Comparing the Use and Discontinuation of Antipsychotics in Clinical Practice: An Observational Study

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Background: There are few independent studies comparing atypical or second-generation antipsychotics (SGAs).

Objective: To compare the patterns of use and discontinuation of commonly used SGAs.

Method: Retrospective review of 11,250 case records (2002–2005) of all mental health care contacts in a discrete geographical setting in Scotland. Patterns of use, mean dose, psychotropic co-prescription, duration of treatment, discontinuation rates, and admission rates were examined for amisulpride, clozapine, olanzapine, quetiapine, and risperidone.

Results: Clozapine had a significantly lower discontinuation rate in individuals with schizophrenia, compared to the other 4 SGAs. Off-license prescribing and polypharmacy were common.

Conclusion: SGAs are variously used for schizophrenia and mood disorder and have heterogeneous outcomes, with clozapine being most effective in this study. Independent observational studies such as this complement randomized controlled trials.

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Debate continues[1–4] over the comparative benefits and risks of atypical or second-generation antipsychotics (SGAs). While the SGAs command widespread clinician confidence and have been recommended by influential guidelines,[5] it is not clear that the SGAs are a homogenous group with a clear class effect. Coupled with this apparent heterogeneity are the increasing licensed uses for some SGAs that have evolved in recent years from schizophrenia and related psychoses to specific phases of bipolar disorder. Deciding which SGA should be used in a particular circumstance is therefore often a matter of trial and error.

Discontinuation rate of SGAs has been adopted as a measure of effectiveness in the landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies.[1,6] We also decided to examine discontinuation rate, as well as the varying patterns of use of 5 of the most commonly used SGAs in a representative community-based population.

METHOD

Study Design

The county of Lanarkshire in the central belt of Scotland, United Kingdom, comprises approximately 550,000 people in mixed urban and rural settings and is ethnically homogenous with comparatively low socio-economic status.[7] Using an electronic patient record (EPR) system covering all mental health care contacts for a large area in Lanarkshire (approximately 400,000 people), we aimed to describe and compare the patterns of use and discontinuation of SGAs in all individuals prescribed these medications.

The EPR included all typed nursing and medical notes and correspondence for patients aged 16 to 65 from February 2002 to June 2005. The EPR system was searched for information on the most commonly used oral SGAs. Both generic and trade names of medications were used as keywords for the searches. The SGAs most commonly prescribed between 2002 and 2005 were amisulpride, clozapine, olanzapine, quetiapine, and risperidone. Chlorpromazine and haloperidol were not chosen as compara-

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Table 1. Diagnoses and Use of Second-Generation Antipsychotic (SGA) Medication in a Retrospective Review of 11,250 Case Records

Variable	Amisulpride	Olanzapine	Quetiapine	Risperidone	Clozapine
Total prescribed SGA, N	340	893	436	192	152
Available for analysis, N	251	632	309	136	136
Diagnosis, N (%)					
Schizophrenia/psychosis	159 (63)	323 (51)	121 (39)	74 (54)	132 (97)
Bipolar disorder	28 (11)	101 (16)	65 (21)	7 (5)	4 (3)
Depression/anxiety	52 (21)	153 (24)	106 (34)	42 (31)	0 (0)
Personality disorder	4 (2)	10 (2)	11 (4)	4 (3)	0 (0)
Other[a]	8 (3)	45 (7)	6 (2)	9 (7)	0 (0)

[a]Includes posttraumatic stress disorder and dementia.

tors, as searches indicated these were only rarely used for maintenance treatment.

Measures and Outcomes

After initial identification from the EPR, every medical case record containing information on 1 or more of the 5 SGAs under study were manually scrutinized for demographic and clinical information including all diagnoses, dosage of medication, and co-prescribed psychotropic medication.

Cross checking between the EPR and 10% of individual case records was done to ensure accuracy of the EPR. All diagnostic groups were included. Diagnoses were always made by experienced psychiatrists (with a minimum of 4 years postgraduate medical training) using clinical ICD-10 criteria.[8]

After the initial analysis of the total sample, only those cases with a diagnosis of schizophrenia or related psychoses (F2 category, ICD-10) were selected for further analysis to allow valid comparisons between clinically comparable groups. Medical case records were only excluded from analysis if there was insufficient clinical or demographic information available.

In this selected population, discontinuation rates for individual SGAs were only calculated in cases where the SGA had been initiated after the EPR commenced (i.e., not including those on the medication prior to the introduction of the EPR), in which it was clearly a definite discontinuation with evidence of a prescription being ceased. Discontinuation rates were adjusted to account for the duration of record by dividing raw discontinuation rate by length of record. Reasons for the discontinuation noted in the EPR and medical case record were assigned to 3 groups: discontinuation due to intolerable side effects, due to inefficacy, or due to other reasons (e.g., patient choice). The mean number of days until discontinuation for each SGA was also calculated.

Hospital admission rates were calculated for each SGA, but again only in those cases where the SGA was initiated after the EPR commenced.

In order to examine any relationship between mean dosage of SGA and discontinuation rate, we calculated the mean maximum dose of SGA used in cases in which subjects both continued and discontinued a particular SGA.

Statistical Analysis

StatsDirect (Issue 1.8.9, StatsDirect Ltd., Chesire, United Kingdom) was used for simple descriptive statistics. Significance was set at 2-tailed $p < .05$, and 95% confidence intervals were calculated where appropriate.

RESULTS

Diagnostic Categories and Dosage of Medication

A total of 11,250 case records were searched. Of those, 2013 individuals (18% of the total) were prescribed 1 or more of the 5 SGAs under scrutiny, but only 1464 individuals (13% of the total) had case records of sufficient quality (defined as having 2 or more independent documents mentioning the SGA in question) to allow thorough analysis. This relative proportion of case records available for analysis is illustrated in Table 1, along with the patterns of use of the 5 SGAs across broad diagnostic categories.

Diagnostic categories placed in the "other" group include posttraumatic stress disorder and dementia. Unsurprisingly, clozapine is used almost exclusively for schizophrenia and related psychoses. Quetiapine, in contrast, was used in the majority of cases not for schizophrenia but for mood disorder and anxiety.

Table 2 reveals the mean dosages of the 5 SGAs over the entire duration of treatment for all diagnostic categories, i.e., schizophrenia and related psychoses; bipolar disorder; and "other" diagnostic categories, which include depression, anxiety, and personality disorder.

Table 2 shows that the mean dose for all 5 medications studied is lower in bipolar disorder than schizophrenia (with average dose reduction between SGAs ranging from 16% [clozapine] to 59% [risperidone]).

Patient Characteristics

For further analyses, only those individuals with a diagnosis of schizophrenia or related psychosis who had

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Table 2. Mean Dose[a] of Second-Generation Antipsychotics

	Mean Dose, mg/d				
Diagnosis	Amisulpride (N = 251)	Olanzapine (N = 632)	Quetiapine (N = 309)	Risperidone (N = 136)	Clozapine (N = 136)
Schizophrenia	589	15.5	441	6.0	427
Bipolar disorder	396	14.0	375	2.5	350
Other	356	10.0	240	2.5	…

[a]Rounded to the nearest 0.5 mg.
Symbol: … = not applicable.

Table 3. Characteristics of Individuals With Schizophrenia Newly Started on Second-Generation Antipsychotic Treatment

Characteristic	Amisulpride (N = 95)	Olanzapine (N = 148)	Quetiapine (N = 78)	Risperidone (N = 39)	Clozapine (N = 40)	p
Age, y						NS
Mean	41	40	41	43	37	
95% CI	38 to 43	39 to 42	38 to 44	39 to 47	33 to 40	
Men, % (N)	63 (60)	64 (95)	38 (30)	62 (24)	65 (26)	.0006[a]
History of alcohol misuse, % (N)[b]	36 (34)	34 (51)	23 (18)	28 (11)	38 (15)	NS
History of illicit substance use, % (N)[c]	22 (21)	23 (34)	27 (21)	10 (4)	28 (11)	NS
Co-prescription, % (N)						
Antidepressant	46 (44)	55 (81)	62 (48)	46 (18)	43 (17)	NS
Mood stabilizer	18 (17)	8 (12)	14 (11)	15 (6)	13 (5)	NS
Antipsychotic	37 (35)	27 (40)	26 (20)	31 (12)	8 (3)	.098[d]

[a]$\chi^2 = 19.4$, df = 4, p = .0006.
[b]Any record of lifetime history of alcohol consumption greater than recommended safe limits (> 21 units or standard drinks per week for men, > 14 units for women), or any diagnostic record of misuse or dependency.
[c]Any record of lifetime history of regular illicit substance use.
[d]$\chi^2 = 7.8$, df = 4, p = .098.
Abbreviation: NS = not significant.

commenced the relevant SGA after the start of the EPR were selected. The numbers of case records meeting these inclusion criteria are given in Table 3, along with related demographic and clinical characteristics.

Table 3 indicates there were no significant differences in age between the 5 groups, with this being a middle-aged population. Quetiapine was preferred in female patients (p = .0006), but no other gender differences existed. The rate of drug and alcohol misuse in the entire population, as recorded in the patients' clinical records, was relatively high, but no inter-group differences existed in substance comorbidity. The most common drug of misuse was cannabis.

A high rate of psychotropic co-prescription is also documented in Table 3, with co-prescribed antidepressants and, perhaps surprisingly, a second antipsychotic medication being common. Clozapine is the SGA least likely to be combined with another antipsychotic ($\chi^2 = 7.8$, df = 4, p = .098). No significant differences between the rates of co-prescription of antipsychotics among the other SGAs were observed.

Clinical Outcomes

There were significant differences in the length of case record available in this selected population, as illustrated in Table 4, with the longest mean duration of record being for amisulpride (approximately 2 years) and the shortest mean duration being for risperidone (approximately 17 months). Overall medication discontinuation rate was significantly lower for clozapine than the other 4 SGAs studied, and this remained the case after adjusting for the length of psychiatric case record available, as illustrated by the 95% confidence intervals provided in Table 4. Removing clozapine from the analysis revealed that there was no significant difference in medication discontinuation rate between amisulpride, olanzapine, quetiapine, and risperidone.

Further analysis, as shown in Table 4, indicates that discontinuation due to side effects was lower for risperidone and clozapine compared to the other 3 SGAs, although the numbers are low. Discontinuation with clozapine was associated with nonadherence rather than lack of efficacy, and a weak trend (p = .12) toward a higher mean number of days to discontinuation was also observed with clozapine. Other reasons for discontinuation were firstly nonadherence with medication, followed by improvement in clinical state, followed by unidentified reasons. No significant differences in hospital admission rates between the 5 SGAs were evident.

Further analysis showed that those who continued treatment with risperidone were taking a significantly higher maximum dose (5.4 mg vs. 3.2 mg; t = 1.9, df = 36, p = .03) than those discontinuing treatment. There was no significant relationship between mean dos-

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Table 4. Discontinuation Rates, Hospital Admission Rates, and Duration of Treatment With Second-Generation Antipsychotics (SGAs)

Variable	Amisulpride (N = 95)	Olanzapine (N = 148)	Quetiapine (N = 78)	Risperidone (N = 39)	Clozapine (N = 40)	p
Duration of record, d						.016[a]
Mean (A)	716	644	670	530	705	
95% CI	655 to 778	594 to 694	608 to 733	430 to 629	613 to 797	
Discontinuation rate (B), % (N)	51 (48)	41 (60)	36 (28)	28 (11)	18 (7)	.02[b]
Adjusted discontinuation rate[c]						…
B/A	0.71	0.64	0.54	0.53	0.25	
95% CI	0.66 to 0.78	0.59 to 0.69	0.49 to 0.59	0.45 to 0.65	0.23 to 0.29	
Discontinuation reasons, % (N)						
Side effects	35 (17)	32 (19)	46 (13)	0 (0)	14 (1)	.03[d]
Inefficacy	33 (16)	28 (17)	36 (10)	73 (8)	0 (0)	.097[e]
Other	32 (15)	40 (24)	18 (5)	27 (3)	86 (6)	NS
No. of days to discontinuation						.12[f]
Mean	232	256	191	152	427	
95% CI	165 to 299	194 to 318	113 to 231	74 to 231	108 to 746	
Hospital admission during time of record, % (N)	24 (23)	25 (37)	29 (23)	13 (5)	35 (14)	NS

[a]$F = 3.1$, df = 4,399; $p = .016$.
[b]$\chi^2 = 4.3$, df = 1, $p = .02$ (clozapine vs. the other 4 SGAs), but no significant difference between the 4 SGAs excluding clozapine.
[c]Adjusted discontinuation rate (B/A) = discontinuation rate/mean duration of record.
[d]$\chi^2 = 10.8$, df = 4, $p = .03$.
[e]$\chi^2 = 7.9$, df = 4, $p = .097$.
[f]$F = 1.9$, df = 4,151; $p = .12$.
Abbreviation: NS = not significant.
Symbol: … = not applicable.

age and discontinuation as opposed to continuation of treatment for the other 4 SGAs under examination.

DISCUSSION

We have reported on the comparative patterns of use and discontinuation of 5 of the most commonly used oral antipsychotic medications in a large representative community-based population. The study period was approximately 2 years.

Concerns have been expressed[9] regarding the relative dearth of independent head-to-head comparison studies of antipsychotic medications. Additionally, while randomized controlled trials (RCTs) test a specific question in a rigorous manner, they arguably have limited generalizability as they exclude complicated patients, whereas pragmatic or observational studies can have better external but less internal validity. Recent RCTs[1] have placed emphasis on inclusive study designs that test treatment effectiveness by examining time to treatment discontinuation, and we also chose to adopt this outcome measure in a large independent observational study.

Approximately 18% of all individuals in contact with mental health services were prescribed SGAs. Numerically, medications preferentially chosen here were olanzapine > quetiapine > amisulpride > risperidone > clozapine. Across Scotland, according to government figures,[10] 0.84% of the adult population are in receipt of daily antipsychotic prescriptions, and, by volume, olanzapine, quetiapine, and risperidone are most frequently used nationally along with chlorpromazine (which is mostly used by family doctors or on an "as required" basis).

Principal Findings

Clozapine had a significantly lower discontinuation rate than amisulpride, olanzapine, quetiapine, and risperidone in this study and a (nonsignificant) lower age of initiation. The superior effectiveness of clozapine has been noted elsewhere,[2,11,12] and a large industry sponsored observational study[13] found both clozapine and olanzapine to have lower discontinuation rates than the other 3 SGAs we studied. Clozapine was also significantly less likely to be combined with another antipsychotic medication, which is arguably a measure of individual medication effectiveness. It is worth noting that in the United Kingdom, clozapine treatment requires patients to have regular contact with health professionals due to blood monitoring, and that clozapine is licensed only for treatment-resistant schizophrenia due to its adverse side effect profile.

In this study, there was no association between our measures of effectiveness and mean dose as a proportion of the maximum recommended dose[14] in any of the antipsychotics studied, suggesting that effectiveness was not confounded by suboptimal dosing, although the dose-response relationship with antipsychotics is complex.[15]

Once clozapine was excluded from analysis, no significant difference in discontinuation rate between amisulpride, quetiapine, olanzapine, and risperidone was observed. This is in contrast to some large studies,[1,2] although others[16] have put forward analyses suggesting SGAs may be differentiated only by side effect profile

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and not efficacy. One of the major if somewhat surprising findings of the CATIE study was the high antipsychotic discontinuation rate.[1,6] Our discontinuation rates are lower and possibly more representative of normal clinical practice, although our lower discontinuation rates could also be attributable to differences in community-based health care delivery between the United Kingdom and the United States, as well as differences arising from the demands of conducting RCTs, such as CATIE, in this population. This reinforces the value of routinely collected observational data. Additionally, the reasons given here for discontinuation need to be taken cautiously in view of the low numbers involved.

The patterns of use of SGAs described here for the period 2002 to 2005 demonstrate that off-license prescribing and polypharmacy were common. One survey[17] found that 65% of U.K. psychiatrists "admitted" to prescribing off license in the preceding month. We found that quetiapine (especially for women) and then olanzapine were the preferred choices for mood disorder, with quetiapine being used as an antipsychotic only in a minority of cases. This reflects other evidence suggesting these medications are useful in bipolar disorder.[18,19] The dose range of all 5 medications studied was lower in bipolar disorder than in schizophrenia, and this may be a consequence of antipsychotic medication in bipolar disorder often being employed as an adjunct to a mood stabilizer such as lithium or valproate as opposed to antipsychotic monotherapy in schizophrenia.

Using the restricted subpopulation of community-based individuals with schizophrenia or related psychosis, with a prescription for a SGA initiated after the electronic record commenced, we showed that quetiapine was used significantly more frequently in women than the other 4 SGAs (which were used in men usually). Also, the relatively high documented rates (up to 38%) of alcohol and drug misuse in this population reflects the "real world" nature of the study. Psychotropic co-prescription was common, and except for clozapine over a quarter of those studied were prescribed a second antipsychotic medication. A survey of over 4000 psychiatry inpatients in the United Kingdom found nearly one half were prescribed 2 or more antipsychotics,[20] while other authors[21,22] have highlighted an association between antipsychotic polypharmacy and increased mortality or adverse events. On the other hand, Tiihonen et al.[2] demonstrated an increase in mortality in those individuals not using any antipsychotic medication after an initial hospitalization.

Study Strengths and Limitations

We must also mention the particular strengths and limitations of this study. This was essentially a retrospective case note review, with all the limitations of unstructured assessment and recording, but it was a large and electronic survey, covering a discrete representative community sample of all secondary mental health care contacts. It is possible that human error occurred during the manual counting of the various clinical measures, although it is highly unlikely that this could have occurred in a systematic manner. The use of a large, representative, naturalistic population should have reduced the possibility of selection bias and enhanced the generalizability of the findings, and sponsorship bias for this particular study has also been avoided.

Drug names: chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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