Comparing the Effectiveness of Aripiprazole and Quetiapine in Schizophrenia and Related Psychoses: A Naturalistic, Retrospective Chart Review Study

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Background: Naturalistic studies offer advantages over randomized clinical trials by including patients seen in routine practice. Aripiprazole and quetiapine are the most recent second-generation antipsychotics available in the United Kingdom. We aimed to study all patients who were prescribed these medications in a defined geographic area in order to identify and compare those who had a good clinical response.

Method: We conducted an electronic chart review of a sample of all people attending secondary mental health care in the county of Lanarkshire, Scotland, who were treated with aripiprazole or quetiapine for schizophrenia and related psychoses (ICD-10 criteria) between 2002 and 2007. To measure effectiveness, we retrospectively assigned Clinical Global Impressions (CGI) scores and examined medication discontinuation rates.

Results: Eighty-nine patients were started on treatment with aripiprazole and 132 patients with quetiapine over the 5-year period. Those treated with quetiapine had a higher initial illness severity (CGI-Severity of Illness scale) ($p = .0003$), were more likely to be starting rather than switching antipsychotics ($p = .0003$), were more likely to have a mood disorder ($p = .03$), were less likely to be treatment resistant ($p = .005$), and had lower rates of prescription of additional antipsychotics ($p = .009$). After adjusting for these variables, the proportions who improved according to CGI were 74% with aripiprazole and 67% with quetiapine. Overall medication discontinuation rates were also similar, 42% for aripiprazole and 45% for quetiapine, with early discontinuation of aripiprazole being noticeable, often due to agitation (13% of all patients treated with the drug).

Conclusions: Despite their different pharmacologic properties, aripiprazole and quetiapine were similarly effective in the majority of patients. Early discontinuation of aripiprazole due to agitation was an important finding.

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Randomized controlled trials (RCTs) exclude patients commonly seen in routine clinical practice, such as those with comorbid medical problems, unstable illness, polypharmacy, and alcohol and drug misuse. Naturalistic or observational studies can complement RCTs by examining effectiveness in representative populations in which such issues frequently occur and can yield valuable information on individuals who are too severely ill or unable to consent to enter a RCT. Naturalistic studies can also often provide longer-term data on outcomes compared to the usually more brief RCTs. In RCTs there is a pressure to keep patients in the trial, whereas in routine clinical practice, switching medications may occur more frequently.

Aripiprazole and quetiapine are the 2 most recent second-generation antipsychotics (SGAs) available in the United Kingdom. Randomized controlled trials[1–3] have shown efficacy and good tolerability for aripiprazole in comparison to placebo and other agents. However, a recent Cochrane review[4] did not find aripiprazole to differ from some typical or other SGAs in schizophrenia and suggested further trials were needed to evaluate its position in routine clinical practice. Studies of the comparative efficacy between quetiapine and other SGAs have

shown comparable effectiveness in some[5–7] and equivocal[8] or inferior effectiveness in others.[9,10] Aripiprazole has a different mode of action than quetiapine and other established SGAs, namely, partial agonist activity at dopamine D_2 receptors and serotonin $5HT_{1A}$ receptors, and antagonist activity at $5HT_{2A}$ receptors.[11] Quetiapine, also a SGA, has multireceptor antagonist properties.[12] Despite these different pharmacologic properties, both are used to treat patients with psychotic disorders, and it is important to compare how they are used in clinical practice.

We aimed to retrospectively identify and compare patients who had a good clinical response after commencing aripiprazole and quetiapine using the Clinical Global Impressions (CGI) scale.[13] Antipsychotics such as aripiprazole and quetiapine are commonly used for long-term maintenance treatment of conditions such as schizophrenia and related psychoses, and we have postulated[14] that in these conditions, medication discontinuation rates and time to discontinuation can be considered important measures of antipsychotic effectiveness.[15] Therefore, we also aimed to examine discontinuation rates and time to discontinuation to compare the effectiveness of aripiprazole and quetiapine.

METHOD

The electronic patient records covering all secondary care contacts for psychiatry in a discrete geographic area (the county of Lanarkshire, Scotland; population 550,000) were examined. The electronic records ran from June 2002 until June 2007. A total of 22,000 individual records were available and were searched for the keywords *aripiprazole*, *Abilify*, *quetiapine*, and *Seroquel*. The ICD-10[16] diagnoses included in our study were schizophrenia (F20), persistent delusional disorders (F22), schizoaffective disorders (F25), and depressive disorder with psychotic symptoms (F32.5 or F33.3). All other ICD-10 diagnoses were excluded. Patient records resulting from this search that were considered inadequate for analysis, i.e., those in which the drug was started before the electronic record became available or those with only a single mental health contact were excluded. No other exclusion criteria were applied.

Demographic and clinical variables were extracted from the records. These included age and gender, duration of contact with mental health services, illness severity at onset of treatment, improvement while on treatment with the medication of interest, lifetime history of drug or alcohol misuse, initial and maximum doses of medication, concurrent psychotropic medication, previous or subsequent clozapine treatment, discontinuation rate, and time to discontinuation.

The clinical status of subjects was assessed using the CGI-Severity of Illness (CGI-S) and CGI-Improvement (CGI-I) scales. The proportion who improved as defined by CGI-I scores of 1–4 (very much improved to minimally improved) was the primary outcome measure. The rationale for this broad definition was that in clinical practice, any degree of improvement is of potential value. Our CGI scores were based on records and assigned retrospectively by experienced psychiatrists, all having a minimum of 5 years postgraduate experience in psychiatry. Severity rating was assigned at the start of treatment and at the end of treatment if the drug was discontinued, or at the end of the medical record. Improvement scores were assigned due to the perceived effects of the commenced medication and therefore took into account baseline severity of illness. This procedure has been used by others[17–19] for examining clinical response to antipsychotics, including aripiprazole. Our interrater reliability for these measures resulted in high levels of agreement ($\kappa > 0.8$). The proportions improved by CGI-I (< 5) and discontinuation rates were calculated for all patients and separately after excluding each of the following: those who had a depressive psychosis, those being started on treatment with antipsychotics for the first time, those on treatment with other regular additional antipsychotics, those who had a history of alcohol or substance misuse, or those who had been prescribed or considered for clozapine during their medical record (a putative measure of treatment resistance). The reason for examining these patients separately was that these variables were considered clinically relevant in terms of potentially confounding the comparison between the 2 drugs.

Additional antipsychotics were defined as being another regular (not "as required") antipsychotic drug prescribed at least 50% of the time that patients were on treatment with either aripiprazole or quetiapine. This measure was quantified by converting doses to percentage of British National Formulary (BNF)[20]-defined maximum dosage. For example, 100 mg per day of chlorpromazine equal 10% of maximum BNF daily dose. This measure is important in our clinical practice, in which BNF-defined maximum dosages are linked to high-dose antipsychotic protocols.

Time to discontinuation was examined for all causes and also subcategorized into time to discontinuation due to inefficacy or adverse effects. When investigators noted more than one reason for discontinuation, we used the most significant reason identified for the statistical analyses.

We used StatsDirect software (StatsDirect Ltd., Altrincham, U.K., available at www.statsdirect.com) to perform our statistical analyses. Continuous data were reported as means with 95% confidence intervals and compared using analysis of variance and t tests. Categorical and nonparametric data were analyzed using χ^2 tests and were log-transformed as appropriate. We used Kaplan-Meier survival curves to illustrate the probability of treatment discontinuation over time. We performed survival analyses on all the subjects and separately after excluding

Table 1. Clinical Profile of All Patients Started on Treatment With Aripiprazole and Quetiapine

Characteristic	Aripiprazole (N = 89)	Quetiapine (N = 132)	Significance
Age, mean (95% CI), y	39.6 (37.3 to 41.9)	36.7 (34.1 to 39.3)	NS
Duration of contact with mental health services, N (%)			p = .018[a]
0–1 y	3 (3)	10 (8)	
1–3 y	9 (10)	25 (19)	
> 3 y	76 (85)	94 (71)	
Male, %	58	52	NS
History of alcohol misuse, %	33	33	NS
History of substance misuse, %	25	33	NS
Diagnosis schizoaffective or depressive psychoses, %	20	34	p = .03[b]
Previously treated with antipsychotics (i.e., those "switching" medications), %	94	76	p = .0003[c]
Starting dose, mean (95% CI), mg/d	10.2 (9.2 to 11.2)	91 (72 to 110)	
Maximum dose, mean (95% CI), mg/d	18.7 (16.9 to 20.5)	422 (382 to 462)	
On treatment with regular additional antipsychotic, %	34	18	p = .009[d]
Additional antipsychotic dose (mean percent of BNF maximum)	39.5	36.8	NS
Coprescription (antidepressant), %	48	62	p = .04[e]
Coprescription (mood stabilizer), %[f]	7	12	NS
Previous or subsequent history/consideration of clozapine treatment, %	25	11	p = .005[g]
Admission to hospital (mental health unit) during treatment with medication, %	23	27	NS

[a]$\chi^2 = 5.6$, df = 1, p = .018.
[b]$\chi^2 = 4.5$, df = 1, p = .03.
[c]$\chi^2 = 13.2$, df = 1, p = .0003.
[d]$\chi^2 = 6.8$, df = 1, p = .009.
[e]$\chi^2 = 4.1$, df = 1, p = .04.
[f]Mood stabilizers included lithium salts, semi sodium valproate, carbamazepine, and lamotrigine.
[g]$\chi^2 = 7.8$ df = 1, p = .005.
Abbreviations: BNF = British National Formulary, NS = not significant.

Table 2. Proportion of Patients Who Improved According to Clinical Global Impressions-Improvement Scale (< 5)

Variable	Aripiprazole, %	Quetiapine, %
All patients	60 (N = 53/89)	69 (N = 91/132)
Excluding treatment resistance[a]	69 (N = 46/67)	71 (N = 84/118)
Excluding depressive psychosis	59 (N = 48/81)	64 (N = 66/103)
Excluding alcohol and substance misuse	58 (N = 31/53)	70 (N = 48/69)
Excluding newly starting antipsychotics	58 (N = 49/84)	68 (N = 67/99)
Excluding those taking additional antipsychotics	64 (N = 38/59)	70 (N = 76/108)
Excluding those with service contact > 3 years	83 (N = 10/12)	63 (N = 10/16)
Excluding those discontinuing due to agitation	66 (N = 51/77)	…

[a]Clozapine considered or prescribed before or after treatment with aripiprazole or quetiapine was commenced.
Symbol: … = not applicable.

patients with depressive psychoses, treatment resistance, new starts, and antipsychotic polypharmacy. We also performed separate survival analyses for those discontinuing due to inefficacy or side effects. Significance levels required 2-tailed p values < .05.

RESULTS

Table 1 presents the clinical characteristics of all patients. Eighty-nine patients were commenced on treatment with aripiprazole and 132 patients with quetiapine over the 5-year study period, and the majority had had contact with mental health services for over 3 years. A large number of individuals on treatment with aripiprazole and with quetiapine had a lifetime history of either alcohol or drug misuse (or both), as defined by clinician judgment.

Patients prescribed quetiapine were more likely to have a mood disorder, i.e., schizoaffective disorders or depressive disorder with psychotic symptoms (p = .03), and similarly were more likely to be coprescribed an antidepressant (p = .04). A higher proportion of patients on treatment with aripiprazole had previously been treated with another antipsychotic, i.e., were switching medications, p = .0003, and the proportion who were presumed treatment resistant (defined by previous or subsequent consideration or treatment with clozapine) was higher for those treated with aripiprazole (25% versus 11%, p = .005). Patients treated with aripiprazole were also more likely to be treated with a regular additional antipsychotic (34% versus 18%, p = .009).

Table 2 shows the proportion of patients who improved according to CGI-I (< 5) for all patients and adjusted after excluding specific groups of interest. With aripiprazole, excluding those who were treatment resistant and those with psychiatric service contact greater than 3 years yielded a greater proportion of patients who improved, although none of these results showed statistically significant differences.

Results presented in Table 3 are divided into 2 groups: group A includes all patients, whereas group B excludes patients with depressive psychoses, treatment resistance, newly starting antipsychotics, and antipsychotic poly-

Table 3. Clinical Global Impressions Scale Scores, Duration of Treatment, and Discontinuation Rates

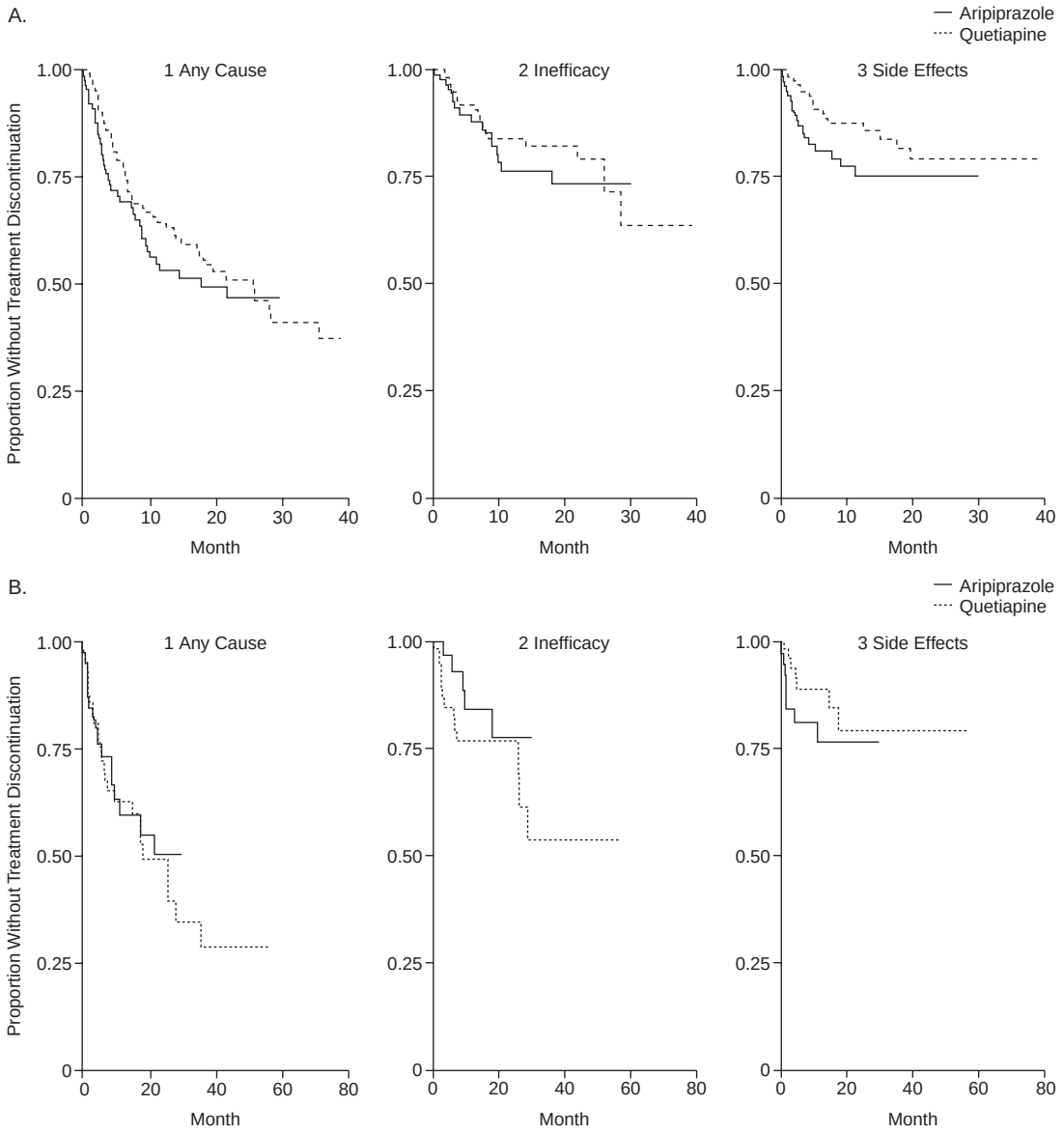
	All Patients (Group A)			Excluding Patients With Depressive Psychoses, Treatment Resistance, New Starts, and Antipsychotic Polypharmacy (Group B)		
CGI and Discontinuation Measure	Aripiprazole (N = 89)	Quetiapine (N = 132)	Significance	Aripiprazole (N = 38)	Quetiapine (N = 58)	Significance
CGI-S score at onset of treatment, mean (95% CI)	3.9 (3.7 to 4.1)	4.4 (4.2 to 4.5)	p = .0003[a]	3.7 (3.4 to 4.1)	4.1 (3.9 to 4.4)	p = .06[b]
CGI-S score at end of treatment or record, mean (95% CI)	3.1 (2.8 to 3.4)	3.5 (3.3 to 3.7)	p = .025[c]	2.6 (2.2 to 3.0)	3.4 (3.1 to 3.8)	p = .003[d]
CGI-I score, mean (95% CI)	4.1 (3.7 to 4.5)	3.7 (3.5 to 4.0)	NS	3.6 (3.0 to 4.2)	3.7 (3.3 to 4.1)	NS
Improved (CGI-I < 5), all patients, % (N)	60 (53)	69 (91)	NS	74 (28)	67 (39)	NS
CGI-I category, % (N)[e]						
1 Very much improved	5.9 (4)	6.7 (8)		7.8 (3)	8.6 (5)	
2 Much improved	25.4 (17)	21.2 (25)		21.0 (8)	22.4 (13)	
3 Moderately improved	20.8 (14)	19.5 (23)		31.6 (12)	8.6 (5)	
4 Minimally improved	16.4 (11)	23.7 (28)		13.1 (5)	27.6 (16)	
5 No change	16.4 (11)	16.1 (19)		7.9 (3)	20.7 (12)	
6 Minimally worse	2.9 (2)	6.7 (8)		5.3 (2)	6.9 (4)	
7 Moderately worse	11.9 (8)	5.1 (6)		13.2 (5)	5.2 (3)	
8 Much worse	0 (0)	0.8 (1)		0 (0)	0 (0)	
Duration of drug treatment, mean (95% CI), d	488 (403 to 572)	450 (361 to 540)	NS	386 (288 to 485)	409 (297 to 520)	NS
Discontinuation rate, % (N)	45 (40)	42 (56)	NS	42 (16)	45 (26)	NS
Discontinuation reason, % (N)			NS			
Adverse effects	48 (19)[f]	34 (19)[g]		50 (8)	27 (7)	
Inefficacy	37 (15)	43 (24)		31 (5)	54 (14)	
Other	15 (6)	27 (15)		19 (3)	19 (5)	
Time to discontinuation, all causes, median (range), d	103 (–663)	175 (–544)	p = .01[h]	127 (–662)	172 (–1061)	NS
Time to discontinuation, insufficient efficacy, median (range), d	175 (–544)	203 (–818)	NS	270 (–460)	99 (–818)	NS
Time to discontinuation, adverse effects, median (range), d	64 (–338)	148 (–569)	p = .02[i]	49 (–338)	138 (–506)	NS
Time to discontinuation, agitation, median (range), d	124 (–638)	…	…	…	…	…

[a]2-tailed t = 3.7, df = 219, p = .0003.
[b]2-tailed t = 1.9, df = 94, p = .06.
[c]2-tailed t = 2.3, df = 219, p = .025.
[d]2-tailed t = 3.1, df = 94, p = .003.
[e]CGI-I scores were not available for some patients.
[f]Reasons for discontinuing aripiprazole: agitation (N = 12), nausea (N = 2), arthralgia (N = 1), delirium (N = 1), headache (N = 1), sedation (N = 1), unknown side effects (N = 1).
[g]Reasons for discontinuing quetiapine: unknown side effects (N = 4), weight gain (N = 3), sedation (N = 3), palpitations (N = 2), headache (N = 1), blood dyscrasia (N = 1), nausea (N = 1), derealization (N = 1), raised prolactin level (N = 1), low mood (N = 1), sexual dysfunction (N = 1).
[h]2-tailed t = 2.7, df = 69, p = .01.
[i]2-tailed t = 2.6, df = 30, p = .02.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, NS = not significant.
Symbol: … = not applicable

pharmacy. The rationale for excluding these patients was that demographic and clinical findings indicated that these were among potentially important differences between those started on treatment with aripiprazole and those started on treatment with quetiapine. Patients prescribed quetiapine generally had a more severe illness at the beginning and end of treatment or case record. The majority of individuals in both groups (A and B) for both medications improved, according to CGI-I scores, during an average follow-up of between 1 and 2 years. There were no significant differences between the 2 drugs whether using a broad definition of improvement (CGI-I < 5) or a narrow definition of improvement (CGI-I = 1 or 2). No correlation was found for CGI-S score at the start of treatment with CGI-I scores for either drug. There were also no statistical differences in overall discontinuation rates between aripiprazole and quetiapine, with just under half of all individuals discontinuing their medication over the study period. The experience of adverse events was the most frequent reason for discontinuation of aripiprazole, whereas inefficacy was noted as the most common reason for quetiapine discontinuation. After adjustment, there were no significant differences in median time to discontinuation (all causes, inefficacy, or side effects). The most common single reason for aripiprazole discontinuation was agitation (N = 12), followed by noncompliance (N = 10).

Figure 1 illustrates Kaplan-Meier survival curves for treatment discontinuation. The upper 3 graphs show the

Figure 1. Time to Discontinuation Due to (1) Any Cause, (2) Inefficacy, and (3) Side-Effects Among All Patients (A) and Excluding Patients With Depressive Psychoses, Treatment Resistance, New Starts, and Antipsychotic Polypharmacy (B)



pattern for all patients, and the lower 3 graphs show the pattern after adjustment by excluding patients with depressive psychoses, treatment resistance, new starts, and antipsychotic polypharmacy. Following adjustment, the rate of discontinuation due to inefficacy was lower and the rate of discontinuation due to side effects was greater with aripiprazole. None of the adjusted graphs showed statistically significant differences between the 2 drugs.

DISCUSSION

This naturalistic observational study of a complete population of mental health service users revealed some important similarities and differences between aripiprazole and quetiapine. Both were used in a variety of psychotic disorders over a prolonged period of time, and both were often used in conjunction with other psychotropics including coprescribed antipsychotics. The proportion of individuals prescribed aripiprazole and a second antipsychotic was significantly higher, perhaps as a consequence of the activating effect of aripiprazole leading to agitation, which in turn led patient and doctor to seek an additional sedative antipsychotic. Those commenced on treatment with quetiapine were more likely to be new to antipsychotics as opposed to switching medications; were more likely to have a mood disorder, and had a higher

initial illness severity. These findings suggest clinicians may have favored quetiapine in the earlier stages of psychotic illness and may have had greater confidence in a medication that had been established longer in clinical practice. Antidepressant coprescription in this study of maintenance treatment in psychoses was high, at 62% with quetiapine and 48% with aripiprazole, and clinicians favored quetiapine when a mood component to the presentation was identified. This may reflect higher mood disturbance in patients commenced on treatment with quetiapine and greater clinician confidence in quetiapine as a mood regulator, or possibly an attempt to medicate the negative symptoms of schizophrenia. Individuals commenced on treatment with aripiprazole were more likely to be switching from another antipsychotic and were likely to have been tried on or considered for clozapine treatment, perhaps reflecting aripiprazole's more recent availability and putative mode of action. Despite these differences, both medications had remarkably similar outcomes and were clinically effective in the majority of patients.

Our primary outcome measure, the proportion of patients improved according to CGI-I (< 5), was similar for both medications. Although CGI scores were designed to be collected prospectively, retrospective assignment of CGI has been used in other naturalistic studies[17,18] and is comparable to the practice of drug history reviews conducted in routine clinical care. In RCTs, clinical response usually has a stringent definition of CGI-I scores of 1 or 2 (very much or much improved), which may not capture the range of functional or behavioral improvements seen in clinical practice. Patients commenced on treatment with aripiprazole and quetiapine in the current study were those requiring maintenance or long-term treatment, and the majority were switching from another antipsychotic. Therefore, even a minor amelioration in symptoms may have been clinically important, and using our broad definition of improvement (CGI-I score = 1–4), over two thirds of all patients were rated as improved. With aripiprazole, the proportion who improved was greater (83%) when examining patients who had been in contact with psychiatric services less than 3 years. Although caution should be exercised in translation of service contact to illness duration, this finding supports the effectiveness of aripiprazole in patients with likely short illness duration.

Medication discontinuation is considered an increasingly important global outcome measure in antipsychotic treatment evaluation.[15] In conditions such as schizophrenia, in which maintenance treatment is required, discontinuation indicates that a medication strategy has failed and a change is necessary. Here the overall medication discontinuation rate was similar for both aripiprazole and quetiapine (42% and 45%, respectively), which is comparable to an earlier related study[14] but lower than that observed in the Clinical Antipsychotic Trials of Intervention Effectiveness.[10,15] Patients commenced on treatment with aripiprazole discontinued earlier than those on treatment with quetiapine, and this was due to side effects rather than inefficacy. Early agitation was the single most common reason for aripiprazole discontinuation (13% of all patients studied) and is a clinically important finding. Excluding those patients who discontinued due to early agitation from aripiprazole did improve the proportion responding in terms of CGI-I by 10%, although this failed to reach statistical significance in our sample. However, it suggests that if patients do not discontinue from aripiprazole due to agitation, their outcome may be more favorable. It also supports the short-term coprescription of a benzodiazepine to aid initial adherence to aripiprazole, although this was not routine practice in Lanarkshire during the study period and was not possible to quantify in our sample. Other authors[21–23] have also noted that exacerbation of psychosis or agitation may occur during switch to aripiprazole, possibly due to functional hypodopaminergia induced by previous antipsychotic administration, and recommend that careful cross taper and monitoring occur. Early discontinuation was not apparent with quetiapine, suggesting greater tolerability in early stages of treatment. Many patients remained on their medications for over 2 years, implying a long-term tolerability for both drugs once beyond a certain period, e.g., after 3–6 months.

Coprescription with other regular psychotropic medications was high, particularly for antidepressants and additional antipsychotic medications. Such antipsychotic polypharmacy is usually regarded as undesirable and is associated with increased mortality.[24,25] However, it is known to frequently occur[14,26] and has been associated with reduced overall treatment discontinuation for aripiprazole.[19] Coprescription of an additional regular antipsychotic in this study did not affect the proportion who improved for either aripiprazole or quetiapine.

The clinical relevance of the current study lies in its all-inclusive design, e.g., severely ill or unstable patients, those unable or unwilling to consent to participation in clinical trials, and those with serious comorbidity or substance misuse. These groups are typically excluded from RCTs. We must, however, acknowledge the limitations of this retrospective observational study. The selection of medication was a reflection of clinician and patient choice rather than following strict a priori criteria or randomization. Selection bias is possible but was minimized by including all available records derived from all contacts with mental health services in a large geographic area over a 5-year period. The raters of illness severity were not blind to diagnosis or medication, but a good interrater reliability was established, and an internationally accepted scale for measuring improvement (CGI) was used. Our population was predominantly white, chronically ill, and middle-

aged; therefore, our findings may not necessarily be generalizable, for example, to first-episode psychosis. Although derived from a relatively large population base, the number of patients studied was limited, and further independent studies including, for example, first-episode patients are required. The confounding effects of polypharmacy and substance misuse could not be ignored, but reflect everyday clinical practice. Finally, bias toward any particular medication was reduced by funding and conducting the study independently from the pharmaceutical industry.

In conclusion, despite their different pharmacologic properties, aripiprazole and quetiapine were similarly effective in the majority of patients, and early discontinuation of aripiprazole due to agitation was an important finding.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (FazaClo, Clozaril, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), quetiapine (Seroquel), valproate sodium (Depacon and others).

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