

Clinical Advantages of Amisulpride in the Treatment of Acute Schizophrenia

T BURNS¹ AND R BALE²

¹Department of Psychiatry; ²Department of Community Psychiatry, St George's Hospital Medical School, London, UK

Five studies have been conducted with the atypical anti-psychotic amisulpride (100 – 1200 mg/day) involving 1358 patients with acute exacerbations of schizophrenia; four studies were short-term (4 – 8 weeks), double-blind studies and one was a 12-month, open, randomized comparison. Amisulpride improved positive symptoms consistently, and changes were more pronounced than with haloperidol, flupenthixol and risperidone; amisulpride showed a more rapid onset of action compared to haloperidol, and

improvement in negative symptoms was more effective than with any comparator. An optimum response was obtained with amisulpride doses 400 – 800 mg/day. The long-term study confirmed the usefulness of amisulpride for maintenance treatment in schizophrenia, with a clear advantage over haloperidol, leading to better functioning and quality of life. Amisulpride caused fewer neurological side-effects than conventional anti-psychotics and less weight gain than risperidone, both of which are crucial factors for long-term compliance.

KEY WORDS: AMISULPRIDE; ANTI-PSYCHOTIC; SCHIZOPHRENIA; ACUTE EXACERBATION

Introduction

Schizophrenia is a common and disabling condition, comprising cognitive, emotional and behavioural disturbances, that carries a lifetime prevalence of 0.5 – 1.0%.^{1,2} The symptoms of schizophrenia can be classified as either positive or negative,³ the latter being more difficult to treat. Acute exacerbations are characterized by positive symptoms, including acute-onset delusions, hallucinations, formal thought disorder and bizarre behaviour. Negative symptoms, such as blunted affect, poverty of speech/thought and social withdrawal, can be divided into primary symptoms, arising directly from the pathology of schizophrenia, and secondary symptoms related to the secondary effects of the disease or its treatment.⁴

The disease pattern of schizophrenia can be highly variable, i.e. acute, chronic or relapsing–remitting. Some patients (14%)⁵ may experience one psychotic episode and complete remission; others (7%)⁵ have periods of psychosis lasting most of the time. Even the remission period cannot be regarded as a symptom-free state, as approximately 50% of all patients experience a progressive decline,⁶ although some late improvement in condition may happen in many cases.⁷

Conventional, or typical, anti-psychotic agents (e.g. haloperidol) are the standard pharmacological treatments for schizophrenia. They are effective against the positive symptoms of schizophrenia, but 50% of patients experience incomplete or no

response.^{8,9} Moreover, up to 60% of patients relapse after 1 year of therapy.¹⁰ The benefits of conventional anti-psychotics are further limited by distressing adverse effects, particularly the extrapyramidal syndrome (EPS)¹¹ consisting of dystonia, akathisia and parkinsonism, and a late-onset adverse event, tardive dyskinesia.⁹ Non-compliance is a major problem in the management of schizophrenia, and EPS is a primary reason why patients fail to comply with treatment.^{12,13} Patients' attitudes to treatment and its associated side-effects may also be important, and lack of motivation, perhaps caused by negative symptoms, may increase the risk of relapse.^{14,15} Shortcomings of existing treatments have fuelled the search for more effective and better tolerated anti-psychotics.

From a pharmacological perspective, positive symptoms might be linked to dopaminergic hyperfunction, and negative symptoms to dopaminergic hypofunction.¹⁶ The hypothesis that activity at limbic dopamine receptors is related to anti-psychotic effects, and that antagonism of striatal dopamine receptors leads to EPS, has been confirmed in clinical practice using atypical anti-psychotic drugs that block limbic dopamine receptors preferentially.¹⁷

Amisulpride, a substituted benzamide, is an atypical anti-psychotic that differs from conventional and other atypical neuroleptics due to its unique neurochemical and psychopharmacological profile.¹⁸ Amisulpride displays selectivity for limbic rather than striatal structures;^{19,20} this is predictive of a side-effect profile with a low risk of EPS or other effects such as sedation, anti-cholinergic symptoms or hypotension, linked to interaction with other receptors. The clinical efficacy of amisulpride against acute psychotic symptoms at high doses, and predominant negative symptoms at low doses, may be explained by its preferential

affinity for pre-synaptic dopamine D₂ and D₃ autoreceptor subtypes at low doses, while higher doses result in antagonism of post-synaptic dopamine receptors.^{19,20}

Clinical investigations with amisulpride centre on its efficacy and safety in two different populations of patients with schizophrenia: those with acute exacerbations²¹⁻²⁵ and those with predominantly negative symptoms,²⁶⁻²⁹ thus covering the spectrum of schizophrenic symptomatology, from acute to chronic forms of disease. This review presents the results of five studies using amisulpride for the treatment of patients with acute exacerbations of schizophrenia.

Patients and methods

STUDY DESIGNS

Five randomized studies involving over 1300 patients (Table 1) were performed.²¹⁻²⁵ All treatments, including comparator drugs, were taken twice daily by the oral route and all double-blind studies included a washout period of 3-7 days. The dose-ranging study tested four fixed dosages of amisulpride and the conventional anti-psychotic haloperidol; the amisulpride 100 mg/day dose was regarded as a potentially inactive control, placebo treatment being considered unethical in Europe.²⁴ Amisulpride was directly compared with the conventional anti-psychotics, haloperidol²² or flupenthixol,²⁵ and with an atypical anti-psychotic, risperidone.²³ The fifth study was a 12-month, open-label investigation of the long-term safety and efficacy of amisulpride and haloperidol.²¹

INCLUSION/EXCLUSION CRITERIA

Men and women up to 65 years of age (60 years in two studies^{22,24}), who gave written, informed consent to participate, were eligible for inclusion. In four studies, patients had to fulfil DSM-III-R criteria³⁰ for acute exacerbation of schizophrenia,^{21,22,24,25}

TABLE 1:
Main characteristics of the five clinical studies

Study	Design	Mean duration of illness (years)	No. of patients	Drug doses (mg/day) given orally twice daily	Duration (weeks)
Colonna <i>et al.</i> 2000 ²¹	O, PG, R	12	488	A 200 – 800 (max 1200) H 5 – 20 (max 30)	52
Möller <i>et al.</i> 1997 ²²	DB, PG	9.5	191	A 800 (600 ^a) H 20 (15 ^a)	6
Peuskens <i>et al.</i> 1999 ²³	DB, PG	9	227	A 800 Ri 8 (after 3-day titration)	8
Puech <i>et al.</i> 1998 ²⁴	DB, PG	10.1	319	A 100, 400, 800, 1200 H 16	4
Wetzel <i>et al.</i> 1998 ²⁵	DB, PG	Not available	133	A 1000 (600 ^a) F 25 (15 ^a)	6

^aDosage reduced to this amount if drug not well tolerated.

DB, double-blind; PG, parallel-group; O, open; R, randomized; A, amisulpride; H, haloperidol; F, flupenthixol; Ri, risperidone; max, maximum.

while DSM-IV criteria³¹ was used in the fifth study.²³ Patients with paranoid, disorganized or undifferentiated types of schizophrenia were included,^{21–24} except in the comparison of amisulpride and flupenthixol, where only patients with paranoid or undifferentiated subtypes of schizophrenia were included.²⁵

To ensure the predominance of psychotic schizophrenic symptoms, on inclusion patients in four studies had to score a minimum of ≥ 12 on four Brief Psychiatric Rating Scale (BPRS)³² psychosis items (i.e. conceptual disorganization, unusual thought content, hallucinatory behaviour and suspiciousness).^{21–24} A total score < 55 on the Scale for Assessment of Negative Symptoms (SANS)³³ was employed in one investigation to confirm that any negative symptomatology was of limited severity.²⁵

The main exclusion criteria were: psychotic symptomatology not meeting the diagnostic criteria for schizophrenia; clinically significant cardiovascular, renal

or liver disease; Parkinson's disease; phaeochromocytoma; hypersensitivity to the study medication; and pregnancy or child-bearing potential.

EFFICACY ASSESSMENTS

The principal instrument used for evaluating the efficacy of amisulpride in all investigations of psychotic symptomatology was the BPRS.³²

There were three secondary efficacy measures: effect of treatment on positive and negative symptoms and the number of responders. The 7-item subscales of the Positive and Negative Syndrome Scale (PANSS)³⁴ was one method for evaluating symptoms in four investigations;^{21–24} the Scale for Assessment of Positive Symptoms (SAPS)³³ and the SANS³³ were also used in one trial.²⁵ The Clinical Global Impressions (CGI) scale³⁵ was used to define treatment responders (percentage of patients who were 'very much' or 'much' improved on CGI item II).^{22–25}

Patient functioning was assessed in two studies^{21,23} using the Global Assessment of Functioning (GAF) scale,³⁶ or the Social and Occupational Functioning Assessment Scale (SOFAS).³⁷ The former focuses on an individual's level of psychological, social and occupational functioning and is scored from 1 (severe impairment) to 100 (superior functioning), whereas the latter concentrates only on social and occupational functioning with scores ranging from 1 (severe impairment) to 100 (superior functioning). Quality of life was evaluated in the long-term study of amisulpride²¹ using the 21-item Quality of Life Scale (QLS). The QLS uses a 6-point scale to rate how well a patient is functioning and how they perform activities of daily living, the quality of their relationships with others, and their occupational or school capability.³⁸ Symptoms of retardation and depression were assessed in one study²⁵ using the Bech-Rafaelsen Melancholia Scale (BRMS).³⁹

Onset of action was analysed in a pooled analysis of both short-term studies^{22,24} comparing amisulpride (400 and 800 mg/day dose levels only) and haloperidol (15 – 20 mg/day), using the percentage of responders (reduction in BPRS score of at least 50%) after 1 and 2 weeks of treatment.

Long-term efficacy was assessed in one study²¹ using the change in BPRS total score and the proportion of responder patients (reduction in BPRS score \geq 50%), as well as the CGI-item II scale.

SAFETY ASSESSMENTS

In all studies, the Simpson–Angus Scale (SAS),⁴⁰ Barnes Akathisia Scale (BAS),⁴¹ and Abnormal Involuntary Movement Symptoms (AIMS) scale⁴² were used for the assessment of parkinsonism, akathisia and tardive dyskinesia, respectively. Vital signs and laboratory parameters (haematology, blood chemistry) were recorded in all trials, and

electrocardiogram (ECG) tracings were obtained in three studies.^{21,23,25}

STATISTICAL ANALYSIS

The results of the four double-blind, short-term studies^{22–25} were included in a pooled analysis as their designs and objectives were similar. The differences between amisulpride and comparators in terms of change in BPRS total score (baseline to endpoint) and the corresponding 95% confidence intervals (CI) were calculated.

The principal evaluation was the intention-to-treat (ITT) analysis of the change in BPRS total score from baseline to study endpoint. To compare treatment groups, ANOVA and, when appropriate (i.e. in the dose-ranging study),²⁴ Dunnett's test were utilized. Similar methods were used for secondary efficacy variables (e.g. PANSS, BPRS factors, SANS, SAPS, neurological rating scales). A χ^2 -test for dichotomous qualitative variables and a Cochran–Mantel–Haenszel test for ordered qualitative variables were also performed.

When there were significant differences at baseline in the comparison of amisulpride and flupenthixol, ANCOVA was performed with doses or baseline values as covariates.²⁵ In the comparison of amisulpride and risperidone, the ITT analysis of change in BPRS total score (baseline to endpoint) was performed using a one-sided equivalence hypothesis with a 6-point interval of non-inferiority.²³ A difference of > 6 points is generally considered clinically significant, and is consistently smaller than the difference seen when active doses of newly developed anti-psychotics are assessed against placebo.^{43–49}

A χ^2 -test was used to compare treatment groups for onset of action.^{22,24} To compare the evolution profiles of total scores in the randomized, long-term study,²¹ an analysis with repeated measures was performed using

the 'last observation carried forward' (LOCF) procedure. *P*-values of < 0.05 were taken as significant.

Results

PATIENT POPULATION

The main features of the five studies are listed in Table 1, whereas Table 2 includes key patient characteristics. Of the 1358 patients studied, 905 (67%) received amisulpride and 453 (33%) received a comparator drug (haloperidol, flupenthixol or risperidone). The mean age of the population was 36.3 years, and approximately two-thirds (63%) were male. The predominant type of schizophrenia was disorganized (42%), followed by paranoid and undifferentiated types. Patients were hospitalized in three short-term studies^{22,24,25} and were either in- or out-patients in the other two trials.^{21,23} Patients were generally chronically ill, with the mean duration of illness ranging from 9 years to 12 years.

Reasons for dropout

There were fewer dropouts with amisulpride than with either haloperidol or flupenthixol. In the dose-ranging study, the drop-out rate varied between 15% in the amisulpride 800 mg/day group and 33% in the haloperidol 16 mg/day group,²⁴ and the drop-out rate with amisulpride was significantly lower than that with haloperidol in another study (26% versus 41%, *P* < 0.05).²²

Similarly, in the long-term study, the percentage of premature withdrawals was less important in the amisulpride (45%) than in the haloperidol group (52%); the majority of withdrawals occurred during the first 3 months of treatment. The main reason for dropout in the amisulpride group was unco-operativeness (21%) compared with lack of efficacy (17%) and unco-operativeness (14%) in the haloperidol group.²¹

The drop-out rate was lower with amisulpride in the comparison against

TABLE 2:
Patient characteristics by treatment group in the five trials^{21–25}

Parameter	Amisulpride	Haloperidol	Flupenthixol	Risperidone	Total
No. of patients	905	278	62	113	1358
Mean age ± SD and range (years)	36.2 ± 10.9 (17 – 65)	37.3 ± 11.3 (18 – 65)	32.6 ± 9.2 (18 – 58)	37.0 ± 12.2 (17 – 64)	36.3 ± 11.1 (17 – 65)
Age groups (years): <i>n</i> (%)					
< 18	1 (0.1)	–	–	1 (0.9)	2 (0.1)
18 – 49	775 (85.6)	237 (85)	57 (92)	91 (80.5)	1160 (85.4)
50 – 64	125 (13.8)	39 (14)	5 (8)	21 (18.6)	190 (14)
> 64	4 (0.5)	2 (1)	–	–	6 (0.5)
Male/female gender (%)	584/321 (65/35)	167/111 (60/40)	38/24 (61/39)	66/47 (58/42)	855/503 (63/37)
Schizophrenia type (%)					
Disorganized	358 (40)	109 (39)	35 (56)	29 (26)	573 (42)
Paranoid	314 (35)	97 (35)	–	71 (63)	440 (32)
Undifferentiated	233 (26)	71 (26)	27 (44)	13 (12)	344 (25)

Amisulpride in the treatment of schizophrenia

flupenthixol (27% versus 40%), and significantly fewer patients terminated the study prematurely due to adverse events in the amisulpride group ($P = 0.03$).²⁵ Premature withdrawals were equally balanced between amisulpride (32%) and risperidone (28%) in the head-to-head comparison.²³

EFFICACY

The mean baseline, endpoint and change in BPRS total scores for the four double-blind studies are shown in Table 3 and Fig. 1. In the dose-ranging study, patients who received amisulpride in doses of ≥ 400 mg/day had a greater improvement in BPRS score than in the amisulpride 100 mg/day group; the improvement with the 800 mg/day dose was statistically significantly greater than with

the 100 mg/day dose ($P < 0.05$ after Dunnett's procedure).²⁴ The dose-response curve was bell-shaped, with both 100 mg and 1200 mg doses resulting in a lesser response than 400 mg and 800 mg doses.

Brief Psychiatric Rating Scale: analysis of double-blind studies

The BPRS data from the four double-blind studies were included in a pooled analysis. Baseline BPRS values were in the approximate range 49 – 64, reflecting the severity of the positive symptomatology. The pooled results of the differences in mean BPRS change at endpoint with amisulpride and comparators, together with the corresponding 95% CI, are shown in Fig. 2. Amisulpride was more

TABLE 3: Brief Psychiatric Rating Scale (BPRS) total scores (ITT analysis) in the double-blind trials^{22–25}

Trial name and daily dosage (mg/day)	n	Mean BPRS total score \pm SD			P-value
		Baseline	Endpoint	Change in score	
<i>Möller et al. 1997</i> ²²					
A 800	94	61.4 \pm 10.8	40.4 \pm 18.7	20.9 \pm 18.5	–
H 20	94	61.6 \pm 11.5	44.2 \pm 16.8	17.2 \pm 18.1	A versus H: NS
<i>Peuskens et al. 1999</i> ²³					
A 800	115	55.6 \pm 10.7	38.0 \pm 15.1	17.7 \pm 14.9	–
Ri 8	113	54.6 \pm 8.7	39.5 \pm 14.9	15.2 \pm 13.9	A versus Ri: $P < 0.0005^a$
<i>Puech et al. 1998</i> ²⁴					
A 100	58	60.1 \pm 12.8	41.7 \pm 17.6	18.4 \pm 17.0	–
A 400	62	63.5 \pm 10.3	38.6 \pm 17.9	24.9 \pm 18.4	NS
A 800	63	61.2 \pm 10.2	35.2 \pm 12.7	26.0 \pm 14.9	$P < 0.05$ versus A 100 mg ^b
A 1200	65	61.4 \pm 11.2	40.7 \pm 17.5	20.7 \pm 17.4	NS
H 16	61	58.9 \pm 12.4	40.0 \pm 15.1	18.9 \pm 16.0	NS
<i>Wetzel et al. 1998</i> ²⁵					
A 1000	66	56.1 \pm 10.8	32.4 \pm 15.5	23.2 \pm 13.3	–
F 25	61	49.8 \pm 9.3	33.3 \pm 15.6	16.2 \pm 15.5	A versus F: NS

^aUnilateral equivalence test with a threshold of non-inferiority of 6 points.

^bANOVA with Dunnett's procedure.

ITT, intent-to-treat; A, amisulpride; H, haloperidol; F, flupenthixol; Ri, risperidone; NS, not significant.

Amisulpride in the treatment of schizophrenia

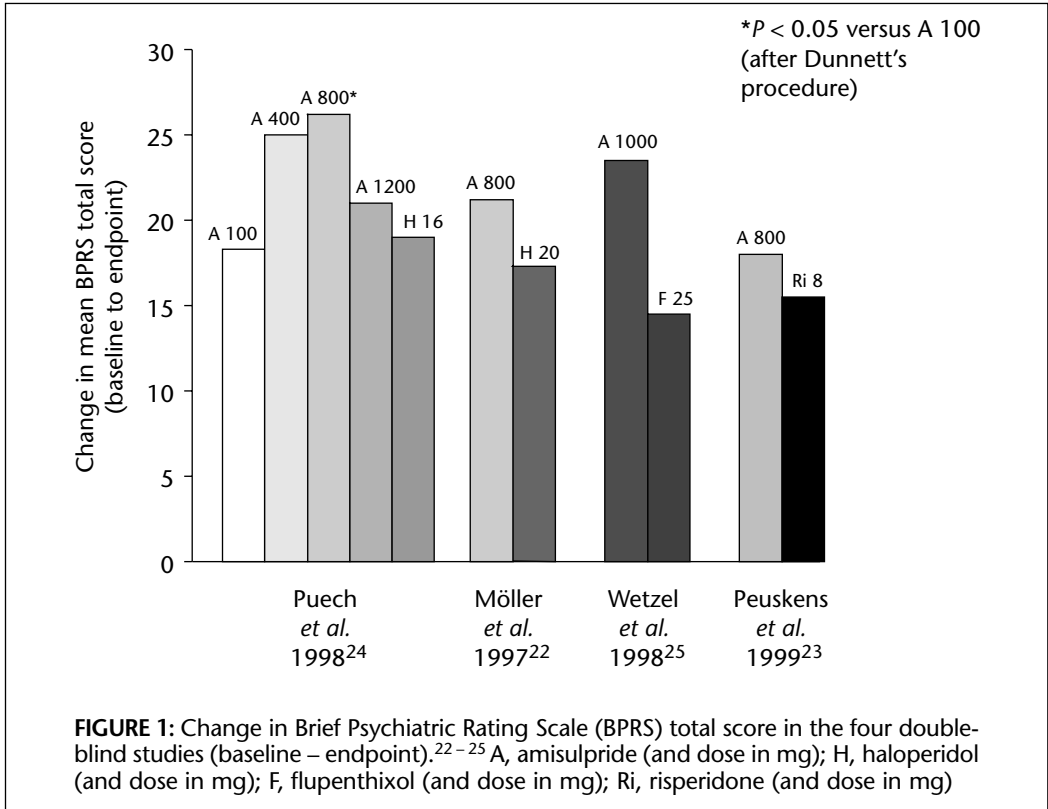


FIGURE 1: Change in Brief Psychiatric Rating Scale (BPRS) total score in the four double-blind studies (baseline – endpoint).^{22–25} A, amisulpride (and dose in mg); H, haloperidol (and dose in mg); F, flupenthixol (and dose in mg); Ri, risperidone (and dose in mg)

effective than haloperidol when a comparison was made using 4 weeks' treatment as a cut-off point (95% CI: 2.0, 9.2 for amisulpride versus haloperidol) and was also more effective when comparator data were combined (95% CI: 2.7, 7.4 for amisulpride versus comparators).

Positive symptom ratings

Amisulpride improved positive symptoms consistently, and changes were more pronounced under amisulpride than with comparators (Table 4). In the dose-ranging study, patients receiving amisulpride in doses of ≥ 400 mg/day had a greater improvement in PANSS positive score than those receiving 100 mg/day; the improvement with 800 mg/day was statistically significant versus 100 mg/day ($P < 0.05$). The dose-response curve was again bell-shaped,

with the best responses apparent at 400 mg/day and 800 mg/day doses. The haloperidol group showed an improvement similar to that seen in the amisulpride 100 mg/day group.

Responders and non-responders

Results for the four double-blind studies are shown in Fig. 3. The highest response (78%) was seen with amisulpride 800 mg/day in the dose-ranging study, and this was significantly superior to amisulpride 100 mg/day (52%; $P = 0.01$). In all other studies using amisulpride doses > 400 mg/day, the response was $> 60\%$. In a comparison of amisulpride and haloperidol, the proportion of responders in the amisulpride 800 mg/day group (62%) was significantly superior to haloperidol 20 mg/day (44%; $P < 0.05$).²²

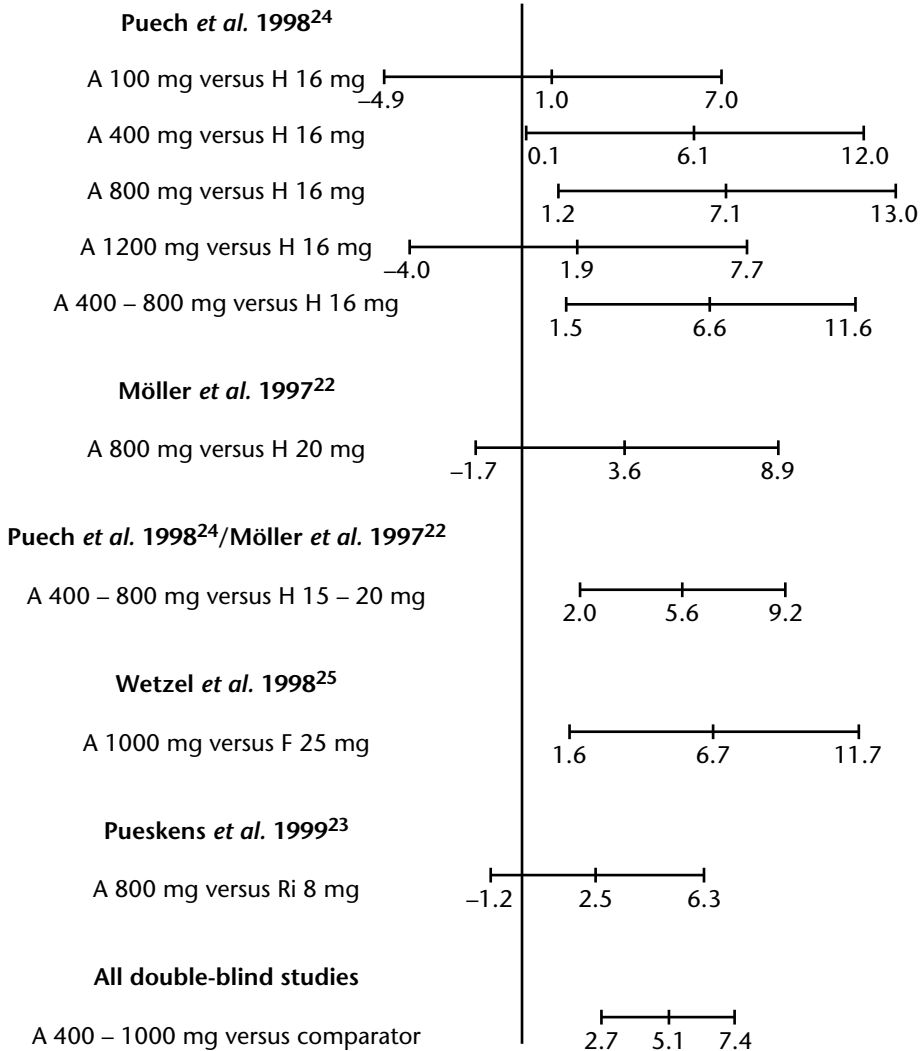


FIGURE 2: 95% confidence interval of difference in mean Brief Psychiatric Rating Scale (BPRS) changes at endpoint.^{22 – 25} Values lying to the right of the vertical line imply that amisulpride was more effective in reducing BPRS than the respective comparator. A, amisulpride; H, haloperidol; F, flupenthixol; Ri, risperidone

Negative symptom ratings

Amisulpride, at anti-psychotic doses, improved both positive and negative symptoms in acute schizophrenia. The PANSS negative subscale scores were improved by a range of 6.9 – 9.6 points with amisulpride compared with a range of

5.1 – 7.4 points with haloperidol and 5.3 points with risperidone.² When data from these studies were pooled, amisulpride doses of 400 – 800 mg/day were superior to the reference compounds: the mean change from baseline was 7.9 with amisulpride (95% CI: 7.0, 8.7) and 5.7 for haloperidol plus

TABLE 4:
Change in Positive and Negative Syndrome Scale (PANSS) or Scale for Assessment of Positive Symptoms (SAPS) scores (ITT analysis) in the four double-blind trials^{22–25}

Trial name and daily dosage (mg/day)	<i>n</i>	Change in PANSS score ± SD	<i>P</i> -value
<i>Möller et al. 1997</i> ²²			
A 800	94	10.4 ± 8.5	–
H 20	94	9.4 ± 9.0	A versus H: NS
<i>Peuskens et al. 1999</i> ²³			
A 800	115	9.6 ± 8.5	–
Ri 8	113	8.6 ± 7.4	A versus Ri: NS
<i>Puech et al. 1998</i> ²⁴			
A 100	58	7.9 ± 8.4	–
A 400	62	10.8 ± 9.2	NS
A 800	63	12.0 ± 6.9	<i>P</i> < 0.05 versus A 100 mg ^a
A 1200	65	10.0 ± 9.3	NS
H 16	61	8.5 ± 9.0	NS
Trial name and daily dosage (mg/day)	<i>n</i>	Change in SAPS score ± SD	<i>P</i> -value
<i>Wetzel et al. 1998</i> ²⁵			
A 1000	66	42.7 ± 21.8	–
F 25	61	32.5 ± 30.1	A versus F: NS

^aANOVA with Dunnett's procedure.

ITT, intent-to-treat; A, amisulpride; H, haloperidol; F, flupenthixol; Ri, risperidone; NS, not significant.

risperidone (95% CI: 4.8, 6.6; *P* < 0.05 for the difference between groups). Amisulpride also reduced the SANS score by approximately twice as much as did flupenthixol.²⁵

Onset of action

Onset of action was significantly superior after 1 and 2 weeks of treatment with amisulpride (400 – 800 mg doses only) compared with haloperidol.^{22,24} The percentage of responders was superior with amisulpride compared with haloperidol at day 7 (13% and 4%, respectively; *P* = 0.003) and at day 14 (38% and 24%; *P* = 0.004).

Long-term efficacy

Improvement from baseline in mean total BPRS score was significantly higher in the

amisulpride than in the haloperidol group at the end of the 12-month study (17 versus 12.8, *P* = 0.01) (Fig. 4).²¹ The decrease in BPRS was maintained over the study period in the amisulpride group, whereas in the haloperidol group, the initial change observed between baseline and month 6 tapered off between month 6 and endpoint. This difference in profile was significant (*P* = 0.026). There were no significant differences between these treatments with respect to improvement in positive symptoms on the PANSS (8.8 versus 8.3), but the PANSS negative score showed a significantly greater improvement with amisulpride than with haloperidol (7.1 versus 3.7; *P* < 0.001).²¹ The response rate in terms of CGI-improvement ('very much' or 'much'

Amisulpride in the treatment of schizophrenia

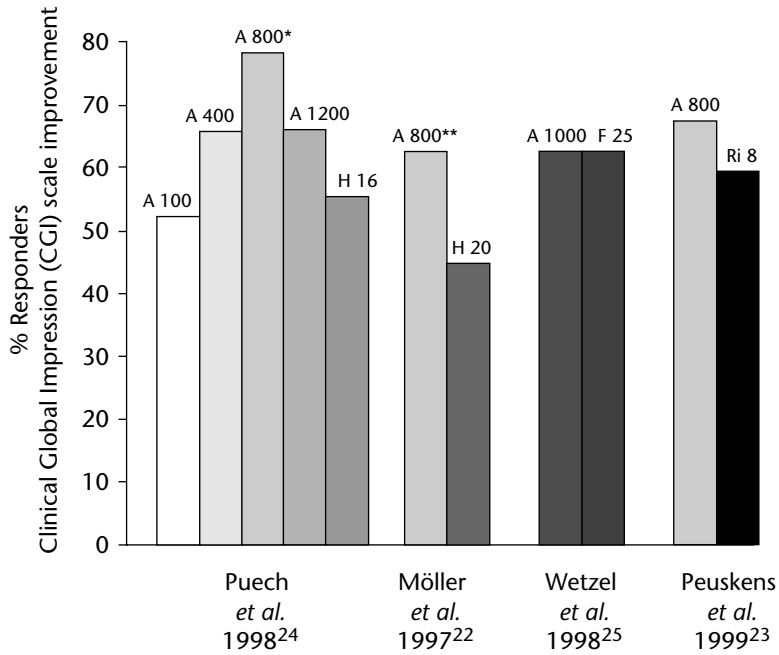


FIGURE 3: Percentage of responders (CGI-improvement defined as 'very much' or 'much' improved) to amisulpride or comparator drugs.²²⁻²⁵ A, amisulpride (and dose in mg); H, haloperidol (and dose in mg); F, flupenthixol (and dose in mg); Ri, risperidone (and dose in mg). * $P = 0.01$ versus A 100; ** $P < 0.05$ versus H 20

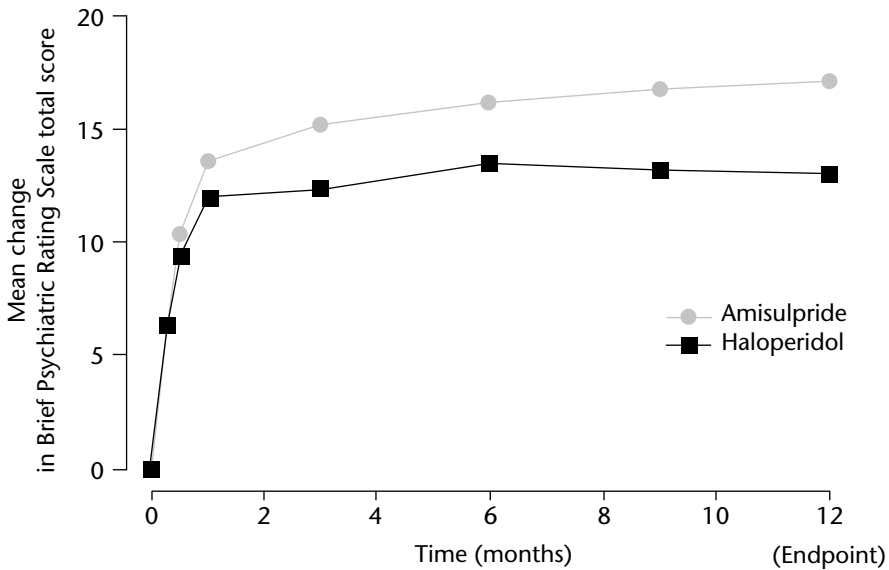


FIGURE 4: Mean changes from baseline in Brief Psychiatric Rating Scale total score over time.²¹ Amisulpride, $n = 365$; haloperidol, $n = 117$

improved) showed a trend towards superiority in the amisulpride compared with the haloperidol group (55% versus 44%, $P = 0.057$).

In this study, the effect of amisulpride on GAF score (baseline – endpoint) was significantly greater than that with haloperidol (-20.1 versus -13.6 ; $P = 0.001$). Similarly, the improvement in QLS score was significantly greater with amisulpride than haloperidol (-0.64 versus -0.30 , $P = 0.02$).²¹ This improved response with amisulpride was seen in three of the four QLS score subscales: interpersonal relationships ($P = 0.003$), instrumental role ($P = 0.04$) and intrapsychic foundations ($P = 0.012$); results with the fourth scale (objects and activities) were comparable between groups.

Other efficacy measures

Symptoms of retardation/depression were assessed in one study using the BRMS.²⁵ The

improvement in BRMS score from baseline to endpoint was significantly superior with amisulpride 1000 mg/day compared with flupenthixol 25 mg/day (8.0 ± 7.2 versus 5.2 ± 8.8 ; $P < 0.05$).⁵⁰

Effect of treatment on social functioning was assessed in another study²³ using SOFAS, and both amisulpride and risperidone produced similar improvement (14.3 ± 16.9 versus 12.7 ± 17.1).

SAFETY

Neurological symptoms: short-term studies

In the comparisons with haloperidol and flupenthixol, amisulpride provoked significantly less parkinsonism (assessed using the SAS scale) than the comparator drugs ($P < 0.01$);^{22,24,25} in the comparison with risperidone, scores were low at baseline and showed no overall change (Table 5).²³ In the

TABLE 5:
Effect of treatment on Simpson-Angus Scale for parkinsonism in the four individual short-term, double-blind studies^{22–25}

Trial name and daily dosage (mg/day)	Baseline	Endpoint	Change	P-value
Möller <i>et al.</i> 1997 ²²				
A 800	0.46 ± 0.54	0.40 ± 0.51	0.06 ± 0.51	(A versus H: $P < 0.01$) ^a
H 20	0.44 ± 0.47	0.63 ± 0.59	-0.19 ± 0.70	
Peuskens <i>et al.</i> 1999 ²³				
A 800	0.28 ± 0.45	0.29 ± 0.44	-0.01 ± 0.47	A versus R: NS
Ri 8	0.36 ± 0.50	0.35 ± 0.47	0.01 ± 0.46	
Puech <i>et al.</i> 1998 ²⁴				
A 100	0.23 ± 0.43	0.18 ± 0.33	0.05 ± 0.31	–
A 400	0.17 ± 0.28	0.20 ± 0.33	-0.04 ± 0.34	NS
A 800	0.26 ± 0.45	0.26 ± 0.45	-0.01 ± 0.56	NS
A 1200	0.18 ± 0.31	0.23 ± 0.40	-0.05 ± 0.49	NS
H 16	0.19 ± 0.34	0.40 ± 0.45	-0.21 ± 0.53	(A 100 versus H: $P < 0.01$) ^b
Wetzel <i>et al.</i> 1998 ²⁵				
A 1000	1.1 ± 2.6	–	1.1 ± 3.7	(A versus F: $P < 0.01$) ^a
F 25	1.0 ± 2.4	–	3.8 ± 5.9	

^aANOVA.

^bANOVA with Dunnett's procedure.

A, amisulpride; H, haloperidol; F, flupenthixol; Ri, risperidone; NS, not significant.

dose-ranging study, there were no significant differences between amisulpride 400 mg/day and 800 mg/day and the 100 mg/day dose.

Amisulpride was significantly less likely than flupenthixol to provoke akathisia or tardive dyskinesia.²⁵ The mean change in BAS total score was significantly smaller with amisulpride (0.2 ± 1.9 , $P < 0.01$) than with flupenthixol (1.6 ± 2.4); a similar pattern was noted in relation to the mean change in AIMS score (0.0 ± 2.8 versus 1.8 ± 4.4 , $P < 0.01$).²⁵ No significant differences were observed between amisulpride and haloperidol^{22,24} or risperidone²³ on the AIMS.

Long-term effects

Amisulpride was superior to haloperidol with respect to neurological safety.²¹ The results from the parkinsonism scale (SAS) showed that there was a significant difference between treatments in favour of amisulpride in terms of change from baseline to endpoint ($P < 0.001$) (Table 6). The change in AIMS score and the proportion of patients with no or questionable akathisia were also

significantly in favour of amisulpride ($P < 0.05$), but the baseline values for both parameters were low and the change at endpoint was only minimal.²¹

Tolerability

Amisulpride had no clinically significant effect on vital signs, ECG or laboratory parameters.^{21–25} The only notable difference in weight gain was observed in patients treated with risperidone who experienced a significant increase (1.4 kg, $P = 0.026$), not found in those receiving amisulpride (0.4 kg).

Discussion

The patient with schizophrenia lives with a three-way challenge. First, there is the affliction of the psychotic (positive) symptoms, including paranoid delusions and hallucinations, that induce major social handicap and disruptive behaviour. Secondly, during periods of remission, motivation and cognitive functioning can be impaired further, leading to social isolation, poverty and loss of independence. Thirdly,

TABLE 6:
Effect of long-term treatment on extrapyramidal symptoms²¹

	Baseline <i>n</i> = 370	Endpoint <i>n</i> = 118	Change	<i>P</i> -value
SAS score \pm SD				
Amisulpride	0.35 \pm 0.50	0.24 \pm 0.41	0.11 \pm 0.43	<i>P</i> = 0.0001
Haloperidol	0.42 \pm 0.56	0.65 \pm 0.71	-0.22 \pm 0.66	
BAS (% patients with no akathisia ^a)				
Amisulpride, <i>n</i>	90	92	–	<i>P</i> < 0.0001
Haloperidol, <i>n</i>	84	79	–	
AIMS total score \pm SD				
Amisulpride	2.4 \pm 4.7	1.8 \pm 4.0	0.6 \pm 3.9	<i>P</i> < 0.014
Haloperidol	2.8 \pm 5.0	3.0 \pm 4.8	-0.2 \pm 4.7	

^aNo akathisia or questionable akathisia. SAS, Simpson-Angus Scale; BAS, Barnes Akathisia Scale; AIMS, Abnormal Involuntary Movement Symptoms.

people with schizophrenia are at increased risk of self-harm, as the illness is associated with a 10% mortality from suicide.⁵¹ As well as having a significant effect on national healthcare resources, the burden of schizophrenia is also shared with family members, particularly since patients increasingly receive long-term care in the community and may be financially and emotionally dependent on their relatives. There is, therefore, a need for an effective and safe treatment that can control symptoms and help the patients to lead a more normal life.

The efficacy and safety of the novel, atypical anti-psychotic agent amisulpride has been demonstrated extensively in clinical studies,²¹⁻²⁹ which indicate that the drug is effective on all the disease states of schizophrenia.⁵²

Amisulpride has shown potent and consistent efficacy in the treatment of acute symptoms of schizophrenia in four well-controlled, short-term, double-blind comparative studies²²⁻²⁵ and one long-term, open-label, randomized investigation.²¹ This new agent was as effective as the typical anti-psychotics haloperidol^{21,22,24} and flupenthixol,²⁵ and the atypical agent risperidone.²³ Amisulpride can be used as a first-line treatment in acute exacerbations of schizophrenia because of its potent action on delusions, agitation and hallucinations. In this challenging acute phase of the disease, a substantial number of patients treated with amisulpride show a 50% reduction of symptoms after 1 and 2 weeks of treatment. This is in contrast with the expected interval of 15 – 20 days expected before the beginning of therapeutic effect with traditional agents.⁵³

Amisulpride also has a very good effect on negative symptoms in productive states, as shown by a greater reduction in PANSS negative subscale and SANS scores with

amisulpride than with haloperidol, risperidone or flupenthixol. Benefit appeared even though study periods were relatively short.

In the chronic phase of schizophrenia, amisulpride can also be used. Long-term findings²¹ show that most patients maintain efficacy beyond 1 year, and that this is associated with a significant reduction in secondary negative symptoms and improvement in quality of life. This important finding shows that better performance on symptoms improvement leads to better personal and social functioning, which is of particular interest in these chronically ill patients.

The dose-ranging study demonstrated an optimum response with amisulpride at doses of 400 – 800 mg/day;²⁴ therefore, dosage can be tailored to individuals. The fixed dose of haloperidol 16 mg/day administered during the dose-ranging trial was in the upper range of the therapeutic margin for this agent, but was justified by the selection of patients with acute exacerbations of disease. Amisulpride dosage is also flexible during the chronic course of schizophrenia and should be adjusted according to individual response, mean dose usually ranging from 400 mg/day to 600 mg/day.

Amisulpride has another advantage over typical anti-psychotics in that it has a significantly lower propensity to induce EPS compared with haloperidol, both short-²²⁻²⁵ and long-term.²¹ There was no significant difference between amisulpride and risperidone in neurological side-effects.²³ These findings are consistent with amisulpride's pharmacological profile,^{19,20} and preferential limbic, rather than striatal, binding.

A noticeable difference in weight gain was observed in the head-to-head study,²³ risperidone leading to a significant increase of 1.4 kg which was not found in patients

receiving amisulpride, which is a crucial finding for long-term patient compliance.

Conclusion

This review of five comparative studies in patients with acute exacerbations of schizophrenia has shown that amisulpride, at doses of 400 – 800 mg/day, consistently demonstrates a potent anti-psychotic action with a rapid onset of action. Amisulpride also showed significant improvement in negative symptoms and was more effective than any comparator in this respect. Findings from the long-term study showed that amisulpride therapy can continue into

the chronic phase of schizophrenia, with a clear advantage over haloperidol, thus leading to better functioning and quality of life. Amisulpride caused fewer neurological side-effects than the conventional anti-psychotics and less weight gain than risperidone. Both of these factors are crucial for long-term compliance.

Amisulpride provides an optimal first-line drug for patients with acute exacerbations of schizophrenia as well as for subsequent long-term treatment.

Acknowledgement

We thank Sanofi-Synthelabo for supporting us in this work.

• Received for publication 25 June 2001 • Accepted 14 August 2001

©2001 Cambridge Medical Publications

References

- Eaton WW: Epidemiology of schizophrenia. *Epidemiologic Rev* 1985; **7**: 105 – 126.
- Regier DA, Boyd JH, Burke JD, Rae DS, Myers JK, Kramer M, *et al*: One month prevalence of mental disorders in the US: based on five epidemiological catchment area (ECA) sites. *Arch Gen Psychiatry* 1988; **45**: 977 – 986.
- Andreasen NC: Positive and negative schizophrenia: a critical evaluation. *Schizophr Bull* 1985; **11**: 380 – 389.
- Carpenter WT, Heinrichs DW, Alphas LD: Treatment of negative symptoms. *Schizophr Bull* 1985; **11**: 453 – 456.
- Harding CM: Course types in schizophrenia. *Schizophr Bull* 1988; **14**: 633 – 644.
- Shepherd M, Watt D, Falloon I, Smeeton N: The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenia. *Psychol Med* 1989; Monograph Supplement **15**: 1 – 46.
- van Os J, Wright P, Murray RM: Follow-up studies of schizophrenia I: natural history and non-psychopathological predictors of outcome. *Eur Psychiatry* 1997; **12** (Suppl 5): 327S – 341S.
- Kane JMS: Schizophrenia. *N Engl J Med* 1996; **334**: 34 – 41.
- Kane JM: What are the therapeutic needs in schizophrenia and how are they satisfied by new antipsychotics? *Int Clin Psychopharmacol* 1997; **12** (Suppl 2): S3 – S6.
- Hegarty JD, Baldessarini RJ, Tohen M, Waternaux C, Oepen G: One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994; **151**: 1409 – 1416.
- Casey DE: Motor and mental aspects of extrapyramidal syndromes. *Int Clin Psychopharmacol* 1995; **10** (Suppl 3): 105 – 114.
- van Putten T: Why do schizophrenic patients refuse to take their drugs? *Arch Gen Psychiatry* 1974; **31**: 67 – 72.
- van Putten T: Drug refusal in schizophrenia: causes and prescribing hints. *Hosp Community Psychiatry* 1978; **29**: 110 – 112.
- Garavan J, Browne S, Gervin M, Lane A, Larkin C, O'Callaghan E: Compliance with neuroleptic medication in outpatients with schizophrenia; relationship to subjective response to neuroleptics; attitudes to medication and insight. *Compr Psychiatry* 1998; **39**: 215 – 219.
- Cabeza IG, Amador MS, Lopez CA, Gonzalez de Chavez M: Subjective response to antipsychotics in schizophrenic patients: clinical implications and related factors. *Schizophr Res* 2000; **41**: 349 – 355.
- Kahn RS, Davis KL: New developments in dopamine and schizophrenia. In: *Psychopharmacology: the Fourth Generation of Progress* (Bloom FE, Kupfer DJ, eds). New York: Raven Press Ltd, 1995; pp1193 – 1203.
- Csernansky JG, Wrona CT, Bardgett ME, Early TS, Newcomer JW: Subcortical dopamine

- and serotonin turnover during acute and subchronic administration of typical and atypical neuroleptics. *Psychopharmacology* 1993; **110**: 145 – 151.
- 18 Scatton B, Clautre Y, Cudennec A, Oblin A, Perrault G, Sanger DJ, *et al*: Amisulpride: from animal pharmacology to therapeutic action. *Int Clin Psychopharmacol* 1997; **12** (Suppl 2): S29 – S36.
 - 19 Perrault G, Depoortere R, Morel E, Sanger DJ, Scatton B: Psychopharmacological profile of amisulpride: an antipsychotic drug with presynaptic D2/D3 dopamine receptor antagonist activity and limbic selectivity. *J Pharmacol Exp Ther* 1997; **280**: 73 – 82.
 - 20 Schoemaker H, Clautre Y, Fage D, Rouquier L, Chergui K, Curet O, *et al*: Neurochemical characteristics of amisulpride, an atypical dopamine D2/D3 receptor antagonist with both presynaptic and limbic selectivity. *J Pharmacol Exp Ther* 1997; **280**: 83 – 97.
 - 21 Colonna L, Saleem P, Dondey-Nouvel L, Rein W and the Amisulpride Study Group: Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. *Int Clin Psychopharmacol* 2000; **15**: 13 – 22.
 - 22 Möller JH, Boyer P, Fleurot O, Rein W, PRO-ASLP Study Group: Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. *Psychopharmacology* 1997; **132**: 396 – 401.
 - 23 Peuskens J, Bech P, Möller HJ, Bale R, Fleurot O, Rein W, *et al*: Amisulpride vs. risperidone in the treatment of acute exacerbations of schizophrenia. *Psychiatry Res* 1999; **88**: 107 – 117.
 - 24 Puech AJ, Fleurot O, Rein W, the Amisulpride Study Group: Amisulpride, an atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. *Acta Psychiatr Scand* 1998; **98**: 65 – 72.
 - 25 Wetzel H, Philipp M, Hillert A, Gattaz WF, Sauer H, Adler G, *et al*: Amisulpride versus flupenthixol in schizophrenia with predominantly positive symptomatology – a double-blind controlled study comparing a selective D₂-like antagonist to a mixed D₁/D₂-like antagonist. *Psychopharmacology* 1998; **137**: 223 – 232.
 - 26 Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F: Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry* 1995; **166**: 68 – 72.
 - 27 Danion JM, Rein W, Fleurot O and the Amisulpride Study Group: Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *Am J Psychiatry* 1999; **156**: 610 – 616.
 - 28 Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O: Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *Br J Psychiatry* 1997; **170**: 18 – 22.
 - 29 Paillère-Martinot ML, Lecrubier Y, Martinot JL, Aubin F: Improvement of some schizophrenic deficit symptoms with low doses of amisulpride. *Am J Psychiatry* 1995; **152**: 130 – 133.
 - 30 American Psychiatric Association (ed): *DSM-III-R*. Washington, DC: American Psychiatric Association, 1987.
 - 31 American Psychiatric Association (ed): *DSM-IV*. Washington, DC: American Psychiatric Association, 1994.
 - 32 Overall JE, Gorham DR: The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; **10**: 799 – 812.
 - 33 Andreasen N, Olsen S: Negative versus positive schizophrenia: definition and validation. *Arch Gen Psychiatry* 1982; **39**: 789 – 794.
 - 34 Kay SR, Fiszbein A, Opler LA: The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261 – 276.
 - 35 Guy W (ed): *ECDEU Assessment Manual for Psychopharmacology*, US DHEW, Washington, DC, 1976.
 - 36 American Psychiatric Association (ed): *General Assessment of Functioning Scale – DSM-III-R*. Washington, DC: American Psychiatric Association, 1987.
 - 37 American Psychiatric Association (ed): *Social and Occupational Functioning Assessment Scale – DSM-III-R*. Washington, DC: American Psychiatric Association, 1994.
 - 38 Heinrichs DW, Hanlon TE, Carpenter WT, Jr: The quality of life scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull* 1984; **3**: 388 – 396.
 - 39 Bech P: Rating scales for affective disorders: their validity and consistency. *Acta Psychiatr Scand* 1981; **295** (Suppl): 64.
 - 40 Simpson G, Angus JA: A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand* 1970; **45** (Suppl 212): 11 – 18.
 - 41 Barnes TRE: A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989; **154**: 672 – 676.
 - 42 National Institutes of Mental Health: Abnormal Involuntary Movement Scale. In: *ECDEU. Assessment Manual for Psychopharmacology*, revised (Guy W, ed). Rockville: National Institute for Mental Health, 1976: pp534 – 537.
 - 43 Arvanitis LA, Miller BG, the Seroquel Trial 13 Study Group: Multiple fixed doses of 'Seroquel' (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry* 1997; **42**: 233 – 246.
 - 44 Beasley CM, Tollefson GD, Tran P, Satterlee W, Sanger T, Hamilton S, *et al*: Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. *Psychopharmacology* 1996; **124**: 159 – 167.
 - 45 Beasley CM, Tollefson GD, Tran P, Satterlee W, Sanger T, Hamilton S, *et al*: Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine

- trial. *Neuropsychopharmacology* 1996; **14**: 105 – 118.
- 46 Chouinard G, Jones B, Remington G, Bloom D, Addington D, MacEwan GW, *et al*: A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. *J Clin Psychopharmacol* 1993; **13**: 25 – 40.
- 47 Marder SR, Meilbach RC: Risperidone in the treatment of schizophrenia. *Am J Psychiatry* 1994; **151**: 825 – 835.
- 48 Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG and the Seroquel study group: Quetiapine in patients with schizophrenia. *Arch Gen Psychiatry* 1997; **54**: 549 – 557.
- 49 van Kammen DP, McEvoy KP, Targum SD, Kardatzke D, Seebree TB, the Sertindole Study Group: A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. *Psychopharmacology* 1996; **124**: 168 – 175.
- 50 Freeman HL: Amisulpride compared with standard neuroleptics in acute exacerbations of schizophrenia: three efficacy studies. *Int Clin Psychopharmacol* 1997; **12** (Suppl 2): S11 – S17.
- 51 Caldwell CB, Gottesman II: Schizophrenia, a high risk factor for suicide: clues to risk reduction. *Suicide and Life-threatening Behavior* 1992; **22**: 479 – 493.
- 52 Coukell AJ, Spencer CM, Benfield P: Amisulpride: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of schizophrenia. *CNS Drugs* 1996; **6**: 231 – 256.
- 53 American Psychiatric Association: Practice guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 1997; **154** (Suppl 4): 1 – 63.

Address for correspondence

Professor T Burns

Department of Psychiatry, St George's Hospital Medical School,
Jenner Wing, Cranmer Terrace, London SW17 0RE, UK.

E-mail: tburns@sghms.ac.uk