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Comparative effectiveness of second-generation antipsychotics and haloperidol in acute schizophrenia[†]

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Background There is little information on the comparative effectiveness of second-generation antipsychotic agents.

Aims To determine if any of five second-generation antipsychotics or haloperidol is more effective in treating acutely ill patients with schizophrenia, schizoaffective disorder or schizophreniform disorder.

Method A sample of 327 newly admitted patients were randomised to open-label treatment with aripiprazole, haloperidol, olanzapine, quetiapine, risperidone or ziprasidone for a minimum of 3 weeks. Measures of effectiveness were improvement in mental status so that the patient no longer required acute in-patient care, and changes in Brief Psychiatric Rating Scale (BPRS) scores.

Results By the first measure, haloperidol (89%), olanzapine (92%) and risperidone (88%) were significantly more effective than aripiprazole (64%), quetiapine (64%) and ziprasidone (64%). Changes in BPRS ratings were not significant among treatments.

Conclusions Haloperidol, olanzapine and risperidone are superior to aripiprazole, quetiapine and ziprasidone for the acute treatment of psychosis in hospitalised patients with schizophrenia, schizoaffective disorder or schizophreniform disorder.

Declaration of interest None.

[†]See editorial, pp. 391–392, this issue.

Second-generation antipsychotic drugs have been heralded as a significant advance in the treatment of patients with schizophrenia. However, except for clozapine, none has been conclusively shown to be superior in resolving the symptoms of schizophrenia. Head-to-head studies are lacking. There is little rational basis for selecting one over another other than a patient's history of response, lack of response or side-effects. The purpose of this study was to determine if any of five second-generation antipsychotics was more effective in treating acutely ill hospitalised patients with schizophrenia, schizoaffective disorder or schizophreniform disorder, and whether any of these drugs had an advantage over haloperidol. Two important features of this study were that it was designed to reflect clinical practice as a pragmatic clinical trial (March *et al*, 2005) and that it was not supported by pharmaceutical companies.

METHOD

Sample

The study examined patients 18 years and older of either gender, who were newly admitted to the hospital's psychiatric in-patient service between January 2004 and February 2005. The 135-bed psychiatric in-patient service treats acutely ill adult patients and is part of a 413-bed general hospital which serves an impoverished urban population. Approximately 70% of admissions are involuntary.

All patients in the study were diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder according to DSM–IV criteria (American Psychiatric Association, 1994). Patients with a history of substance misuse were included if the above diagnoses were present. Patients were included regardless of whether they had recently taken antipsychotics before admission. Only patients who understood the nature of the study when it was fully explained to them and who signed an informed consent statement were included. Institutional review board approval was obtained for this study.

Pregnant or lactating women and patients with a medical condition in which pharmacotherapy would prove a significant clinical risk were excluded. Patients who had a clear history of response or lack of response to a particular antipsychotic drug and who, in the judgement of the treating psychiatrist, would best be treated accordingly, were not entered into the study. Patients with a diagnosis of bipolar disorder, major depressive disorder or substance-induced psychotic disorder were also excluded.

Study design

Patients were admitted to one of the six general adult in-patient psychiatric units based on bed availability, and this determined the treating psychiatrist. All units have the same number of patients and staffing, and are indistinguishable with respect to diagnoses and acuity of patients. Newly admitted patients with a diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder were given information about the study and asked to participate and provide informed consent.

Consenting patients were randomly assigned to treatment with one of six antipsychotics: aripiprazole, haloperidol, olanzapine, quetiapine, risperidone and ziprasidone. A randomised medication assignment list was prepared before the study using the randomisation website http://www.randomization.com. Hospital staff with no clinical responsibilities and no knowledge of the patients oversaw the assignment procedure and assigned medications in sequential order, strictly following the randomised list. The treating psychiatrist did not have access to this list. Both the patient and the treating psychiatrist were aware of the antipsychotic being prescribed. The treating psychiatrists followed standardised dosing guidelines based on the manufacturers' recommendations, with the objective of obtaining a maximum recommended dosage within 1–2 weeks. Patients were given at least a 3-week trial of the antipsychotic to determine its effectiveness. As needed doses of haloperidol, lorazepam and diphenhydramine for agitation were permitted. Following current practice at the facility, these medications are generally administered together and

intramuscularly for aggressive and threatening behaviour. Oral doses of diphenhydramine were also administered, at the patient's request, for sleep. Benzatropine could also be prescribed for extrapyramidal side-effects; it was the treating psychiatrist's decision whether to prescribe this prophylactically or after side-effects developed. After the second week of treatment, an antidepressant, mood stabiliser or anxiolytic could be added at the psychiatrist's discretion for significant mood symptoms or impulsivity. These medications are often considered essential in the acute treatment of schizophrenia (McCue *et al*, 2003).

If the treating psychiatrist assessed the patient to be improving on the medication, it was continued until the patient was well enough to be discharged. On the other hand, if the patient showed no significant improvement after at least 3 weeks of treatment with the randomly assigned antipsychotic, the treating psychiatrist could discontinue the medication and the patient would be withdrawn from the study. A period of 3 weeks was chosen because treatment guidelines (American Psychiatric Association, 2004) have recommended waiting 2–4 weeks before changing antipsychotic pharmacotherapy, although there is evidence that the lack of improvement in the first week or so of treatment predicts non-response (Correll *et al*, 2003). At any time, if the treating psychiatrist believed that continuing treatment with the selected antipsychotic would not be in the patient's best interest (e.g. significant side-effects, medical instability and clinical deterioration), the medication was discontinued.

Classification of outcome

The antipsychotic was classified as effective if the patient's mental status improved sufficiently to no longer necessitate acute in-patient care. Such patients were either discharged to the community or moved to an alternative form of care. The antipsychotic was classified as ineffective if, in the treating psychiatrist's assessment, the patient had made no significant improvement after at least 3 weeks of treatment, and the drug was discontinued. If the medication was discontinued before the end of a 3-week trial owing to side-effects or significant deterioration in the patient's mental state, it was also classified as ineffective. The study site was a public hospital, with the psychiatric in-patient service having minimal involvement with managed-care health insurance plans; as a result, decisions about discharge were made solely on clinical grounds and not influenced by insurance arrangements.

Data collection

The two main measures of effectiveness used were the ability to discharge the patient from acute in-patient care and the total score on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1988). Ratings were made at baseline, weekly up to 3 weeks, and at end-point. The end-point was when the antipsychotic was determined to be effective or ineffective.

A clinician masked to the patient's antipsychotic regimen administered the BPRS. Before the study began, this clinician had 6 h of training per week for 2 months with the study's senior authors (R.E.M. and L.U.) in using the BPRS. At the end of the training period there was a sufficiently high correlation of BPRS ratings. At the study's midpoint, a revalidation of the clinician's BPRS ratings was performed with the study's senior authors (R.E.M. and L.U.).

Side-effects were recorded concurrently with BPRS ratings by a clinician masked to the patient's antipsychotic regimen. Side-effect data were elicited by spontaneous report and clinical evaluation. A clinician masked to the patient's treatment assessed Parkinsonian side-effects with the Simpson–Angus Scale (Simpson & Angus, 1970) and akathisia with the Barnes Akathisia Rating Scale (Barnes, 1989).

Data analyses

An *a priori* power analysis was performed using G*POWER (Erdfelder *et al*, 1996). For six experimental groups, an α of 0.05 and a postulated modest effect size of 0.25, the study needed a total sample size of 324 to have a power $(1-\beta)$ of 0.95. Using these assumptions, the goal was to have each treatment cell contain approximately 54 patients. The software StatView version 5.0 (SAS Institute, Cary, North Carolina, USA) was used for all other analyses. The primary hypothesis was that the six treatments would be differentially effective in treating acutely ill patients with schizophrenia, schizoaffective disorder or schizophreniform disorder. The effect of the antipsychotic on the main continuous outcome variable (BPRS score) was analysed with analysis of variance evaluating change from baseline. Other continuous variables were also examined with analyses of variance. Categorical variables were analysed using a χ^2 test. Logistic regression was used to explore the effect of other independent variables on the categorical outcome variable. All initial analyses used a two-tailed α level of 0.05.

RESULTS

From January 2004 to February 2005 a total of 584 admissions to the psychiatric in-patient service with the diagnoses of schizophrenia, schizoaffective disorder or schizophreniform disorder were screened for entry into the study; 368 were randomised. This included some patients who had previously participated in the study and who were rehospitalised during its course and were randomised a second time if they consented. For the purpose of this study, only the first randomised entry of those entered more than once (n=41) was used for data analysis. Of the 327 patients randomised, 8 were withdrawn from the study for reasons unrelated to antipsychotic treatment and were not included in the data analysis. A total of 319 patients were included in the analysis: of these, 301 had at least a 3-week trial of the antipsychotic and in 18 cases participation was discontinued because of side-effects or clinical deterioration (Fig. 1).

Patient characteristics

Table 1 shows the baseline characteristics of the 319 patients whose data were used for analysis. No significant difference was found among the six groups in BPRS total score, gender, diagnosis, length of illness or comorbid substance misuse. There was a significant difference in the age of participants among the six treatment groups: *post hoc* analyses using Fisher's protected least significant difference (PLSD) test showed that patients in the olanzapine group were significantly younger than patients in the aripiprazole (P=0.004), risperidone (P=0.03) and quetiapine (P=0.03) groups. In addition, patients given haloperidol were significantly younger than those given aripiprazole (P=0.03). As a result, age was included in analyses as a covariable.

Treatment characteristics

The maximum daily dosage of antipsychotic used in each treatment group was as follows: aripiprazole, mean

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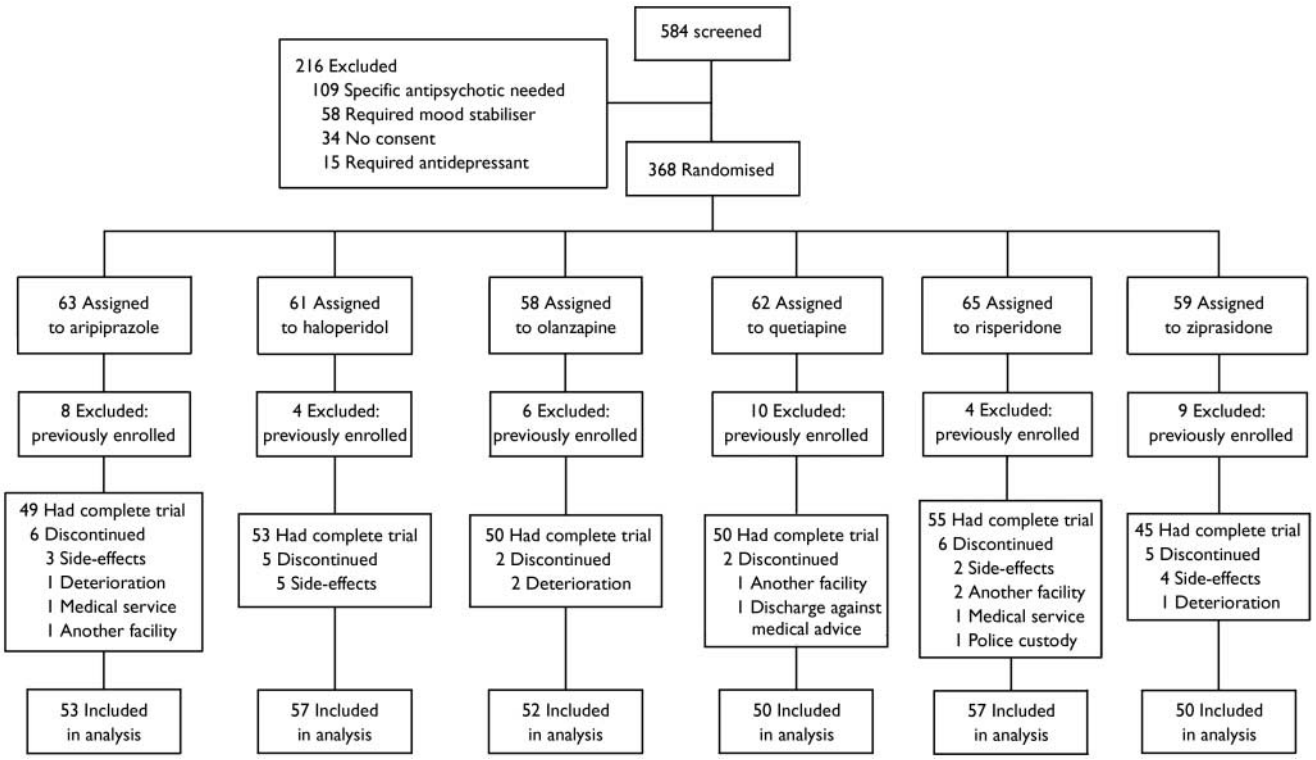

Fig. 1 Progress of participants through the trial.

21.8 mg, s.d.=8.1, range 10–45; haloperidol, mean 16.0 mg, s.d.=7.6, range 4–30; olanzapine, mean 19.1 mg, s.d.=7.1, range 5–40; quetiapine, mean 652.5 mg, s.d. =280.8, range 50–1200; risperidone, mean 5.2 mg, s.d.=1.8, range 2–9; ziprasidone, mean 151.2 mg, s.d.=32.4, range 40–240. These fell within the recommended dosage range for each medication (American Psychiatric Association, 2004).

The use of additional medication throughout the study is shown in Table 2. There was no significant overall difference among the six treatment groups in the need for haloperidol and lorazepam for aggressive or agitated behaviour. The use of diphenhydramine was significantly different among the six groups, and there was a significant medication × age interaction effect (F=2.63, d.f.=5,307, P=0.02). Using *post hoc* analyses with Fisher's PLSD test, patients treated with aripiprazole required significantly more diphenhydramine than patients treated with olanzapine

Table 1 Baseline characteristics of participants receiving randomised treatment with one of six antipsychotics

	Antipsychotic treatment group						Test	Analysis	
	Aripiprazole n=53	Haloperidol n=57	Olanzapine n=52	Quetiapine n=50	Risperidone n=57	Ziprasidone n=50		d.f.	P
Age, years: mean (s.d.)	40.5 (12.6)	35.7 (10.8)	33.8 (10.1)	39.0 (11.0)	38.6 (12.9)	38.3 (11.9)	F=2.30	5,313	0.04
BPRS total score: mean (s.d.)	41.3 (10.2)	42.0 (11.3)	41.1 (11.0)	43.6 (10.4)	42.3 (9.0)	43.4 (11.0)	F=0.49	5,313	0.78
Length of illness, years: mean (s.d.)	14.9 (11.4)	12.2 (10.3)	11.7 (8.6)	14.5 (9.4)	13.1 (10.7)	12.9 (9.5)	F=0.81	5,313	0.54
Gender, n (%)							χ^2=10.25	5	0.07
Male	27 (51)	42 (74)	37 (71)	32 (64)	34 (60)	26 (52)			
Female	26 (49)	15 (26)	15 (29)	18 (36)	23 (40)	24 (48)			
Diagnosis, n (%)							χ^2=11.45	10	0.32
Schizophrenia	41 (77)	43 (75)	39 (75)	36 (72)	45 (79)	38 (76)			
Schizoaffective	12 (23)	9 (16)	9 (17)	12 (24)	8 (14)	12 (24)			
Schizophreniform	0 (0)	5 (9)	4 (8)	2 (4)	4 (7)	0 (0)			
Substance misuse, n (%)							χ^2=6.22	5	0.29
Yes	20 (38)	22 (39)	25 (48)	16 (32)	17 (30)	14 (28)			
No	33 (62)	35 (61)	27 (52)	34 (68)	40 (70)	36 (72)			

BPRS, Brief Psychiatric Rating Scale.

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Table 2 Psychotropic and anticholinergic medication used in addition to the randomised antipsychotic

Additional medication	Antipsychotic treatment group						Test	Analysis	
	Aripiprazole *n*=53	Haloperidol *n*=57	Olanzapine *n*=52	Quetiapine *n*=50	Risperidone *n*=57	Ziprasidone *n*=50		d.f.	*P*
Dosage: mean (s.d.)									
Haloperidol[1]	22.1 (39.9)	11.1 (18.5)	12.5 (19.0)	20.7 (34.2)	9.0 (16.8)	17.3 (28.4)	F=1.58[2]	5,307	0.16
Lorazepam[1]	7.7 (13.7)	4.7 (8.4)	4.6 (7.7)	7.9 (11.9)	2.8 (5.3)	7.3 (12.0)	F=1.73[2]	5,307	0.13
Diphenhydramine[1]	104.2 (225.2)	51.2 (95.6)	35.6 (66.1)	76.7 (181.1)	72.8 (152.4)	65.0 (154.3)	F=3.57[2]	5,307	0.004
Benzatropine[3]	0 (0)	1.9 (0.6)	0 (0)	2.2 (1.1)	1.7 (0.5)	2.8 (1.1)	F=0.91[2]	3,46	0.44
Patients receiving additional medication, *n* (%)									
Mood stabiliser[4]	7 (13)	4 (7)	1 (2)	4 (8)	5 (9)	1 (2)	χ^2=7.57	5	0.18
Antidepressant[4]	0 (0)	3 (5)	2 (4)	1 (2)	0 (0)	1 (2)	χ^2=5.65	5	0.34
Anxiolytic[4]	3 (6)	4 (7)	5 (10)	4 (8)	3 (5)	5 (10)	χ^2=1.49	5	0.91
Anticholinergic[5]	0 (0)	27 (47)	0 (0)	5 (10)	17 (30)	5 (10)	χ^2=69.11	5	<0.0001

1. Total amount of medication in milligrams used as required for agitated or aggressive behaviour throughout the study period.
2. Age used as a covariate.
3. Daily dosage in milligrams.
4. Psychotic medication added after the second week of antipsychotic treatment for significant mood symptoms or impulsivity.
5. Benzatropine used on an ongoing basis for extrapyramidal side-effects.

(P=0.02). To examine the interaction effect, patients were divided into two groups by the median age (38 years). For older patients, there was no significant difference in diphenhydramine use among treatments (F=1.28, d.f.=5,155, P=0.27); however, there was a significant difference for younger patients (F=3.53, d.f.=5,152, P=0.005). Using the Fisher's PLSD test, younger patients taking aripiprazole required significantly more diphenhydramine (mean 234.5 mg, s.d.=316.6) than patients taking haloperidol (mean 70.0 mg, s.d.=120.1, P=0.002), olanzapine (mean 28.7 mg, s.d.=66.3, P<0.0001), quetiapine (mean 99.3 mg, s.d.=227.3, P=0.02), risperidone (mean 65.4 mg, s.d.=149.5, P=0.002) and ziprasidone (mean 89.6 mg, s.d.=193.9, P=0.009).

There was a significant difference in the use of benzatropine for extrapyramidal side-effects (Table 2); significantly more patients treated with haloperidol or risperidone were prescribed benzatropine, whereas no patient treated with aripiprazole or olanzapine was. For those patients taking this anticholinergic medication there was no significant difference in the mean daily dosage of benzatropine among the treatments.

The six treatment groups did not differ significantly in the addition of a mood stabiliser (divalproex 12 patients, gabapentin 5 patients, lithium 2 patients, lamotrigine 2 patients, oxcarbazepine 2 patients, carbamazepine 1 patient), antidepressant (sertraline 3 patients, bupropion 1 patient, escitalopram 1 patient, mirtazapine 1 patient, paroxetine 1 patient) or anxiolytic (clonazepam 11 patients, lorazepam 5 patients, hydroxyzine 3 patients, buspirone 2 patients, diphenhydramine 2 patients, alprazolam 1 patient) after the second week of treatment.

Clinical outcome

Of 319 patients, 301 (94.4%) received at least a 3-week trial of the randomised antipsychotic. The antipsychotic was prematurely discontinued in 18 patients (5.6%) – in 14 (4.4%) as a result of side-effects and in 4 (1.2%) because of a worsening of the patient's mental state. Table 3 shows the outcome of each medication group.

There was an overall significant difference in effectiveness among the six antipsychotics, with haloperidol, olanzapine and risperidone being the most effective. To examine the influence of age on the effectiveness of the antipsychotics, age was included with medication in a logistic regression of clinical outcome. Results of the logistic likelihood ratio test indicate that antipsychotic treatment (χ^2=31.89, d.f.=5, P<0.0001) had a significant effect on clinical improvement, but age (χ^2=0.20, d.f.=1, P=0.65) did not. Pairwise comparisons by logistic regression of each antipsychotic's effectiveness are given in Table 4. Again, haloperidol, olanzapine and risperidone were significantly more effective than aripiprazole, quetiapine and ziprasidone, but not significantly better than each other. In addition, aripiprazole, quetiapine and ziprasidone did not differ significantly from one another. There was no significant difference among treatments in the number of days until a patient's treatment was classified as effective.

Improvement in the BPRS total score from baseline to study end-point did not differ significantly among the six treatments. However, as a group, patients taking haloperidol, olanzapine or risperidone tended to have a greater decrease in BPRS total score (mean 15.6, s.d.=11.1) than the group of patients who took aripiprazole, quetiapine or ziprasidone (mean 13.8, s.d.=12.5; t=1.38, d.f.=317, P=0.08, one-tailed). There was significantly greater improvement (t=8.55, d.f.=317, P<0.0001) in the BPRS total scores of patients whose treatment was classified as effective (mean 17.5, s.d.=10.5) compared with those with ineffective treatment (mean 5.3, s.d.=11.2).

Changes in BPRS factors (Guy, 1976) from baseline to end-point were also examined. Differences among the six medications were not statistically significant for thought disturbance (F=0.70, d.f.=5,307, P=0.62; age as covariable), negativism (F=0.85, d.f.=5,307, P=0.51; age as covariable), anxiety/depression (F=0.98, d.f.=5,307, P=0.43; age as covariable), hostility (F=0.76, d.f.=5,307, P=0.58; age as covariable) and activation (F=0.65, d.f.=5,307, P=0.66; age as covariable).

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Table 3 Clinical outcome of participants analysed according to antipsychotic treatment group

	Antipsychotic treatment group						Test	Analysis	
	Aripiprazole *n*=53	Haloperidol *n*=57	Olanzapine *n*=52	Quetiapine *n*=50	Risperidone *n*=57	Ziprasidone *n*=50		d.f.	*P*
Patient outcome, *n* (%)									
Effective[1]	34 (64)	51 (89)	48 (92)	32 (64)	50 (88)	32 (64)	χ^2=30.44	5	<0.0001
Ineffective	19 (36)	6 (11)	4 (8)	18 (36)	7 (12)	18 (36)			
Lack of clinical response[2]	15 (28)	1 (2)	2 (4)	18 (36)	5 (9)	13 (26)			
Side-effects[3]	3 (6)	5 (9)	0 (0)	0 (0)	2 (4)	4 (8)			
Deterioration[4]	1 (2)	0 (0)	2 (4)	0 (0)	0 (0)	1 (2)			
Change in BPRS total score: mean (s.d.)[5]	12.9 (12.3)	16.4 (11.4)	14.9 (11.3)	14.2 (12.5)	15.4 (10.6)	14.2 (12.9)	*F*=1.13[6]	5,307	0.34
Time to 'Effective', days: mean (s.d.)[7]	17.6 (10.5)	18.6 (10.6)	19.5 (13.1)	16.8 (8.0)	20.4 (13.5)	19.5 (8.5)	*F*=0.24[6]	5,235	0.94

BPRS, Brief Psychiatric Rating Scale.
1. No longer needing acute in-patient care.
2. Minimal or no improvement after at least a 3-week trial.
3. Unable to complete a 3-week trial because of side-effects.
4. Unable to complete a 3-week trial because of worsening of mental state.
5. Change in BPRS total score from baseline to end-point.
6. Age used as a covariate.
7. Number of days of treatment until a patient's medication was classified as effective.

Side-effects

The following side-effects caused 14 patients to leave the trial: nausea, dizziness and akathisia (aripiprazole); tremors, Parkinsonism and akathisia (haloperidol); anxiety and tachycardia (risperidone); and rash, akathisia, dystonia and derealisation (ziprasidone). The haloperidol and ziprasidone groups had the most withdrawals because of side-effects whereas the olanzapine and quetiapine groups had none. The difference among the six treatments in rate of withdrawals because of side-effects was not statistically significant (χ^2=9.15, d.f.=5, *P*=0.10).

The proportion of patients reporting side-effects throughout the first 3 weeks of the trial and at the end-point was examined. After a week of treatment there was a significant difference among treatments (χ^2=12.42, d.f.=5, *P*=0.03). A significantly larger proportion of patients treated with either haloperidol (55%) or ziprasidone (58%) reported side-effects, whereas patients treated with aripiprazole reported significantly fewer (31%). Throughout the remaining 2 weeks of the study, including at end-point, there was no significant difference among the six treatments in the proportion of patients reporting side-effects (week 2: χ^2=8.24, d.f.=5, *P*=0.14; week 3: χ^2=2.89, d.f.=5, *P*=0.72; end-point: χ^2=4.43, d.f.=5, *P*=0.49).

There was no significant difference among treatment groups in change in Simpson–Angus Scale ratings from baseline to end-point (*F*=0.61, d.f.=5,307, *P*=0.69; age as covariable). In addition, there was no significant difference among treatment groups in the change in score on the Barnes Akathisia Rating Scale from baseline to end-point (*F*=1.45, d.f.=5,307, *P*=0.20; age as covariable).

DISCUSSION

This study demonstrates differences in effectiveness among six antipsychotics in treating acutely ill hospitalised patients with schizophrenia, schizoaffective disorder or schizophreniform disorder. Haloperidol, olanzapine and risperidone were more effective than aripiprazole, quetiapine and ziprasidone. These results were obtained with minimum bias, using a randomised design, without support from the pharmaceutical industry. The latter point is important as a study's findings must be interpreted in light of the source of funding (Als-Nielsen *et al*, 2003). The definition of effectiveness was a pragmatic one that mirrored clinical practice: an ill patient is admitted, treated and, when sufficiently improved, is discharged. In this study, an effective antipsychotic improved a patient's psychosis enough so that he or she could be

Table 4 Comparisons of the relative effectiveness of the six antipsychotics used (logistic regressions with age included as an independent variable)

Reference antipsychotic	Comparison antipsychotic									
	Aripiprazole		Haloperidol		Olanzapine		Quetiapine		Risperidone	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Haloperidol	0.20 (0.07–0.57)	0.002								
Olanzapine	0.14 (0.04–0.47)	0.001	0.70 (0.19–2.64)	0.60						
Quetiapine	1.00 (0.45–2.24)	1.00	4.87 (1.74–13.62)	0.002	6.95 (2.14–22.60)	0.001				
Risperidone	0.25 (0.09–0.65)	0.005	1.21 (0.38–3.85)	0.75	1.72 (0.47–6.29)	0.41	0.24 (0.09–0.66)	0.005		
Ziprasidone	0.99 (0.44–2.23)	0.99	4.85 (1.74–13.56)	0.003	6.92 (2.13–22.48)	0.001	1.00 (0.44–2.26)	0.99	4.02 (1.51–10.70)	0.005

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discharged. This outcome is meaningful to both clinicians and their patients.

Comparisons among second-generation antipsychotics

Although treatment guidelines for schizophrenia (McEvoy *et al*, 1999; National Institute for Clinical Excellence, 2002; American Psychiatric Association, 2004) recommend starting with a second-generation antipsychotic because of the improved side-effect profile, there is little to guide clinicians in choosing among them. Studies that have compared risperidone and olanzapine have not been definitive. One study (Tran *et al*, 1997) compared olanzapine and risperidone in a double-blind prospective trial and found some advantage with olanzapine, whereas Conley & Mahmoud (2001) also compared these two medications and found that risperidone was more efficacious. Both of these studies were supported by pharmaceutical companies. A third study (Ho *et al*, 1999), without such support, found risperidone and olanzapine to be equally effective in the acute treatment of schizophrenia. Of these three studies, the first two dealt with efficacy (how a drug performs in controlled trials) and the third studied effectiveness (how a drug works in real-world populations). Effectiveness studies such as the one reported here may provide clinically useful information about pharmacotherapy that is not obtainable from studies of efficacy (Summerfelt & Meltzer, 1998).

Comparison with haloperidol

We chose haloperidol as a comparator because of its proven efficacy in treating schizophrenia. Although there were more withdrawals because of side-effects with this drug, those who were able to tolerate it had a response rate of 98%. Trials that have examined efficacy of the second-generation antipsychotics used in this study (Marder & Meibach, 1994; Beasley *et al*, 1996; Arvanitis & Miller, 1997; Carnahan *et al*, 2001; Kane *et al*, 2002) reported that these drugs were equal to first-generation antipsychotics such as haloperidol. Subsequent meta-analyses that have compared efficacy between second-generation antipsychotics and haloperidol have been inconclusive. Leucht *et al* (1999) found a slight advantage of risperidone and olanzapine over haloperidol for efficacy, and a larger advantage of risperidone, olanzapine and quetiapine over haloperidol for extrapyramidal side-effects. The meta-analysis by Davis *et al* (2003) found risperidone and olanzapine to be more efficacious than first-generation antipsychotics, including haloperidol. Geddes *et al* (2000) found no advantage of the second-generation antipsychotics over haloperidol for either efficacy or side-effects when an optimal dosage of haloperidol of 6–12 mg per day was used. The mean daily dosage of 16 mg in our study was higher than this. Perhaps if lower dosages had been used in conjunction with prophylactic anticholinergic medication, side-effects would have been less of a problem. The use of haloperidol as an effective and inexpensive treatment, even compared with olanzapine and risperidone, has had additional support (Hunter *et al*, 2003; Rosenheck *et al*, 2003; Keefe *et al*, 2004; Kilian *et al*, 2004).

Concomitant psychotropic medication

The use of as needed medication, including haloperidol, during the study period was an unavoidable complicating factor. For safety reasons it was necessary for the staff to have at their disposal the conventional treatments used for emergency situations. Although not to a degree of statistical significance, patients treated with aripiprazole, quetiapine and ziprasidone required more haloperidol and lorazepam than patients in the other three medication groups. However, this extra use of haloperidol, one of the more effective antipsychotics in this trial, would probably have had a positive effect on the clinical outcome of patients treated with it. The as needed use of haloperidol might also have obscured a difference in its effectiveness as the primary antipsychotic and the other two more effective drugs, olanzapine and risperidone.

Younger patients prescribed aripiprazole required significantly more diphenhydramine compared with younger patients taking other medications. An interpretation is that aripiprazole was much more activating in younger patients. However, diphenhydramine is usually administered with haloperidol and lorazepam when as needed medication is used at the facility. It is also possible that younger patients taking aripiprazole required diphenhydramine more often for sleep. At this point, firm conclusions cannot be drawn from this finding.

Side-effects

More patients taking haloperidol and ziprasidone left the study because of side-effects, whereas no one taking olanzapine or quetiapine did so. Patients in all six medication groups reported having side-effects about one-third or more of the time. Patients taking haloperidol and ziprasidone had more complaints at the beginning, but at endpoint the distribution of side-effects was fairly even among the six treatments. Except for those elicited by rating scales, side-effects were obtained from the patient's report. The validity of these reported side-effects is open to question, as patients were often taking other medications or had physical symptoms possibly unrelated to antipsychotic treatment. However, these reported side-effects are relevant: the patient's perception that they were caused by the antipsychotic would certainly affect the individual's present comfort and future adherence to the drug regime.

Patients given aripiprazole or olanzapine required no concomitant anticholinergic medication, whereas a small percentage of patients on quetiapine or ziprasidone and a significant minority of patients on haloperidol or risperidone did need it. These results are consistent with each drug's reported propensity to cause extrapyramidal side-effects. No significant change was found among treatments in ratings of parkinsonism and akathisia using the Simpson–Angus Scale and the Barnes Akathisia Rating Scale. An interpretation of this result is that extrapyramidal side-effects were not a problem for the majority of patients in this study and were resolved with anticholinergic medication if present. An exception is a small number of patients taking haloperidol who had significant problems with these side-effects. As fewer than half of the patients given haloperidol were also given anticholinergic medication, a more consistent use of it prophylactically might have prevented extrapyramidal side-effects. Owing to the relatively short treatment period of this study, the important side-effects of weight gain, hyperglycaemia, lipid abnormalities and tardive dyskinesia were not evaluated.

Study limitations

Qualifying any conclusion about effectiveness is the lack of differentiation among the antipsychotics with respect to the BPRS total score. As there was a significant difference in this variable between effectively and ineffectively treated patients, the BPRS total score did have validity as an indicator of clinical improvement. As a group, the

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more effective antipsychotics were associated with a greater mean change in BPRS total score than the less effective ones, although not to a statistically significant degree. A likely possibility is that our study might not have had sufficient power to detect differences among the six treatments. A *post hoc* power analysis of this comparison showed a power of 0.39. There might also have been aspects of the patient's clinical condition relating to discharge that were not reflected in the BPRS total score; for example, haloperidol, olanzapine and risperidone might have been more successful at controlling disturbed behaviour and as a result patients treated with these would have been more readily discharged. However, if sedation alone accounted for the results then quetiapine – one of the most sedating of the six antipsychotics – would have had an advantage. In addition, no difference was found among the medications in changes in the BPRS factors, including hostility and activation. Although the definition of effectiveness used in this study may be a reflection of improvement in only some of the clinical manifestations of schizophrenia, improving the condition of patients so that they can be discharged sooner remains a clinically important objective.

The presence of a statistically significant – although not clearly clinically significant – difference in age among the treatment groups may indicate that there was unsuccessful randomisation. The patients were assigned treatment from a list prepared before the study began and by someone who had no knowledge of the patients, including their age, so it is unlikely that this represented an intentional bias. Although the differences in age cannot be explained, age was not a significant factor in determining effectiveness.

A major weakness of this study is its questionable generalisability. The results, although robust, may reflect idiosyncrasies of clinical practice by the psychiatric in-patient service at our facility. Also, the definition of effectiveness was relevant to hospitalised patients. The effectiveness of these medications in out-patients might be different. By American guidelines, a 3-week minimum trial would be sufficient to determine an antipsychotic's effectiveness; however, this might be considered too short for European psychiatric practice, where a minimum of 6 weeks is needed (National Institute for Clinical Excellence, 2002). Since all of the antipsychotics were effective for the majority of the patients by the criteria used in this study, the marginal benefit of a longer trial would probably be minimal.

A psychiatrist who was not masked to the antipsychotic being used made the decision that a patient no longer needed acute in-patient care, a major outcome variable. However, this decision was not made by the treating psychiatrist in isolation and was the product of input from the patient, the patient's family and other members of the treatment team. During the study period there was no significant difference in the length of stay of patients of the 14 psychiatrists who participated in the study (F=1.50, d.f.=13,164, P=0.12). There is also the possibility that, as a result of bias, the psychiatrists waited longer with some of the drugs before classifying them as ineffective, thereby increasing the chance of a favourable outcome. However, in addition to there being no difference in the time needed for a drug to be effective, there was no significant difference in the number of days until a treatment was classified as ineffective (F=0.82, d.f.=5,48, P=0.54). Another limitation of the study is that although standard recommended dosages were used, optimal therapeutic dosing for the newer second-generation antipsychotics is still uncertain. As aripiprazole, quetiapine and ziprasidone are further studied, perhaps the recommended therapeutic dosages of these drugs will be revised and, hence, their effectiveness.

Clinical implications

Based on these findings, haloperidol, risperidone and olanzapine are more effective antipsychotics for the acute treatment of hospitalised patients with schizophrenia, schizoaffective disorder or schizophreniform disorder. These drugs are reasonable first choices unless the patient's history suggests otherwise. Haloperidol, risperidone and olanzapine are also more potent antagonists of dopamine-2 receptors than the other three antipsychotics tested, which may account for their superior effectiveness (Kapur *et al*, 2000). Olanzapine and risperidone were better tolerated in the short term than haloperidol; however, greater use of anticholinergic medication with haloperidol would probably have improved its tolerability. This study did not address long-term effectiveness and side-effects. The number of patients with schizophrenia, schizoaffective disorder and schizophreniform disorder who require acute treatment is substantial and more studies with minimal bias are greatly needed to assist clinicians in making thoughtful treatment decisions.

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