement Scale (AIMS) was administered (Guy, 1976). Severity of abnormal movements was measured using AIMS ratings: mild=2, moderate=3, severe=4 and recorded in the patient's medical record. A score of 2 in two or more movements or a score of 3 or 4 in any single movement is considered a positive test. We also chose to include those patients with a score of 2 in only a single item if the abnormal movement were deemed objectionable to the patient. Tardive dyskinesia was categorized as reversible or sustained and the persistence of symptoms was categorized as transient (<4 weeks), moderately persistent (<6 months), and persistent (>6 months).

The following calculations were performed;

1) Incidence of TD=total number of TD cases/total number of at-risk patients
2) Incidence rate of TD=total number of TD cases/(total number of years follow-up)(total number of at-risk patients)
3) Rate of TD cases per year=total number of TD cases/total number of years follow-up
4) Number of patients per year treated with atypical antipsychotics=total number of patients treated with atypical antipsychotics/total number of years follow-up
5) Annualized rate of TD cases per years=rate of TD cases per year/number of patients per year treated with atypical antipsychotics

3. Results

Of the 268 patients identified from the records of a psychiatric practice as having received an atypical antipsychotic for symptoms of a mood or anxiety disorder during the period from 1994 to 2009, 15 patients developed TD. The incidence of TD in this population was 5.9% and the incidence rate was 0.38% (15 cases per 4020 patient-years. We observed a mean of one case of TD per year with a mean of 17.9 at-risk patients per year. The annualized rate of TD cases per year was 5.6%. The characteristics of these patients are shown in Table 1. The mean age was 49.2 years and six patients were male (40%). Five patients (33.3%) had a concomitant anxiety disorder and three (20%) had a diagnosis of attention-deficit hyperactivity disorder (ADHD). Eight patients (53.3%) were also receiving a psychostimulant for symptoms of a treatment-resistant mood disorder or adult ADHD. One patient was diagnosed with central nervous system Lyme disease and multiple sclerosis, but there were no neurological comorbidities in any of the other patients.

The average dosage of the offending agent in chlorpromazine equivalents (Woods, 2003) was 350 (range: 67–969) mg/day. It was not clear if this dosage was in excess of the dosage of atypical antipsychotic used in the cohort of patients that did not develop TD. The duration of exposure before emergence of TD was 28.7 months (standard deviation: 29.3; range: 1–83). Three patients developed TD either during a period of overlap of two agents or during sequential treatment. One patient (56, F) developed TD during a trial of ziprasidone. Ziprasidone was tapered and discontinued and aripiprazole was initiated and titrated to 20 mg/day. The patient's dyskinetic symptoms were minimal on aripiprazole; however, she experienced a relapse of her mood disorder and ziprasidone was reinitiated. Minor TD persisted during the period of overlap of ziprasidone and aripiprazole and did not completely clear until both were discontinued and quetiapine 75 mg/day was initiated without TD. Another patient (55, M) was on concomitant ziprasidone and aripiprazole but because of timing of onset of TD, ziprasidone was deemed to be the offending agent. Movements were not subsequently evident provided aripiprazole was administered at <10 mg/day. The third patient (62, M) developed a similar type of TD pattern first to ziprasidone and subsequently to aripiprazole. He was able to tolerate quetiapine, but felt over-sedated and was ultimately stabilized with valproate. Previous exposure to typical antipsychotic agents in this group of patients was minimal with only one patient who was previously treated with typical antipsychotic agents (56, F). She did not develop TD during the course of previous treatment with typical antipsychotic agents nor did any patient develop symptoms consistent with TD before treatment with the index atypical antipsychotic agent.

All patients experienced stereotypy of the oro-buccal-lingual region while one patient also had involvement of the hands. Dyskinesia was classified as severe in almost half the cases (46.7%), but completely resolved in all but one patient. This patient (25, F) was under the care of another physician when she developed TD with risperidone administration. Of note, two (13.3%) patients were lost to follow-up. Despite emergence of TD, the previous psychiatrist did not discontinue risperidone for several months and TD remains persistent, although it has largely subsided and would be assessed as minimal. Dyskinetic symptoms resolved within four weeks of onset in 53.8% of cases, but two patients' (15.4%) symptoms persisted greater than six months. Most patients (90.9%) who consented to a subsequent trial of an atypical antipsychotic did not experience a relapse of TD.

4. Discussion

This is the first study of its kind in patients from psychiatric practice treated with an atypical antipsychotic for symptoms of a mood or anxiety disorder. The observed rate of TD in 5.9% of 268 at-risk patients spanning a 15-year period likely represents a real