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HEALTH CARE UTILIZATION IN PATIENTS WITH SCHIZOPHRENIA MAINTAINED ON ATYPICAL VERSUS CONVENTIONAL ANTIPSYCHOTICS

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Abstract

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1. Patients with schizophrenia who had been stabilized on their antipsychotic medication and subsequently maintained on it for a period of at least 18 months were identified: clozapine (N=15); risperidone (N=15); depot conventional (N=18); oral conventional (N=18).
2. Groups were compared on a clinical measure as well as the use of various health care services: hospitalizations; days in hospital, emergency room visits; physician and non-physician visits.
3. No differences between groups were found for hospitalizations, days in hospital, or emergency room visits, while physician and non-physician visits were highest in the clozapine group, in keeping with the need for routine hematologic monitoring in this population. The clozapine group had the highest baseline clinical scores and greatest number of previous hospitalizations.
4. These treatment groups may reflect different clinical populations. However, the findings suggest that in drawing conclusions regarding long-term benefits of different agents, clinical or economic, it would prove useful to include in the evaluation a comparison of patients who have been stabilized on each of the treatments.

Keywords: atypical antipsychotics, conventional antipsychotics, health care utilization, schizophrenia, stables

Abbreviations: analysis of variance (ANOVA), Clinical Global Impression scale (CGI)

Introduction

The atypical antipsychotics are seen as representing a significant advance over conventional agents in terms of both efficacy and tolerability (Fleischhacker and Hummer 1997; Waddington et al 1997). It has been argued, in turn, that these benefits contribute to improved compliance and outcome, resulting in decreased relapse rates (Weiden et al 1996). To some extent this has been corroborated by more recent reports indicating cost savings with the atypical antipsychotics, derived largely through diminished inpatient bed days (Aitchison and Kerwin 1997; Dickson et al 1999; Glazer and Johnstone 1997; Honigfeld and Patin 1990; Meltzer et al 1993; Rosenheck et al 1999; Viale et al 1997).

Design of studies comparing the atypical and conventional antipsychotics may, however, favor these newer medications. Efficacy studies routinely draw upon individuals in later stages of the illness who are, at best, only partial responders. As such, these subjects have already been tried on at least several conventional antipsychotics, which may even include the conventional agent which is being used in the investigation for the purpose of comparison. In one report where this issue was evaluated, subjects had been exposed to an average of 5.8 antipsychotics beforehand (Joffe et al 1996). Further to this point, studies have

indicated that chance of response to another conventional antipsychotic after failure on one can be as low as 10% (Conley et al 1988; Kane et al 1988; Kinon et al 1993; Pickar et al 1992).

Other approaches, such as mirror image studies are frequently employed to evaluate longer term outcome but face a similar problem. Individuals stabilized on the newer treatment are compared over a similar time interval before the switch, when they were doing less well and frequently exposed to different antipsychotic trials. Choosing to switch antipsychotics, in and of itself, generally reflects less than optimal response with existing treatment and the process of switching can be associated with increased instability and relapse rates (Gardos 1974; Weiden et al 1998). In addition, duration of treatment has been identified as critical to both clinical response and pharmacoeconomic gains (Dickson, et al 1999; Meltzer et al 1993; Revicki 1999; Revicki et al 1990). Thus, it is unfair to compare a time period when the individual has been stabilized and maintained on a new antipsychotic with a similar interval beforehand which may represent multiple conventional antipsychotic trials that are comparatively shorter in duration.

Distinguishing individuals who have completed each time interval from an intent-to-treat group helps prevent such a bias (Glazer and Johnstone 1997) but still does not overcome the problem, as in *all* cases individuals are being started on a new treatment to achieve a better clinical response. Moreover, few reports actually include intent-to-treat data in their analysis and mirror image studies routinely fail to elucidate the specific details of previous treatments.

This selection bias can be circumvented in several ways. One is to compare conventional and atypical agents in individuals who have not been exposed to previous antipsychotic therapy e.g., patients with a first episode psychosis. A second approach is to switch someone stabilized and seen as doing reasonably well on a conventional antipsychotic to an atypical agent, although the ethics of such an intervention would be open to question. A variation of this approach is a parallel comparison of individuals who have been stabilized on conventional antipsychotics based on satisfactory response with a second group stabilized and maintained on atypicals.

This investigation employed the latter approach and chose to evaluate individuals stabilized and maintained on 1 of 4 different treatments: clozapine, risperidone, oral and depot conventional antipsychotics. At the time this evaluation was undertaken, atypical antipsychotics were not clinically available in a depot formulation, and olanzapine and quetiapine, while approved for clinical use, had not been available long enough to meet the duration of treatment required for this project. The authors chose to include a depot group to address the question of compliance. Specifically, it might be argued that those being treated with conventional antipsychotics are less compliant as a result of increased side effects when compared to atypical agents, and a depot conventional antipsychotic group permitted direct measurement of compliance.

Methods

Patient Population

Following approval by the university Science and Ethics Committees, hospital records from the Schizophrenia and Continuing Care Program at out centre were identified for patients between the ages of 18 and 60 who met a DSM-IV diagnosis of schizophrenia (American Psychiatric Association 1994) and received one of the following: an oral or depot conventional antipsychotic, clozapine, or risperidone. The study sample was drawn from a cohort of individuals being followed long-term within a case management model at a large university teaching hospital. To permit a reasonable period of comparability, it was defined *a priori* that individuals would be included if they had been stabilized on one of these treatments for 3-6 months and then maintained on the same treatment for at least 18 months.

Charts were reviewed between the years 1993 and 1995, as clozapine and risperidone had just become available for clinical use in that interval. A cutoff of 1995 allowed for a review of at least 2 years of clinical data when the study was undertaken.

Assessment

For the 18-month interval all hospitalizations and length of stay were recorded, as were emergency room visits and outpatient visits with physicians and non-physician caretakers. Demographic variables recorded included gender, age, duration of illness (from initial diagnosis), and number of previous hospitalizations. The Clinical Global Impression scale (CGI) (Guy 1976) was used to establish severity of illness, and was completed by one of the authors (IK) based on description of symptoms at the beginning and end of the 18-month interval.

Data Analysis

The demographic and outcome measures were compared across treatment groups using 1-way analysis of variance (ANOVA), with the exception of gender distribution where a χ^2 analysis was used, and change in CGI scores from baseline to endpoint where repeated measures ANOVA was employed, The Scheffé F-test was used for *post-hoc* comparisons when applicable.

Results

A total of 314 charts were reviewed, and of these 66 cases were available that met the aforementioned inclusion criteria, that is patients between ages 18 and 60 with a DSM-IV diagnosis of schizophrenia (American Psychiatric Association 1994) and treatment over 18 months with clozapine (N=15), risperidone (N=15), depot conventional antipsychotics (N=18: fluphenazine decanoate 4; flupenthixol decanoate 7; haloperidol decanoate 4; pipotiazine palmitate 3) or oral conventional antipsychotics (N=18: trifluoperazine 8; pimozide 4, loxapine 3, methotrimeprazine 1; perphenazine 1; thioridazine 1) following a stabilization period of 3-6 months. A review of clinical records indicated that 16 of the 18 patients on depot therapy received all injections over the 18 months, and in the 2 who didn't compliance was 89% and 94%, respectively.

Over 90% of individuals in each treatment group received at least 1 other psychotropic medication during the course of follow-up. In most cases they were on these medications at the time data collection commenced, although this was not always so and changes were made in some cases through the follow-up interval. Concomitant psychotropic medications included antiparkinsonians, benzodiazepines, and antidepressants. While specific changes in frequency or pattern of use were not evaluated here, it is necessary to point out that there are reports suggesting that atypical antipsychotics may be associated with a decreased use of concomitant psychotropic agents (Chong et al 2000).

Characteristics of the study sample are outlined in Table 1. Treatment groups were comparable in terms of age, gender, and illness duration although those receiving clozapine or depot treatment tended to be older and have a longer duration of illness. Those treated with clozapine also had significantly more previous hospitalizations than those receiving oral conventional antipsychotics (Scheffé F-test p=0.05). The clozapine-treated group had the highest baseline CGI score, whereas those in the oral conventional group had the lowest scores, significantly less than the other treatments (Scheffé F-test p=0.05).

Table 1

Demographic Information for Subjects Receiving Clozapine, Risperidone, Depot or Oral Conventional Antipsychotics

Variable	Clozapine (N=15)	Risperidone (N=15)	Depot Conventional (N=18)	Oral Conventional (N=18)	p Value
Age (yr), mean ± S.E.M.	33.4 ± 2.5	31.7 ± 2.1	36.5 ± 2.1	31.7 ± 1.7	NS*
Gender, male/female	10/5	8/7	10/8	10/8	NS
Illness duration (yr), Mean ± S.E.M.	11.9 ± 2.3	9.1 ± 2.0	13.7 ± 1.9	8.3 ± 1.7	NS
Previous hospitalizations, Mean ± S.E.M.	11.7 ± 3.2	6.9 ± 1.6	11.1 ± 2.2	3.1 ± 1.0	p = 0.01

*NS – not significant

Table 2 summarizes the various outcome measures. Over the 18 months no significant difference was found between groups with respect to number of hospitalizations, days in hospital, or emergency room visits. The low number of hospitalizations in all groups likely reflects the growing shift towards management outside of hospital, as well as the study sample itself. These individuals were chosen because they had been stabilized on one of the treatments and were therefore less likely to require admission than a population which has not been stabilized on a particular medication. Clozapine had the greatest number of physician visits, significantly greater than those receiving either form of conventional antipsychotic, while risperidone had significantly more visits than those receiving oral conventional antipsychotics. In the case of non-physician visits, clozapine once again was associated with the greatest number of visits, significantly more than the oral conventional antipsychotic group.

In terms of clinical changes, as measured using the CGI, a repeated measures ANOVA indicated significant improvement over the 18 months ($F=109.35$; $df=3,62$; $p=0.0001$). Improvement was significantly greater for those treated with clozapine, risperidone, and depot conventional therapy versus oral conventionals (Scheffé F-test, $p=0.05$). However, baseline scores were lowest for the conventional – oral group.

Table 2

Outcome Measures for Subjects Receiving Clozapine, Risperidone, Depot or Oral Conventional Antipsychotic

Outcome Measure	Clozapine (N=15)		Risperidone (N=15)		Depot Conventional (N=18)		Oral Conventional (N=18)		p Value
	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	Mean	S.E.M.	
Number of Hospitalizations	0.9	0.4	0.9	0.3	1.1	0.4	0.7	0.3	NS*
Days in hospital	35.1	14.1	28.6	11.8	20.8	7.8	31.8	12.4	NS
Physician visits	58.9	6.3	40.9	6.8	23.7	3.3	15.4	3.0	p=.0001[a]
Non-physician Visits	32.2	7.3	17.1	4.6	27.3	3.6	8.4	3.7	p=.004[b]
Emergency room Visits	1.5	0.2	1.4	0.7	2.1	0.8	1.6	0.6	NS
CGI									p=.0001[c]
Baseline	5.8	0.2	5.0	0.3	4.9	0.3	3.9	0.1	
Endpoint	4.1	0.2	3.7	0.3	3.7	0.3	3.4	0.2	

*NS – not significant
[a]Clozapine > Depot Conventional, Oral Conventional
[b]Clozapine > Oral Conventional
[c]Clozapine, Risperidone, Depot Conventional > Oral Conventional

Discussion

Summary of Findings

This paper has approached the comparison of conventional and atypical antipsychotics from a somewhat different perspective. Samples for the larger trials making such comparisons are, as noted earlier, routinely characterized by a selection bias, involving patients who have already demonstrated less than optimal improvement with conventional antipsychotic therapy and who may not be stabilized and maintained on a particular treatment. To address this issue, the present investigation compared conventional and atypical antipsychotics in patients stabilized on one or the other. Under these conditions, there was no indication that the typical antipsychotics were less effective from the standpoint of re-hospitalization rates, days in hospital, emergency room visits, or use of physician and non-physician services.

Study Limitations

These results must be viewed within the context of several caveats. The groups in this study had been stabilized on their antipsychotic treatment, but this is not to say that they were homogeneous clinically. Mean baseline CGI scores were highest in the clozapine sample (5.8), and lowest in those receiving oral conventional antipsychotics (3.9). The scores for the risperidone and depot samples were similar (5.0 and 4.9, respectively) and fell between the clozapine and oral conventional groups. We have alluded to the fact that clozapine is routinely given to individuals who have done poorly with earlier treatments, and this group did have the highest baseline CGI scores. The risperidone- and depot-treated groups had similar scores at baseline, but again scores that were higher than the group receiving oral conventional antipsychotics. These findings are in keeping with clinical practice, at least as it took place at the time this study was carried out. More specifically, it was still common to use oral conventional agents in the early stages of treatment, while risperidone and depots were often employed only after individuals who had been tried on oral conventionals proved to be treatment resistant, intolerant and/or non-compliant. Risperidone is now used more frequently in the initial stages of treatment, whereas clozapine has and continues to be relegated to use in the more refractory population.

The results must also be viewed in the context of prescribing guidelines. It is not so surprising that clozapine-treated patients were associated with the highest use of outpatient services (physician and non-physician visits) given the requirement in North America regarding regular hematologic monitoring, weekly initially and at least twice monthly even at the 6-month interval and beyond. This finding has been reported elsewhere (Rosenheck et al 1997).

The need for routine hematologic monitoring can account for the increased physician visits in those receiving clozapine when compared to conventional antipsychotics. Similarly, the finding that oral, but not depot, conventional antipsychotics were associated with significantly fewer non-physician visits fits with clinical practice, in that the depot group must come in regularly for their injection and this is routinely administered by a nurse/case manager. It was surprising, however, that risperidone was not significantly different from clozapine with respect to number of physician or non-physician visits. A clear explanation for this is not readily evident but several possibilities exist. Risperidone was only recently available at the time this investigation was carried out, and it is possible that clinicians felt the need for more regular monitoring as they became comfortable with its use. Visits with non-physician staff are often tied in with the doctor's appointments, which could have contributed to more visits of this type as well. One might also speculate that clinical improvement, or the expectation of such, in those receiving the atypical antipsychotics is paralleled by a shift in treatment team expectations, which in turn influences their level of intervention.

Related to this last point is the shift in recent years towards evaluating outcome along a number of dimensions (Waddington and O'Callaghan 1997). Because of the retrospective nature of this study clinical outcome evaluation was confined to the CGI, which provides nothing more than a global measure. No difference between the various treatment groups was noted on the CGI here, but data are lacking regarding more specific measures now considered to be important e.g., specific symptom clusters, quality-of-life, functional recovery. It may be that the atypical antipsychotics are superior on at least some of these dimensions, but this investigation did not evaluate such differences.

Clinical and Research Implications

What conclusions can be drawn from the present findings? Taken at face value, the results would argue against the position that the use of atypical antipsychotics is associated with decreased health care use. Indeed, no such differences were found when clozapine- and risperidone-treated groups were compared to individuals on oral or depot conventional antipsychotics. Such a categorical statement cannot be made, though, for the reasons already noted: the choice of different treatments likely reflects different populations and a number of specific outcome measures were not examined here.

However, the data do suggest caution in evaluating measures such as use of health care services by comparing individuals who have been stabilized on antipsychotics and are seen as well enough to continue this line of treatment with those who have not been doing well and are considered candidates for a new medication. Evidence from another line of investigation offers further

support in this respect. It was noted earlier that an alternative means of avoiding this type of selection bias is to compare individuals in the initial stages of the illness, a time when they have a similar likelihood of clinical response and have not already distinguished themselves along a response continuum. Focusing on this approach, one study found olanzapine superior to haloperidol on various clinical measures in 'first episode' patients; however, first episode was defined as within 5 years of psychotic symptoms and 77% of the sample had previous antipsychotic exposure (Sanger et al 1999). In contrast, a first episode study comparing risperidone and haloperidol was carried out wherein 93% of subjects met DSM-IV diagnostic criteria for schizophreniform disorder and only 6% had been exposed to previous conventional antipsychotic therapy (Emsley, 1995). In this case, no clinical differences, beyond side effects, were noted between the 2 agents.

Should all individuals on conventional antipsychotics be switched to one of the atypicals? While there may be reasons for switching to a newer antipsychotic e.g., improvement in specific symptoms, decreased risk of tardive dyskinesia, the present data indicate that in the case of stabilized patients there may be no advantage from the standpoint of health care use or savings. Again, it is important to note that this finding is confined to patients who have been stabilized on their antipsychotic medication, and does not speak to possible benefits along a variety of clinical dimensions.

Conclusion

The reported benefit of atypical antipsychotics with respect to health care utilization was not found here. That the different treatments reflected different clinical populations cannot be ruled out. However, the point is made that studies evaluating different treatments over the longer term should take into consideration a comparison of patients in each group who have done well enough to be maintained on that particular treatment.

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