Eur Arch Psychiatry Clin Neurosci (2006)
DOI 10.1007/s00406-006-0705-z

ORIGINAL PAPER

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The effect of atypical versus typical antipsychotics on tardive dyskinesia

A naturalistic study

Received: 31 May 2006 / Accepted: 18 October 2006 / Published online: 5 December 2006

Abstract *Objective* The aim was testing whether atypical antipsychotics (versus typicals) were associated with less risk of tardive dyskinesia (TD) in 516 severely mentally ill patients. *Methods* The sample included 11% (57/516) with no exposure before current treatment with atypicals; 9% (48/516) with prior and current treatment with atypicals but no exposure to typicals; 18% (94/516) with lifetime exposure to typicals for <5 years (plus atypicals); and 62% (317/516) with lifetime exposure to typicals for ≥5 years (plus atypicals). The Abnormal Involuntary Movement Scale (AIMS) was used to assess dyskinetic movements. Following Schooler and Kane's criteria TD was considered present when mild movements were present in at least two body areas or moderate movements were present in at least one body area. *Results* TD prevalences were 5% (3/57) in previously naïve patients, 19% (9/48) after exposure only to atypicals, 19% (18/94) after typical exposure of <5 years, and 42% (132/317) after typical exposure of ≥5 years. There was no significant effect comparing those taking only atypicals to those exposed to typicals for <5 years (OR = 1.0, CI 0.42–2.5). *Conclusion* This study is limited by the naturalistic design, the relatively small samples in the first two groups, the lack of information on the duration of the atypicals and their relatively recent introduction to the market (ziprasidone and aripiprazole were introduced to the market in the middle of the study). This study raises the question that new TD studies need to establish whether decades of treatment with atypical antipsychotics make a difference.

Key words tardive dyskinesia · atypical antipsychotics · typical antipsychotics · case-control study

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Introduction

The review of the atypical antipsychotic trials which have used typical antipsychotics as a comparison suggests that atypical antipsychotics tend to be associated with less reversible extrapyramidal symptoms [5] and with less propensity to cause tardive dyskinesia (TD) [1], particularly in elderly subjects [6]. A longitudinal study in 240 outpatients also showed less TD with atypicals than with typical antipsychotics [3]. However, a recent large naturalistic study in more than 20,000 geriatric patients suggested that in the clinical environment, and in older patients who have more risk of developing TD, it might not be possible to see a difference between the effects of typicals and atypicals in the development of TD [4]. In summary, the literature appears to suggest that when the more controlled studies are considered, atypicals may be less prone to cause TD. One has to acknowledge that some of these studies may have short-term follow-ups and be funded by pharmaceutical companies. On the other hand, it is not clear that naturalistic studies, looking at effectiveness in the real world, may be able to find TD differences between typical and atypical antipsychotics in the midst of the noisy clinical environment.

The aim of these analyses is to test whether atypical antipsychotics are associated with lower TD prevalence when compared with typical antipsychotics in a previously published naturalistic cross-sectional study of 516 severely mentally ill patients [2].

Table 1 Prevalences and categorical odds ratios (OR) according to antipsychotic intake

Patients	%	% adjusted for confounders	Categorical OR	Categorical OR adjusted for confounders
Naïve	5 (3/57)	5		
			4.2 (CI 1.1–16.3)[a]	4.3 (CI 1.1–17.4)[d]
Only taken atypicals	19 (9/48)	18.5[h]		
			1.0 (CI 0.42–2.5)[b]	1.2 (CI 0.46–2.8)[e]
Typicals for <5 years	19 (18/94)	21.4[i]		
			3.0[g] (CI 1.7–5.3)[c]	2.3[g] (CI 1.3–4.2)[f]
Typicals for ≥5 years	42 (132/317)38.5[j]	38.5[j]		

[a] Wald 4.2, df = 1, $P = 0.04$. It compares patients who have only taken atypicals vs. those who have never been treated on antipsychotics (naïve) before this atypical trial

[b] Wald 0.003, df = 1, $P = 0.95$. It compares patients who have also taken typicals for <5 years versus those who have only taken atypicals

[c] Wald 14.9, df = 1, $P < 0.001$. It compares patients who have taken typicals for ≥5 years versus those who have taken typicals for <5 years

[d] Wald 4.2, df = 1, $P = 0.04$. It compares patients who have only taken atypicals versus those who have never been treated on antipsychotics (naïve) before this atypical trial

[e] Wald 0.089, df = 1, $P = 0.76$. It compares patients who have also taken typicals for <5 years versus those who have only taken atypicals

[f] Wald 8.1, df = 1, $P = 0.005$. It compares patients who have taken typicals for ≥5 years versus those who have taken typicals for <5 years

[g] The decrease of the OR from 3.0 to 2.3 probably reflects the confounding effects of variables on TD. As a matter of fact, only adding the variable age > 45 years, by itself, caused the OR to decrease from 3.0 to 2.6

[h] The adjusted prevalence was computed by $p = m/(1 + m) \times 100 = 18.5$, where $m = 4.3 \times (0.05/(1 - 0.05)) = 0.226$. This computation assumes that the 5% prevalence corresponding to the naïve group was not substantially affected by confounders. The computation is based on the definition of odds (= $p/(1 - p)$, where p is the adjusted prevalence for the group of patients who are taken only atypicals divided by 100), so that the adjusted OR is equal to $4.3 = (p/(1 - p))/ (0.05/(1 - 0.05))$. Solving this equation for p, we obtain the formula used

[i] The adjusted prevalence was computed by $p = m/(1 + m) \times 100$, where $m = 1.2 \times (0.185/(1 - 0.185))$

[j] The adjusted prevalence was computed by $p = m/(1 + m) \times 100$, where $m = 2.3 \times (0.214/(1 - 0.214))$

Methods

The sample of 516 inpatients and outpatients from central Kentucky facilities has been described before and was collected in the context of a pharmacogenetic study [2]. The mean (SD) was 42.4 (12.8) years of age, 26.6 (11.4) years of age at the onset of psychiatric medication, 15.8 (11.6) years of duration on psychiatric medications, 11.3 (11.3) years of duration on typical antipsychotics, and 383 (391) chlorpromazine equivalents as the daily antipsychotic dose. The most frequent antipsychotics were risperidone, 65% (334/516); olanzapine, 17% (85/516); typicals, 14% (70/516), and quetiapine, 13% (69/516). All have taken at least one atypical antipsychotic at some point in their life. The sample included 46% (238/516) females, 32% (153/516) age 45 years or more, 79% (409/516) who had ever taken typical antipsychotics, 61% (317/516) who had taken typical antipsychotics for five or more years, and 11% (57/516) who had never taken antipsychotics before. Diagnoses were clinical DSM-IV diagnoses made by the treating physician. The most frequent were schizophrenic disorders, 49% (schizophrenia 29%, 150/516, and schizoaffective disorders, 20%, 105/516), and mood disorders, 29% (bipolar disorders 18%, 93/516, and major depressive disorders, 11%, 58/516).

The Abnormal Involuntary Movement Scale (AIMS) was used to assess dyskinetic movements. The highest single score among the seven body areas was considered the global severity score. Three quarters of the ratings were conducted by the author and one quarter independently by two experienced research nurses. Inter-rater reliabilities of the three raters have been described [2]. Following Schooler and Kane's criteria [10] TD was considered present when mild movements were present in at least two body areas or moderate movements were present in at least one body area. Once patients were considered as having TD, they were classified as severe if they had severe movement in at least one body area.

For these analyses, the antipsychotic exposure was categorically distributed at four levels (no exposure before current treatment with atypicals, 11% (57/516); prior and current treatment with atypicals but no exposure to typicals, 9% (48/516); lifetime exposure to typicals for <5 years (plus atypicals), 18% (94/516); and lifetime exposure to typicals for ≥5 years (plus atypicals), 62% (317/516). The prevalence of TD was compared using cross-tabulations and categorical odds ratios (ORs) using the repeated contrast method from the Statistical Package for the Social Sciences (SPSS), which compares each category of the predictor variable (antipsychotic exposure) to the category that precedes it. Logistic regression was used to control for significant confounding variables (gender, age >45 years, current antipsychotic and anticholinergic treatment and a polymorphic variation in the glutathione-S-transferase M1; [2] affecting the categorical variable measuring atypical exposure.

Results

The prevalence of TD was 5% in previously naïve patients, 19% in those exposed only to atypicals, 19% in those with typical exposure of <5 years, and 42% in those exposed to typicals for ≥5 years (Table 1).

The categorical ORs suggest that there was a significant effect in those previously naïve versus with those only taking atypicals (OR = 4.2). There was no significant effect in those only taking atypicals versus those with a relatively short treatment with typicals (OR = 1.0). There was a significant effect in those taking typicals for <5 years versus those taking typicals for ≥5 years (OR = 3.0) (Table 1). The categorical ORs, adjusted for significant confounding variables, were similar (Table 1).

When the TD cases were classified according to antipsychotic exposure, most were associated with long-term typical exposure. The TD cases included 2% (3/162) of those previously naïve, 5% (9/162) of those with only atypical exposure, 11% (18/162) of those with typical exposure of <5 years; and most, 82% (132/162), of those associated with typical exposure for ≥5 years.

When severe TD was examined in 162 patients with TD, the patients only on atypicals did not appear to have a better profile. The prevalence of severe TD was 0% (0/3) in those previously naïve, 56% (5/9) in those with only atypical exposure, 28% (5/18) in those with typical exposure for <5 years, and 30% (39/132) in those with typical exposure for ≥5 years.

Discussion

The study was not designed to test this hypothesis (it was a pharmacogenetic study; [2], total duration of atypical exposure was not quantified and the design was limited since the presence of TD was evaluated only as a cross-sectional assessment at a specific moment in time (patients were not followed 3 months later to verify whether dyskinetic movements were still present). The criterion of inclusion in the original pharmacogenetic study may have introduced some biases. Only patients with past or current risperidone treatment who were willing to sign a written informed consent in a study that included a blood collection were included in the sample. Obviously the need to sign a consent form and be willing to cooperate with a blood collection may have biased the sample somewhat, but the first bias (willingness to sign a consent form) is unavoidable in current times. However, after excluding consenting biases, the sample probably well represents Central Kentucky's severely mentally ill patients taking antipsychotics at the time of the study, since risperidone was the most frequently used antipsychotic. In fact, it was unusual to find antipsychotic-prescribed patients who have never taken risperidone.

The sample sizes of the first two groups (naïve and only on atypicals) were relatively small, around 50 patients. The sample size in the third group (typicals for <5 years) was moderate (almost 100); only the patients on typicals ≥5 years comprise a large sample size (>300 subjects).

The duration of psychiatric treatment and of typical exposure was determined by research nurses who reviewed the charts and by asking the patients. Obviously, these were rough estimations but were done without any knowledge that the author was planning to use them in these TD analyses. Moreover, three quarters of the ratings were conducted by the author [2] before looking at the current patient medication and with no knowledge of the duration of the psychiatric treatment estimated independently by the research nurses.

The time frame when this study was conducted (July 2000–March 2003) and the methods of recruitment also limit the possibility of generalizing the results to all atypical antipsychotics. In the US market, risperidone was introduced 6 years before the study's onset (in 1994); olanzapine 5 years before the study's onset (in 1996); quetiapine 3 years before the study's onset (in 1997); ziprasidone 1 year after the study's onset (in 2001) and aripiprazole 2 years after the study's onset (in 2002). Thus, it is very likely that effects (or decreased effects) of ziprasidone and aripiprazole on the risk of TD are not well represented in this study. In the well-controlled short-term studies of the pharmaceutical companies, which use double-blind designs, monotherapy and healthy subjects, ziprasidone and aripiprazole appear to have limited capacity to cause extrapyramidal side effects [8]. However, in the author's clinical experience in the real world, some specific subjects appear to develop clear cases of extrapyramidal side effects even with these two drugs and, in some cases, they can even be severe [7]. Despite these limitations, this study can be considered a naturalistic study that tries to give a first impression of the relative importance of the atypical antipsychotic's contribution to TD in the clinical environment. Due to the tendency of patients to be non-compliant and the tendency of doctors to switch and combine atypical antipsychotics, it is not going to be easy to distinguish the contribution of specific atypicals to the long-term risk of developing tardive dyskinesia in the real world.

The long-term exposure to typical antipsychotics (≥5 years) was a major predictor of TD but shorter exposure to typicals was not significantly different from exposure only to atypicals (OR = 1.0, CI 0.42–2.5), even after correcting for confounding variables (OR = 1.2, CI 0.46–2.8). Thus, this study failed to show major significant benefits of only atypical exposure versus exposure to atypicals and typicals for <5 years. These results are complementary to the large naturalistic study described by Lee et al. [4] since they included different populations. Lee et al.'s study was restricted to patients aged 66 or older with a diagnosis of dementia and excluded patients with a prior diagnosis of abnormal movement disorders. Thus, they probably excluded TD associated with long-term treatment of antipsychotics in the context of severe mental illnesses. As a matter of fact, another article from the same cohort explains that schizophrenia and depression were criteria of exclusion [9]. The current study sample included patients with severe mental illnesses, particularly schizophrenic psychoses and severe mood disorders, who tended to be younger than Lee et al.'s patients; only 4% (23/516) of patients were aged 66 years or older.

Future cross-sectional and prospective studies need to consider that, when comparing atypical versus typical risk for TD, it is important to recognize that longer treatment with typicals may contaminate the results. The complexity of analyzing naturalistic data is due to the fact that the long-term treatments are not randomized and any attempt to divide naturalistic groups results in uneven distributions. Thus, our four samples have different durations of any kind of psychiatric treatment. The median duration of treatment was 1 year for the naïve group, 5 years for

those exposed only to atypicals, 6 years for those with typical exposure of <5 years, and 21 years for those exposed to typicals for ≥5 years. Thus, long-term TD studies (by necessity naturalistic) may never be able to completely rule out the possibility that atypicals pose less risk of causing TD; one can only do that in well-controlled experimental studies with enough power. However, naturalistic studies can provide an idea of whether long-term treatment with atypicals and typicals is associated with clinically relevant differences in the risk of TD or not.

Any way, new studies need to establish whether or not decades of treatment with typical versus decades of treatment with atypical antipsychotics make a difference in long-term TD prognosis in the clinical environment.

Acknowledgements These analyses were conducted without external funding support. Francisco J. Diaz, Ph.D., from the Department of Statistics, Universidad Nacional, Medellin, Colombia, helped to calculate the prevalences adjusted for confounders described in Table 1. The subject recruitment and genetic testing for this sample was conducted for a pharmacogenetic study that was supported by several sources: a researcher-initiated grant from the Eli Lilly Research Foundation to Jose de Leon, M.D. (24% of direct costs), a NARSAD Independent Award to Jose de Leon, M.D. (11% of direct costs), internal funding (37% of direct costs), and finally by Roche Molecular Systems, Inc., which provided free genotyping and laboratory supplies (equivalent to 28% of direct costs). Besides this support, in the past three years Dr. de Leon has 1) been on the advisory board of Bristol-Myers Squibb and Roche Molecular Systems, Inc.; 2) received researcher-initiated grants from Roche Molecular Systems, Inc. and Eli Lilly; and 3) lectured supported by Eli Lilly (once), Bristol-Myers Squibb (once) and by Roche Molecular Systems, Inc. (5 times). The author thanks Lorraine Maw, M.A., for editorial assistance. A shorter preliminary version of this article was presented as an abstract at the 61st Annual Meeting of the Society of Biological Psychiatry, Toronto, Ontario, Canada, May 18–20, 2006.

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