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ORIGINAL PAPER

Hans-Jürgen Möller

Amisulpride: efficacy in the management of chronic patients with predominant negative symptoms of schizophrenia

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Abstract Amisulpride is a dopamine D2/D3-selective antipsychotic drug with potent antipsychotic efficacy in acute exacerbations of schizophrenia. It also possesses substantial efficacy in chronic schizophrenic patients with enduring predominant negative symptoms. This unique property has been demonstrated in a series of short (6 weeks) and medium-/long-term (6–12 months) double-blind placebo-controlled studies. The patients in these studies were carefully selected and assessed to avoid confounding results with non-specific changes in other symptom domains. The results not only show effects on negative symptoms at the optimal dose of 100 mg/day, but also significant improvement in global functioning. The effect observed in short-term studies was maintained over longer treatment periods (6–12 months). Amisulpride was well tolerated with a safety profile similar to placebo. These results open a new therapeutic approach for negative symptoms, one of the most disabling aspects of schizophrenia.

Key words Amisulpride · Atypical antipsychotic · Negative symptoms · Placebo · Schizophrenia

Introduction

The human and societal costs of schizophrenia remain substantial. Schizophrenia is a lifelong illness and the lives of the patient, their family and carers can be disrupted for years or decades. The implications of this chronic course on healthcare resources are important: the direct costs of schizophrenia consume significant fractions of the national health budgets in, for example, the UK (1.6%) [14], France (2%) [32], and in the USA (2.5%) [33].

Schizophrenia is conceptualized as a disease process with multiple causal factors, and is characterized by multiple signs and symptoms involving thought, perception, emotion and motor activity. These manifestations combine in various ways, creating considerable diversity among patients. Initial concepts followed a dichotomous model, distinguishing between "positive" (or productive) symptoms such as thought disturbance, hallucinations and delusions and "negative" symptoms such as affective blunting, emotional withdrawal and poverty of speech. To allow a better understanding of the impact of treatment on negative symptoms, they have been further differentiated into primary negative or deficit symptoms, probably linked to the disease process, and secondary, linked to positive symptoms, extrapyramidal side effects, depression or social understimulation [8].

The main characteristics of primary negative symptoms are that they are enduring, cannot be explained by other psychopathological manifestations, they provoke a chronic social handicap and they are not substantially improved by antipsychotics. Secondary negative symptoms are potentially transient and respond to adequate treatment.

The activity of recently developed antipsychotics on negative symptoms has only been demonstrated in studies designed to prove antipsychotic efficacy. The attempts to demonstrate specific activity on "primary" negative symptoms are indirect and have been criticized for methodological reasons [10, 20, 21, 38, 40]. In addition, the recently published CPMP guidelines on drugs for the treatment of schizophrenia explicitly state that efficacy on negative symptoms should be demonstrated in specifically designed studies including patients selected for persistent predominant negative symptoms [12].

Recently, attempts have been made to integrate the existing knowledge on brain circuitry and drug effects on cerebral neurotransmission to build hypotheses on the pathogenesis of the different symptom clusters of

Hans-Jürgen Möller
Department of Psychiatry
University of Munich
Nussbaumstrasse 7
80336 Munich, Germany
Tel.: +49-89/51 60 55 01
Fax: +49-89/51 60 55 22
E-Mail: hans-juergen.moeller@psy.med.uni-muenchen.de

schizophrenia. One of the hypotheses associates persistent negative symptoms with hypodopaminergic transmission [16, 25]. This hypothesis is of particular interest with respect to amisulpride, which has been shown in animal models to increase dopaminergic transmission via its preferential blockade of presynaptic dopamine D2-like receptors. Amisulpride is a substituted benzamide with selective affinity to dopamine D2 and D3 receptors, it also shows a preferential binding to limbic as compared to striatal dopamine receptors [28, 35]. It has no appreciable affinity for other receptors. At high doses, amisulpride exhibits dopaminergic blocking activity similar to that induced by classical antipsychotics, while at lower doses it appears to facilitate dopaminergic transmission through preferential blockade of presynaptic dopamine autoreceptors. This combination of pharmacological properties may account for its atypical profile in animal models, where it shows activating and prohedonic properties at low doses and an absence of cataleptogenic effect at high doses [34].

This atypical profile may also explain the clinical efficacy of amisulpride against acute psychotic symptoms at high doses and predominant negative symptoms at low doses, as well as its low propensity for causing extrapyramidal symptoms [11]. Amisulpride (400–1200 mg/day) has demonstrated similar clinical efficacy to that of haloperidol (15–20 mg/day) [22, 30], flupenthixol (15–25 mg/day) [41] and risperidone (8 mg/day) [29] in the treatment of patients with acute exacerbations of schizophrenia.

At low doses (50–300 mg), amisulpride is more effective than placebo in well-controlled studies of patients with predominant negative symptoms of schizophrenia [7, 13, 19, 27]. The purpose of this review is to present the efficacy and safety data obtained from these trials and that of a fifth study which used haloperidol as an active control in a very chronically ill, hospitalized population [37].

Methods

Study designs

The results of five double-blind, parallel-group studies involving patients with predominant negative symptoms of schizophrenia are discussed. Four trials were placebo-controlled and one was carried-out versus haloperidol (Table 1). Placebo controls were necessary as there is no standard treatment for the negative symptoms of schizophrenia [9, 18, 20]. One of these studies was regarded as a pilot trial as only a small number of carefully selected patients were included [27], while the other three were pivotal for evidence of efficacy in primary negative symptoms [7, 13, 19]; two of the latter explored the dose-response relationship [7, 13].

Amisulpride was administered for periods ranging from six weeks to up to one year (Table 1). Responders in a six-month trial could continue their blinded treatment for up to one year [31]. Amisulpride dose regimens varied from 50 to 300 mg/day and patients in one long-term study received flexible doses of amisulpride (100–1200 mg/day) and haloperidol (3–30 mg/day) [37]. All studies were carried out in accordance with the Declaration of Helsinki and with appropriate Ethics Committee approval. Patients gave written informed consent to participate.

Patients

The overall inclusion criteria for the studies were as follows: in- or outpatients of either sex, adults except for one study [27], diagnosed with schizophrenic disorder as defined either by DSM-III criteria [1, 7, 27] or by DSM-III-R criteria [2, 13, 19, 37]; in the pilot study [27], patients with schizotypal personality disorder could be included: a minimum score over 60 or 75 on the Scale for Assessment of Negative Symptoms (SANS) [3] or a minimum score of 4 on the negative subscale of the Manchester Scale (MS) [17], and a maximum score of 60 on the Scale for Assessment of Positive Symptoms (SAPS) [4] or the presence of minimal positive symptoms assessed on the positive subscale of the MS.

Main exclusion criteria were other DSM-III or DSM-III-R diagnoses capable of producing negative symptoms, clinically significant cardiovascular, renal or liver diseases, Parkinson's disease or phaeochromocytoma, hypersensitivity to the study medication, alcohol or other substance abuse, pregnancy, breast feeding or child-bearing potential.

Table 1 Main characteristics of clinical studies on amisulpride in patients with predominant negative symptoms

Study investigators	Design	Mean duration of illness	No of pts in study	Oral drug doses (mg/day)	Duration
Paillère-Martinot et al. [27], pilot study	DB, PG	2.8 yrs	27	Amisulpride: 50–100 Placebo od	6 wk (neuroleptic-free for 6 m)
Boyer et al. [7]	DB, PG	8.0 yrs	104	Amisulpride: 100, 300 Placebo bid	6 wk (6 wk placebo run-in for patients pretreated with neuroleptics)
Danion et al. [13]	DB, PG	9.5 yrs	242	Amisulpride: 50, 100 Placebo od	3 m (4 wk placebo run-in)
Loo et al. [19]	DB, PG	10.2 yrs	141	Amisulpride: 100 Placebo od	6 m (12 m extension) (no placebo run-in)
Speller et al. [37]	DB, PG	36.7 yrs*	60	Amisulpride: 100–1200 Haloperidol: 3–30 Flexible dose (bid)	12 m (+3 m after neuroleptic withdrawal) (no placebo run-in)

DB double-blind; *PG* parallel-group; *yrs* years; *pts* patients; *od* once daily; *bid* twice daily; *wk* weeks; *m* months
* Median value

Efficacy

The principal evaluation instrument for determining the efficacy of amisulpride on negative symptomatology was the SANS. This is a 25-item scale grouped into five dimensions (affective blunting, alogia, avolition/apathy, anhedonia/asociality, and attentional impairment); each item is scored from 0 (absent) to 5 (severe) [3]. A 30-item variant of SANS was used in the preliminary pilot study [27]. The SAPS, consisting of 34 items measuring four dimensions (hallucinations, delusions, bizarre behavior and positive formal thought disorder) was used to confirm that patients did not have predominant positive symptoms at baseline and that positive symptoms did not relapse during the study period.

Secondary efficacy criteria varied between studies and included the Brief Psychiatric Rating Scale (BPRS) [26], the Montgomery-Åsberg Depression Rating Scale (MADRS) [23], the Clinical Global Impressions (CGI) scale [15], and the MS and the Global Assessment of Functioning scale (GAF [2]).

Safety

Safety was evaluated in two studies [7, 13] using open reporting of adverse events, while checklists were employed in three trials [19, 27, 37] and laboratory tests in three [13, 19, 37].

Extrapyramidal symptoms were assessed using rating scales in four studies [7, 13, 19, 37], i. e., a 13-item extrapyramidal symptom scale, the Simpson-Angus Scale (SAS [36]), the Webster scale [39], the Barnes Akathisia Scale (BAS [6]) and Tardive Dyskinesia Scale [5], and the Abnormal Involuntary Movement Scale (AIMS [24]).

Statistics

The main efficacy criterion was the change from baseline in SANS total score. Four studies performed an intention-to-treat analysis of efficacy that included all randomized patients who had at least one available treatment evaluation [7, 13, 19, 37]. In the pilot trial, the analysis was performed on the evaluable patient group (last observation carried forward for those patients remaining in the trials for more than three weeks) [27].

The SANS data from the three pivotal placebo-controlled studies with similar designs were compared [7, 13, 19]. The difference between amisulpride and placebo (mean change in SANS total score) and the 95 % CI were calculated.

In the pilot study, the Mann-Whitney U test was used for quantitative variables [27]. Other studies used ANOVA, MANOVA, the two-sample t-test, chi-square test or Wilcoxon test for quantitative data [7, 13, 19, 37]. For categorical or ordinal data the Cochran-Mantel-Haenszel test, Fisher's exact test or the chi-square test was used [13, 19, 27, 37].

Results

Patient population

A total of 575 patients (385 male and 190 female) with predominant negative symptoms of schizophrenia were included in the five studies (Table 2). Of these, 342 (59 %) received amisulpride, 202 (35 %) placebo, and 31 (5 %) haloperidol. The population demographics was representative for schizophrenia (mean age 36.3 years, 67 % male). The type of schizophrenia was mainly the residual type.

The pilot study included young, neuroleptic-naive patients [27] in contrast to the long-term study which recruited chronically hospitalized patients who tended to be older (mean age: 64 years in the amisulpride group and 61 years in the haloperidol group) [37]. Hospitalized patients were included in three studies [7, 27, 37], and either in- or outpatients suffering from chronic illness in two others [13, 19].

Table 2 Patient characteristics by treatment group in five amisulpride trials

Parameter	Placebo	Amisulpride	Haloperidol	Total
No. of pts	202	342	31	575
Mean age ± SD and range (years)	33.6 ± 10.1 (15–66)	35.7 ± 12.6 (15–75)	61.0 ± 10.8 (35–76)	36.3 ± 13.1 (15–76)
Age groups (% pts)				
15–17	6 (3)	6 (2)	–	12 (2)
18–49	178 (88)	290 (85)	4 (13)	472 (82)
50–64	17 (8)	32 (9)	14 (45)	63 (11)
65–76	1 (0)	13 (4)	13 (42)	27 (5)
Male/female gender (%)	136/66 (67/33)	223/119 (65/35)	26/5 (84/16)	385/190 (67/33)

pts patients

Eleven patients dropped out in the 6-week pilot study due to lack of efficacy (three and six patients receiving placebo and amisulpride, respectively) or adverse events (two in the placebo group) [27]. Nineteen patients (18 %) dropped out of another short-term trial: four receiving 100 mg amisulpride (two due to worsening of symptoms, two for other reasons), six receiving 300 mg amisulpride (two due to worsening of symptoms, four for other reasons) and nine in the placebo group (six worsening of symptoms, one due to onset of mixed symptoms, two for other reasons) [7]. More drop-outs occurred in the 3-month trial with placebo than with either amisulpride dose (10 placebo patients vs 8 and 7 in the 50 mg and 100 mg amisulpride groups, respectively) [13]. In the 6-month study, the difference in drop-out rate between amisulpride and placebo was found to be significantly lower in the amisulpride group after three months' treatment (29 % vs 57 %, $p < 0.01$) and persisted at six months (45 % vs 68 %, $p < 0.01$), the main reason for drop-out being lack of efficacy [19]. In the one-year comparison with haloperidol in chronically-ill patients, five and seven patients in the amisulpride and haloperidol groups dropped out, respectively; the most frequent reason was EPS which occurred in four patients receiving haloperidol [37].

Efficacy

Placebo-controlled studies

The SANS total scores from the three pivotal placebo-controlled studies were compared. The difference between amisulpride and placebo (mean change from baseline to endpoint) and the corresponding 95 % CI are shown in Fig. 1. The mean SANS total scores from the individual studies are listed in Table 3. The severity of the negative symptoms at baseline was shown by scores that varied from 73.5 to 97.9. The improvement in negative

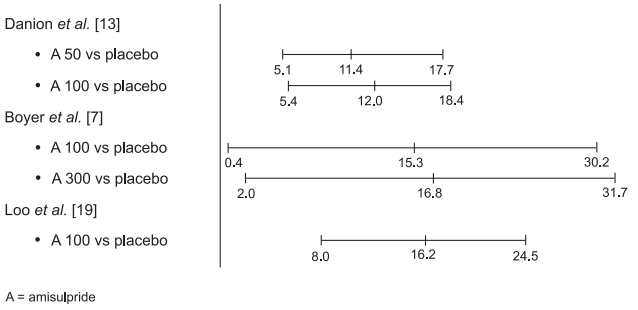

Fig. 1 Difference in mean SANS changes at endpoint and 95 % CI from the three pivotal placebo-controlled studies

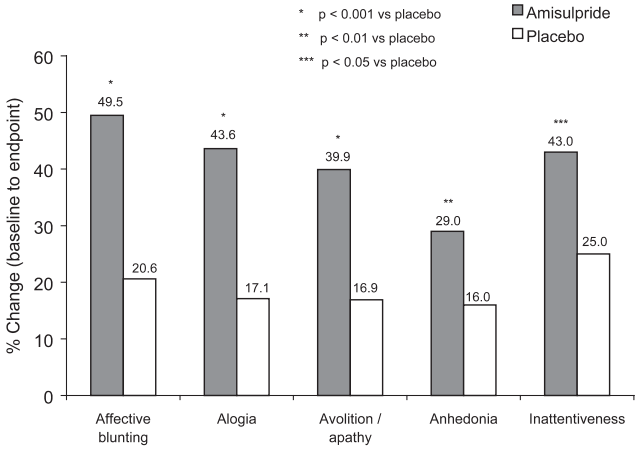

Fig. 2 Effect of amisulpride and placebo on SANS subscores after 6 months treatment [19]

symptom scores was substantial with amisulpride (mean change of 24 to 40 points) compared with placebo (6 to 22 points) and statistically significant ($p < 0.02$) in the three pivotal trials [7, 13, 19] (Table 3). The change in SANS score approached significance in the pilot study ($p = 0.056$) [27].

There was only a minor dose-response effect with no substantial difference between doses (50, 100 and 300 mg/day); evaluation of the overall therapeutic benefit of different doses of amisulpride on negative symptoms suggested that the optimal dose was 100 mg/day.

Analysis of subscores in one long-term study showed that amisulpride significantly ($p < 0.05$) improved all SANS factors compared with placebo (Fig. 2) [19]. Similar findings were observed in one dose-finding study ($p \leq 0.01$) [13]. Significant differences between amisulpride and placebo were also noted in three out of five SANS factors in a six-week trial (alogia, avolition/apathy, attentional impairment; $p < 0.05$) [7], and two out of five factors in the pilot trial (avolition/apathy and attentional impairment; $p < 0.05$) [27].

Positive symptoms measured by SAPS total scores were of a low intensity at baseline in all four placebo-controlled studies ranging from 1.4 to 9.4 in amisulpride-treated patients, and 0.1 to 3.0 in placebo-treated patients [7, 13, 19, 27]. The change from baseline to endpoint after amisulpride treatment was small and not significantly different from placebo in three studies (Table 4) [7, 19, 27]. In one dose-finding study, positive symptoms decreased in the 100 mg amisulpride group and increased in the placebo group, resulting in a significant difference (Table 4).

Secondary efficacy measures confirmed the benefit of amisulpride in negative schizophrenia. The responder rates (CGI improvement) were significantly higher in amisulpride-treated patients in two studies: 49 % vs 52 % vs 20 % ($p < 0.0001$) for amisulpride 50 mg, 100 mg, and placebo, respectively [13]; and 46 % with amisulpride 100 mg/day vs 15.5 % with placebo ($p < 0.001$) [19]. Pa-

Table 3 SANS total scores (evaluable patients*, ITT analysis**, or efficacy population***) in individual double-blind amisulpride trials

Trial and daily dosage	Mean SANS[1] total score±SD				Significance
	n	Baseline	Endpoint	Change in score	
Amisulpride vs placebo					
Paillère-Martinot et al. [27], *pilot study*					
A 50 or 100 mg/day*	10	74.9±16.4	50.9±20.2	−24.0±21.3	–
Placebo*	10	73.5±9.8	67.5±17.1	−6.0±14.7	A vs pla: p=0.056
Boyer et al. [7]					
A 100 mg/day**	34	97.5	59.8	−37.7	–
A 300 mg/day**	36	97.9	57.8	−40.1	
Placebo**	34	96.0	73.6	−22.4	A vs pla: p<0.02
Danion et al. [13]					
A 50 mg/day**	84	76.3±10.7	51.5±23.1	−24.8±19.2	
A 100 mg/day**	74	77.6±12.0	52.1±21.7	−25.4±19.1	
Placebo**	83	74.9±12.4	61.5±24.1	−13.4±23.2	A vs pla: p=0.0002
Loo et al. [19]					
A 100 mg/day**	69	81.9±13.4	48.4±27.0	−33.5±26.2	
Placebo**	71	81.5±13.7	64.8±26.1	−16.7±25.2	A vs pla: p<0.0002
Amisulpride vs haloperidol					
Speller et al. [37]					
A 100–1200 mg/day***	28	81.3±24.1	80.3±30.9	−0.9±17.8	
H 3–30 mg/day***	26	88.0±28.5	90.3±28.7	+2.3±26.3	A vs H: ns

A amisulpride; *H* haloperidol; *pla* placebo; *ns* not significant

[1] 25-item scale except for Boyer et al. (30-item)

Table 4 Change in SAPS scores from baseline-endpoint (evaluable patients*, ITT analysis**) in four placebo-controlled amisulpride trials

Trial and daily dosage	n	Change in SAPS[1] score±SD	Significance
Paillère-Martinot et al. [27], *pilot study*			
A 50 or 100 mg/day*	10	−3.6±9.2	
Placebo*	10	−3.5±7.8	A vs pla: ns
Boyer et al. [7]			
A 100 mg**	34	−9.4	–
A 300 mg**	36	−7.6	
Placebo**	34	−2.6	A vs pla: ns
Danion et al. [13]			
A 50 mg**	84	+0.6±15.2	
A 100 mg**	74	−2.5±15.1	
Placebo**	83	+5.8±17.9	A vs pla: $p < 0.01$
Loo et al. [19]			
A 100 mg/day*	69	−1.7±22.4	
Placebo*	71	−0.1±16.8	A vs pla: ns

A amisulpride; *pla* placebo; *ns* not significant
[1] 25-item scale except for Boyer et al. (30-item)

tients tended to have low baseline MADRS scores and improvements with amisulpride were generally small [13, 27] but statistically significant: the change in MADRS score from baseline to endpoint was −4.1±8.5 with 50 mg/day amisulpride; −3.3±7.9 with 100 mg/day amisulpride; and +0.4±8.9 with placebo ($p < 0.01$ amisulpride vs placebo) [13]. A similar pattern was found with the BPRS score, the change being −4.8±12.4 with 50 mg/day amisulpride, −7.4±12.1 with 100 mg/day amisulpride; and +1.1±14.8 with placebo ($p < 0.001$ amisulpride vs placebo) [13]. Patient functioning improved significantly more with amisulpride than placebo; the changes in GAF score was +11.5±19.7 with amisulpride (100 mg/day) and +4.6±15.7 with placebo ($p < 0.05$) [19].

Long-term studies

Forty-five patients entered an extension phase of six months following an initial double-blind period of six months [19]. Clinical improvement was maintained with amisulpride; SANS total scores in the amisulpride group at six and 12 months were 27.2±13.5 and 26.2±13.4; the corresponding scores in the placebo group were 46.9±22.7 and 52.4±21.7, respectively. Positive symptoms (mean SAPS total score) remained low with amisulpride (7.2±6.8 and 7.8±10.7 at 6 and 12 months) and increased with placebo (16.7±17.8 and 25.2±20.3 at 6 and 12 months) [31].

Negative symptomatology was severe in the highly chronic long-stay patients study [37]; SANS total scores were over 80 at baseline in both treatment groups while positive symptoms were relatively mild at the same time point (BPRS total score between 16 and 18). Seventeen patients in each group received low dose levels at baseline (< 150 mg amisulpride and < 4.5 mg haloperidol daily); low doses were maintained in 76 % of patients receiving amisulpride and 58 % receiving haloperidol. Amisulpride showed a small but consistent improvement of negative symptoms as demonstrated by the change in SANS total score from baseline to endpoint (Table 3). Amisulpride-induced changes in two of the SANS factors (affective flattening and avolition/apathy) approached statistical significance compared with haloperidol ($p = 0.07$ and $p = 0.08$, respectively) and, overall, the improvement in factor scores (baseline to endpoint) were greater with amisulpride than haloperidol. Both treatments were effective in controlling positive symptoms; psychotic exacerbations leading to a dose increase occurred in five amisulpride-treated patients (18 %) and nine haloperidol-treated patients (35 %). Positive symptoms measured on the MS decreased slightly from a low baseline (mean change from baseline to endpoint: −0.21±2.3 with amisulpride vs +0.38±2.3 with haloperidol) and the same pattern was shown with changes in MADRS scores (mean change from baseline to endpoint: −0.57±3.4 with amisulpride and +1.75±9.4 with haloperidol) [37].

Safety

Treatment-emergent adverse events

Amisulpride was very well tolerated in patients with negative symptoms; the most frequently reported events were CNS-related including insomnia, tremor and anxiety. The proportion of patients with at least one treat-

Table 5 Treatment-emergent adverse events, EPS and endocrinological symptoms

Study	n	Event		
		% pts with ≥ 1 treatment-emergent AE	% pts with ≥ 1 EPS	% pts with ≥ 1 endocrinological symptom
Amisulpride vs placebo				
Paillère et al. [27]**, *Pilot study*				
A 50 or 100 mg/day	14	86	86	0
Placebo	13	85	38	8
Boyer et al. [7]*				
A 100 mg/day	34	26	13	0
A 300 mg/day	36	47	13	0
Placebo	34	35	0	0
Danion et al. [13]*				
A 50 mg/day	84	25	6	2
A 100 mg/day	76	24	4	0
Placebo	83	33	2	0
Loo et al. [19]**				
A 100 mg/day	69	59	6	5
Placebo	72	46	3	0
Amisulpride vs haloperidol				
Speller et al. [37]**				
A 100–1200 mg/day	29	48	21	0
H 3–30 mg/day	31	77	52	0

AE adverse event; *pts* patients; *A* amisulpride; *H* haloperidol
* Open reporting of adverse events
** Use of checklists

ment-emergent adverse event, EPS or endocrinological symptom are shown in Table 5. In the placebo-controlled studies, adverse events were noted with a comparable frequency [27], a lower frequency [13], and a higher frequency [19] in amisulpride-treated compared with placebo-treated patients, suggesting that there was no consistent difference in the profile between amisulpride and placebo. The number of patients having experienced EPS is comparable in the amisulpride and placebo treatment groups, but more subjects receiving haloperidol experienced treatment-emergent adverse events and EPS. Endocrine symptoms (amenorrhea) were reported in four out of 23 female patients receiving amisulpride in one trial [19].

Amisulpride produced no consistent effect on weight: there was a small increase compared with baseline in patients receiving 100 mg/day amisulpride [13, 19] or no difference compared with placebo [27]; and a decrease in weight with both amisulpride and haloperidol [37].

Standard rating scales

The results of specific assessments of EPS using standard rating scales are shown in Table 6. There was no significant difference between amisulpride and placebo when parkinsonism was assessed with the 13-item parkinsonism scale although scores were low at baseline; however, the proportion of patients requiring antiparkinsonian medication was slightly higher in the placebo group compared with the two amisulpride groups (9 % vs 7 %) [7]. Parkinsonism scores assessed by the SAS were low at baseline in one trial and remained low at endpoint with no significant difference between the three groups; similar non-significant differences were seen for tardive dyskinesia assessed by AIMS [13]. In addition, there was no significant change in parkinsonism score evaluated on the Webster scale during treatment and, in the same trial, no significant change in BAS akathisia or AIMS tardive dyskinesia scores [19]. In the pilot study which did not use rating scales, EPS were present in many patients (56 %) at baseline and a slightly higher incidence was noted with amisulpride (12 out of 14 patients) compared with placebo (5 out of 13 patients) at endpoint. However, the severity was rated very mild and did not lead to prescription of antiparkinsonian drugs or premature discontinuation [27].

In the long-term comparison of amisulpride and haloperidol, the only significant difference in terms of EPS was a higher global assessment rating of parkinsonism (baseline to endpoint) in the haloperidol-treated group as measured by SAS score ($p < 0.01$) [37]. More patients in the haloperidol group received antiparkinsonian drugs than those in the amisulpride group (84 vs 52 %). Sixteen patients (seven receiving amisulpride, nine receiving haloperidol) entered a withdrawal phase after one year's treatment: tardive dyskinesia (AIMS) scores increased in the haloperidol group but remained unchanged in the amisulpride group indicating a lack of rebound tardive dyskinesia after treatment withdrawal [data on file].

Discussion

Enduring predominant negative symptoms are a major problem in the treatment of schizophrenic patients as they induce substantial social and functional handicap in the long run. Until now drug treatment, including the recently developed antipsychotics, yielded equivocal results. This was mainly due to methodological bias such as inadequate patient selection and non-confirmatory, secondary analyses of studies only designed and powered to prove antipsychotic efficacy [21, 38, 40].

To date, amisulpride is the only antipsychotic to have been investigated for the treatment of predominant negative symptoms in patients with schizophrenia. The studies were specifically designed to assess the direct effect of amisulpride on these enduring negative symptoms and to avoid confounding non-specific effects due to change in other symptom domains such as positive symptoms, depression or parkinsonism. The drug has been used in four placebo-controlled trials and one comparison versus haloperidol. There is unequivocal and substantial evidence that amisulpride is effective in the management of predominant negative symptoms in

Table 6 Effect of treatment on measures of EPS

Trial and daily dosage	Mean score ± SD				Significance
	n	Baseline	Endpoint	Change in score	
Boyer et al. [7]	**Extrapyramidal symptom scale total score**				
A 100 mg/day	34	7.0	6.2	n/c	
A 300 mg/day	36	9.1	5.2	n/c	
Placebo	34	9.2	7.0	n/c	A vs pla: ns
Danion et al. [13]	**SAS total score**				
A 50 mg/day	84	0.2±0.4	0.1±0.3	0.1±0.2	
A 100 mg/day	74	0.3±0.4	0.2±0.3	0.1±0.3	
Placebo	83	0.2±0.4	0.1±0.3	0.1±0.3	A vs pla: ns
Loo et al. [19]	**Webster scale score**				
A 100 mg/day	69	3.8±5.0	2.4±4.0	n/c	
Placebo	71	31.1±3.0	2.4±3.9	n/c	A vs pla: ns

A amisulpride; *pla* placebo; *ns* not significant; *n/c* not calculated

the selected populations as shown by improvements in the SANS total scores from baseline to study endpoint and statistically significant differences compared with placebo in three of the placebo-controlled trials [7, 13, 19]. The factors which comprise the SANS were also significantly improved with amisulpride compared with placebo [7, 19, 27]. The clinical improvement produced by amisulpride was maintained for periods of up to one year, even in chronically hospitalized patients [37], and the benefit was not associated with any psychotic rebound or relapse. An added benefit was that patient functioning was significantly increased with amisulpride compared with placebo [19]. This shows that the improvement in negative symptoms has direct effects on social functioning.

Patients were carefully screened before receiving treatment to ensure the predominance of negative symptoms and minimal positive symptoms. The severity of negative symptoms was confirmed by baseline SANS total scores which ranged between approximately 70 and 100. At baseline, positive symptoms were of a low intensity in all studies as measured by SAPS and BPRS total scores, and amisulpride produced little effect on these ratings. Thus, it can be concluded that the amisulpride-induced improvement in negative symptoms was not linked to any change in positive symptoms.

The ratings obtained from the MADRS suggest that amisulpride improved symptoms of depression significantly compared with placebo, although the baseline scores were low and, as a consequence, the changes were relatively small [13, 27].

Furthermore, the effects of treatment on ratings of EPS (e. g., SAS, 13-item parkinsonism scale, Webster scale) did not show any significant differences between amisulpride and placebo, thereby confirming that the changes in EPS cannot account for the differences in improvement in negative symptoms.

Importantly, amisulpride was also effective against negative schizophrenia in young patients who were neuroleptic naive (or those who had been neuroleptic free for a considerable period) suggesting that the drug may have a useful role in treating the early stages of schizophrenia.

The question as to what is the optimum dose of amisulpride was addressed in two dose-finding studies [7,13]. Amisulpride was found to be effective at doses of 50, 100 and 300 mg/day. Based on the overall results, it can be concluded that 100 mg/day is the optimum dose as 300 mg/day did not produce an additional benefit on SANS scores [7]. Data from one of the studies in negative schizophrenia also suggested that the use of 100 mg/day amisulpride offered some protection against the re-emergence of positive symptoms [27].

The atypical neuroleptic drug, amisulpride, is very well tolerated in patients with negative symptoms and the safety profile is not consistently different from placebo. Amisulpride was less likely to induce parkinsonism or require the concomitant use of antiparkinsonian medication than haloperidol in long-term use.

Conclusion

This existing body of data shows that amisulpride, at the optimal dose of 100 mg/day, has a unique therapeutic potential for the treatment of chronic schizophrenic patients with predominantly negative symptoms. An added benefit is that patient functioning is significantly increased with amisulpride.

Amisulpride can be considered as an important therapeutic tool in the treatment of the most disabling aspect of the disease.

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