Onset of action of atypical and typical antipsychotics in the treatment of adolescent schizophrenic psychoses

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Abstract

OBJECTIVES: The aim of our study was to assess the time to 'first improvement' associated with specific atypical (AAP) and typical (TAP) antipsychotic drugs in patients with early-onset schizophrenia and other related psychotic disorders.
METHODS: This study involved a systematic chart review of all patients receiving routine clinical care in our department, with selected AAPs and TAPs, for schizophrenic psychoses, between 1997 and 2007. During this period, our review identified 296 teenage patients (141 males, 155 females; mean age 16.0 ±1.5 years). The time to first improvement could be estimated in 258 patients; of these, 195 patients (76%) had been treated with AAPs and 63 patients (24%) with TAPs. We found that most patients were taking risperidone (N = 96), followed by olanzapine (64 patients). Other patient numbers were as follows: ziprasidone (16 patients), quetiapine (12 patients), clozapine (7 patients), haloperidol (15 patients), perphenazine (28 patients), and sulpiride (20 patients).
RESULTS: The mean time to first improvement was 6.9 (±4.2) days in the AAP group and 5.8 (±3.5) days in the TAP group; the difference was significant at the trend level (p=0.063). With respect to individual drugs, the mean time to first improvement was 7.1 (±4.1) days for risperidone, 6.7 (±4.2) days for olanzapine, 6.5 (±5.2) days for ziprasidone, 6.1 (±4.4) days for quetiapine, 7.4 (±3.0) days for clozapine, 5.2 (±2.4) days for haloperidol, 5.9 (±3.8) days for perphenazine, and 6.0 (±3.9) days for sulpiride. Differences among drugs were not significant (p=0.680).
CONCLUSIONS: Analysis revealed a significant group level trend indicating that typical antipsychotic drugs have faster onsets of action than atypical antipsychotic drugs.

ORIGINAL ARTICLE

INTRODUCTION

The original research regarding 'onset of action' (sometimes referred to as 'speed of onset of action') was carried out using novel antidepressants such as venlafaxine and mirtazapine (Thase 2001; Thompson 2002), and later extended to include atypical antipsychotics. Onset of action was defined, for these double blind studies, as 'the time to the first statistically significant difference between active and placebo treatment groups'; this time could also be considered 'the time of onset' (Thase 2001). This parameter also appears in the literature and is referred to as 'the time to efficacy,' or 'the time to first improvement.' Some authors underscore the need for a three arm design (active drug, comparative drug, placebo) claiming that it is more accurate (Thompson 2002). However, other methodologies have been established as effective in retrospective studies. 'Onset of efficacy' was defined as the day when the first remark regarding patient improvement appeared in the patient's medical documentation.

Unfortunately, there are few reports available dealing with the onset of action of atypical antipsychotics (AAP) in the treatment of schizophrenia (Agid *et al.* 2008). When the list of studies was narrowed to those that directly compared at least two AAP, only twelve relevant studies, among dozens of published studies, were found. Most of them involved adult populations. There have been reports describing speed of onset of action equivalency of risperidone with clozapine (Heinrich *et al.* 1994), olanzapine (Conley & Mahmoud 2001), quetiapine (Zhong *et al.* 2006), and asenapine (Potkin *et al.* 2007). Other studies reported equivalency of ziprasidone with olanzapine (Simpson *et al.* 2004), and equivalency of quetiapine, risperidone and olanzapine (Sacchetti *et al.* 2008). Some trials reported a faster speed of onset of action for risperidone over clozapine (Bondolfi *et al.* 1998), over olanzapine (Kasper *et al.* 2001), and over quetiapine (Potkin *et al.* 2006); additionally, a faster speed of onset of action has been reported for ziprasidone over aripiprazole (Zimbroff *et al.* 2007) and clozapine (Sacchetti *et al.* 2009). The only pediatric study dealing with mean response time, reported a faster onset of action for olanzapine (1.6 weeks) compared to risperidone (2.3 weeks) and haloperidol (2.4 weeks) (Sikich *et al.* 2004).

The aim of our study was to assess the time to 'first improvement' (i.e. speed of onset of action) associated with specific atypical and typical (TAP) antipsychotic drugs in patients with early-onset schizophrenia and other related psychotic disorders.

METHODS

Procedure and study design

This was a systematic chart review of all patients receiving routine clinical care at the Department of Child Psychiatry who were being treated with selected atypical (risperidone, olanzapine, ziprasidone, quetiapine, clozapine) and typical (haloperidol, perphenazine, sulpiride) antipsychotics for schizophrenia or related psychotic disorders between 1997 and 2007. The inclusion of an antipsychotic into the study was based on frequency of use. Only antipsychotics used in a minimum of at least five cases were included. Sulpiride was classified as a typical antipsychotic drug in agreement with most authors (Sadock & Sadock 2005, Wu *et al.* 2006), although, the opposite point of view also exists (Gerlach & Peacock 1995).

Patients received a 2-hour intake diagnostic and treatment evaluation by a child psychiatrist. All diagnoses were made by a treating child psychiatrist using the ICD-10 criteria (World Health Organization 1992) based on interviews with the parent(s) and child, and after a review of available school and psychological testing reports. No formal, structured interviews were used.

Records of patients were examined to ascertain the psychiatric diagnosis, type of antipsychotic medication and its dose at the end of the first week of treatment, and the first remark regarding any patient improvement recorded by a staff child psychiatrist. The time to first improvement was assessed in agreement with the methodology established for the retrospective studies as 'the number of treatment days prior to the moment when the first remark regarding patient improvement appeared in the patient´s medical documentation'.

Sample and statistics

Inclusion criteria were: (1) schizophrenia diagnosis of F20–29, (2) medical record quality sufficient to evaluate the patient, and (3) only antipsychotic treatments initiated after admission to the Department of Child Psychiatry were analyzed (i.e. the treatment was not used in out-patient care prior to admission).

In the period between 1997 and 2007, our review identified 296 teenage patients (141 males, 155 females; mean age 16.0 ±1.5 years). The time to first improvement could be estimated in 258 patients; of these, 195 patients (76%) had been treated with AAPs and 63 patients (24%) with TAPs. We found that most patients were taking risperidone (N = 96), followed by olanzapine (64 patients). Other patient numbers were as follows: ziprasidone (16 patients), quetiapine (12 patients), clozapine (7 patients), haloperidol (15 patients), perphenazine (28 patients), and sulpiride (20 patients).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 15.0). Descriptive statistics for samples was used. T-test and univariate ANOVA were used to analyze the differences in the onset of action between treatments.

RESULTS

The mean daily dose of medication at the end of the first week was 2.9 (±1.4) mg for risperidone, 13.4 (±5.0) mg for olanzapine, 81.9 (±18.7) mg for ziprasidone, 570.8

(±293.4) mg for quetiapine, 119.6 (±62.8) mg for clozapine, 8.0 (±3.9) mg for haloperidol, 21.2 (±13.7) mg for perphenazine, and 287.5 (±147.7) mg for sulpiride.

The mean time to first improvement was 6.9 (±4.2) days in the AAP group and 5.8 (±3.5) days in the TAP group; the difference was significant at the trend level (p=0.063; Fig. 1). With respect to individual drugs, the mean time to first improvement was 7.1 (±4.1) days for risperidone, 6.7 (±4.2) days for olanzapine, 6.5 (±5.2) days for ziprasidone, 6.1 (±4.4) days for quetiapine, 7.4 (±3.0) days for clozapine, 5.2 (±2.4) days for haloperidol, 5.9 (±3.8) days for perphenazine, and 6.0 (±3.9) days for sulpiride. Differences among drugs were not significant (p=0.680; Figure 2).

DISCUSSION

Our analysis revealed a significant group-level trend indicating that typical antipsychotic drugs have faster onsets of action than atypical antipsychotic drugs. However, differences among individual drugs (including AAPs as well as TAPs) were not significant.

The literature documents twelve reported comparisons involving two, or maximally three, AAPs regarding onset of action. Six of twelve published studies found an equivalent speed of onset of action (Heinrich *et al.* 1994; Conley & Mahmoud 2001; Simpson *et al.* 2004; Zhong *et al.* 2006; Potkin *et al.* 2007; Sacchetti *et al.* 2008) and our results confirmed these observations. The other six published studies, including the only pediatric study, reported significant differences in speed of onset of action (Bondolfi *et al.* 1998; Kasper *et al.* 2001; Sikich *et al.* 2004; Potkin *et al.* 2006; Zimbroff *et al.* 2007; Sacchetti *et al.* 2009).

Our retrospective design enabled us, in one study, to compare five atypical and three typical antipsychotics with regard to speed of onset of action, which makes it the first study to be so inclusive and extensive. This is a major advantage of retrospective studies and enables them to study certain aspects of clinical drugs not generally addressed by double-blind, prospective studies and involve aspects which are particularly well suited for meta-analyses (Bares *et al.* 2009; Hrdlicka *et al.* 2009). On the other hand, retrospective studies, in general, have many methodological limitations, e.g. absence of a control group, less precise design and measurements, no randomization, and unequally sized treatment groups. We are also aware of other methodological limitations in our study. Some of the treatment groups (ziprasidone, quetiapine, clozapine, and haloperidol) had less than 20 patients in the group; thus, it was less likely to detect statistical differences among these groups. Additionally, symptoms that indicated 'first improvement' in medical records were quite heterogeneous and might not have carried the same clinical weight.

This type of naturalistic observation also handicaps evaluation of clozapine, a drug that is generally reserved for treatment-resistant patients. According to our data, clozapine showed (non-significantly) the slowest onset of action (time to first improvement was 7.4 days) of all the assessed drugs. If clozapine was used as described above, it is not surprising that refractory patients would be less responsive and therefore respond slower than the standard patient population, although, no systematic data on the issue are available. Clearly, this represents one probable explanation of our observation regarding the very slow onset of action for clozapine. Another possible explanation would be that the initial titration of clozapine doses was slower than for the other antipsychotic drugs, which corresponds with the doses reached at the end of the first week (see Results).

The parameter of speed of onset of action of antipsychotics has clinical significance, although, research on the topic has, only recently, started to receive greater and well deserved attention. Better knowledge regarding the speed of onset of action of antipsychotic drugs could lead to more precise treatment guidelines in the future. Further studies on the topic are needed.

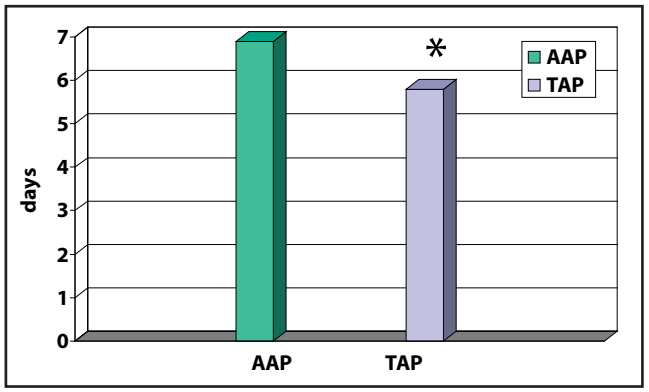

Fig. 1. Atypical versus typical antipsychotics: Mean time to first improvement.
AAP - atypical antipsychotics, TAP - typical antipsychotics.
T-test: t = 3.476; df = 1; p=0.063.

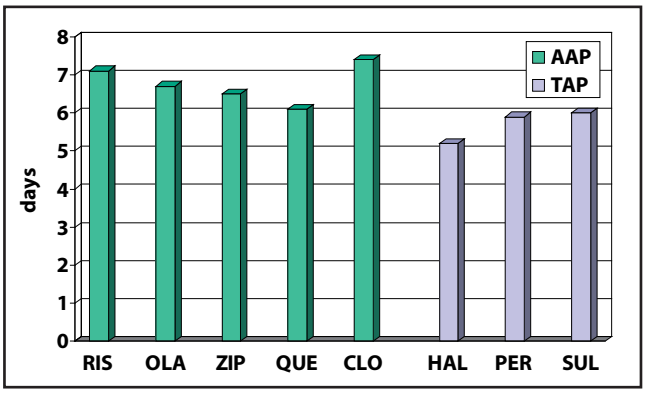

Fig. 2. Mean time to first improvement for individual drugs.
AAP - atypical antipsychotics, TAP - typical antipsychotics,
RIS - risperidone, OLA - olanzapine, ZIP - ziprasidone,
QUE - quetiapine, CLO - clozapine, HAL - haloperidol,
PER - perphenazine, SUL - sulpiride.
Univariate ANOVA: F = 0.690; df = 7; p=0.680.

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