HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2011; **26**: 568–577.
Published online 2 December 2011 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.1246

The acute and long-term effectiveness of amisulpride in patients with schizophrenia: results of a 12-month open-label prospective follow-up study

Yong Min Ahn[1], Kyu Young Lee[2], Chul-Eung Kim[3], Dae-Yeob Kang[4], Jeong-Ho Seok[5], Young Min Shin[6], In-Won Chung[7], Tae-Youn Jun[8], Jae Seung Chang[9] and Yong Sik Kim[1]*

[1]*Department of Psychiatry and Behavioral Science and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea*
[2]*Department of Neuropsychiatry, Eulji University School of Medicine, Eulji General Hospital, Seoul, Korea*
[3]*Department of Psychiatry, Inha University College Medicine, Incheon, Korea*
[4]*Department of Psychiatry, Yong-In Mental Hospital, Yong-In, Korea*
[5]*Department of Psychiatry, Hallym Sacred Heart Hospital, Hallym University College of Medicine, Gyeonggi-do Korea*
[6]*Department of Psychiatry, Seoul Bukbu Geriatric Hospital 48, Seoul, Korea*
[7]*Department of Psychiatry, Dongguk University College of Medicine, Dongguk University International Hospital, Gyeonggi-do Korea*
[8]*Department of Psychiatry, St. Mary's Hospital, The Catholic University, Seoul, Korea*
[9]*Department of Psychiatry, Seoul National University Bundang Hospital, Gyeonggi-do Korea*

Objective To compare the effectiveness of amisulpride in acute (up to 8 weeks) and maintenance (week 8 to 12 months) phases of a 12-month course of treatment in a heterogeneous group of patients with schizophrenia.
Methods We conducted a 12-month, open-label clinical trial with flexible doses of amisulpride among 129 Korean patients with schizophrenia. The Positive and Negative Symptom Scale (PANSS) and several other scales measuring efficacy and tolerability were analyzed during the acute and maintenance phases.
Results The completion rates were 78.3% by week 8 and 55.8% by month 12. Total PANSS scores and scores on the negative-symptom and general-symptom subscales improved significantly during both acute and maintenance periods, but scores on the positive-symptom subscale improved only during the acute phase. Improvement during both treatment phases was significant in all other scales except for the Drug Attitude Inventory. The negative-symptom and mixed-symptom groups showed significant improvement in the PANSS negative subscale, the Clinical Global Impression scale, and the Global Assessment of Functioning during the maintenance period. Hyperprolactinemia and related events were commonly reported.
Conclusions This study demonstrated the significant effectiveness and a good safety profile of amisulpride for treating acute and 12-month phases of schizophrenia under natural conditions. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—amisulpride; acute effectiveness; long-term effectiveness; Korean; schizophrenia; open label

INTRODUCTION

Clinical appraisals of amisulpride indicate a significant effectiveness for both positive and negative symptoms with a low propensity to cause extrapyramidal adverse effects compared with conventional agents (McKeage and Plosker, 2004; Kahn *et al*., 2008; Mortimer, 2009); this characterizes amisulpride as an atypical antipsychotic. Its neurotransmitter receptor binding profile is unique and differs from many other atypical antipsychotics for which atypicality is believed to rely mainly on combined 5-HT_2-D2 antagonism. The atypicality of amisulpride could result from its preferential limbic affinity to D2/D3 receptors (Möller, 2003), high D2 fast-off coefficient, and blocking of presynaptic D2/D3 receptors (Kapur and Seeman, 2001; Meisenzahl *et al*., 2008). By selectively blocking presynaptic D2/D3 prefrontal receptors, low doses of amisulpride appear to enhance dopamine transmission, thereby possibly improving negative symptoms. Higher dosages can antagonize postsynaptic D2/D3 receptors, inhibiting dopamine transmission and be associated

*Correspondence to: Y. S. Kim, Department of Psychiatry and Institute of Human Behavioral Medicine, Seoul National University College of Medicine, 28 Yongon-Dong, Chongro-Gu, Seoul 110-799, Korea. Tel: +82 2 760 2204; Fax: +82 2 744 7241. E-mail: kys@snu.ac.kr
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Received 20 June 2010
Revised 20 July 2011
Accepted 11 October 2011

with a significant improvement in positive symptoms (Kerwin, 2000; Möller, 2003).

High-dose amisulpride demonstrates similar efficacy to that of haloperidol, risperidone, and olanzapine for treating positive symptoms in positive-symptom-predominant patients with schizophrenia, whereas a low dose improves negative symptoms to a greater extent than conventional antipsychotics (McKeage and Plosker, 2004; Mortimer, 2009). These findings support the recommendation by Sanofi-Aventis for an oral dosage of 400–800 mg/day (maximum 1200 mg/day) for an acute psychotic episode with positive symptoms and a dosage of 50–300 mg/day for patients with predominantly negative symptoms (Sanofi-Aventis, 2007).

To date, the majority of existing clinical trials have demonstrated the effectiveness of amisulpride for positive or negative symptoms, enrolling patients with predominantly either positive (Wetzel *et al*., 1998; Martin *et al*., 2002; Mortimer *et al*., 2004) or negative (Boyer *et al*., 1995; Loo *et al*., 1997; Speller *et al*., 1997; Olié *et al*., 2006) symptoms in relatively short-term studies. However, the applicability of these results may be problematic as the separation between positive-predominant versus negative-predominant patients and acute versus chronic patients is more difficult in clinical practice. In this regard, a study was needed to provide information about the effectiveness and dosages of amisulpride in patients presenting heterogeneous manifestations of schizophrenia.

Most patients with schizophrenia generally suffer from acute psychotic episodes (mainly positive symptoms) interspersed with more stable periods of partial remission in which remission is mainly conditioned by negative symptoms and cognitive impairment (Tandon *et al*., 2000). In addition, some atypical antipsychotics such as clozapine exert a delayed effectiveness associated more with the improvement of negative or cognitive symptoms rather than with the control of positive symptoms (Weiden *et al*., 1998). Delayed effectiveness is thus closely related to long-term prognosis as assessed by measuring a patient's social functioning, subjective satisfaction, and drug attitude. However, few open-label studies have reported the long-term effectiveness of amisulpride in patients with first-episode (Kahn *et al*., 2008) and chronic or subchronic schizophrenia (Colonna *et al*., 2000).

The present study describes a 1-year follow-up of a heterogeneous population of patients having schizophrenia treated with a flexible dosage of amisulpride. Clinical assessment was performed during acute and maintenance treatment with the Positive and Negative Syndrome Scale (PANSS), the Clinical Global Impression—Severity scale (CGI-S), the Global Assessment of Functioning (GAF), the Subjective Well-being under Neuroleptics (SWN) measure, and the Drug Attitude Inventory (DAI). Additionally, safety measures were assessed with the Liverpool University Neuroleptic Side-effect Rating Scale (LUNSERS), with the Drug-induced Extrapyramidal Symptoms Scale (DIEPSS), and with laboratory tests measuring such factors as metabolic parameters.

METHODS

Study population

The subjects included in this study were the same inclusion and exclusion criteria as in our previously reported studies (Ahn *et al*., 2009; Hwang *et al*., 2009). Inpatients and outpatients (DSM-IV criteria for schizophrenia or schizophreniform disorder) aged 18–65 years were enrolled at seven sites throughout Korea. Inclusion criterion required the introduction of antipsychotic treatment or switching of antipsychotics to treat an acute psychotic episode for whatever reason (treatment discontinuation, adverse side effects of their current medication, insufficient treatment effectiveness, or any other reason). The exclusion criteria included patients with a psychotic disorder other than schizophrenia or schizophreniform disorder (e.g., schizoaffective disorder) and patients with medical problems contraindicating amisulpride such as a prolactin-dependent tumor, pheochromocytoma, hypersensitivity to metabolites of amisulpride, severe bradycardia, hyperkalemia, or an elongated QT interval in a laboratory test and electrocardiogram. Pregnant or breast-feeding women, patients with clinically significant medical or neurological conditions, and patients refractory to previous treatment (lack of effectiveness to more than two different types of antipsychotic agents for more than 8 weeks) were also excluded.

All participants provided written informed consent prior to enrollment in this study, which was approved by the institutional review board of the participating centers according to local legislation and conducted in accordance with the most recent version of the Declaration of Helsinki.

Amisulpride treatments and other interventions

The amisulpride treatment dosage recommendation is the use of a high dose (400–800 mg/day, maximum to 1200 mg/day) for positive symptoms and a low dose (50–300 mg/day) for negative symptoms. However, clinician judgment was ultimately recommended (50–1200 mg/day) to best mimic real-life clinical

DOI: 10.1002/hup

practice. In cases in which a previous antipsychotic agent had already been prescribed, a temporary amisulpride crossover co-treatment was allowed for the first week of the trial. Benzodiazepines (diazepam [≤40 mg/day], oxazepam [≤150 mg/day], and lorazepam [≤7.5 mg/day]), zolpidem, zopiclone, antiparkinson drugs, and other drugs were also allowed for anxiety, insomnia, behavioral problems, and extrapyramidal symptoms, respectively. However, psychotropic medications such as other antipsychotics, antidepressants, mood stabilizers, and levodopa were not permitted during the study.

Assessments

The primary effectiveness measures were the total score and the positive-symptom and negative-symptom subscale scores of the PANSS. The secondary effectiveness measures were the CGI, GAF, 20-item SWN, and 10-item DAI. The standardized Korean version of PANSS, SWN, and DAI were used in this study (Yi *et al*., 2001; Yoon *et al*., 2005; Kim *et al*., 2007). Scores from the PANSS and CGI were assessed at baseline; weeks 1, 2, 4, and 8; as well as at months 4, 8, and 12. The GAF, SWN, and DAI were assessed at baseline, week 8, and the 12-month endpoint.

We assessed the LUNSERS in terms of its ability to quantify subjective tolerability (Day *et al*., 1995; Morrison *et al*., 2000; Jung *et al*., 2005) and the DIEPSS in terms of its ability to evaluate the global severity of EPS; both were evaluated as measures of safety (Inada. 1996; Kim *et al*., 2002). We also performed laboratory tests (including serum prolactin levels) and checked body weight and body mass index (BMI).

Statistical analysis

All effectiveness analyses were performed on the modified intent-to-treat (ITT) population and with the Last Observation Carried Forward method because of the exclusion of five patients who withdrew before the post-baseline evaluation. Two time-frame periods were considered during the study: the acute treatment phase started from baseline and ended at week 8; the maintenance phase lasted from week 8 to the 12-month endpoint. Primary effectiveness measures were changes in the PANSS total score and in the positive and negative subscale scores of all ITT patients; these were analyzed by a paired *t*-test during the acute and maintenance phases. Changes in scores on the CGI-S, GAF, SWN, and DAI were assessed as those used for the primary effectiveness measures.

All patients were classified into the three groups (positive-symptom, negative- symptom, and mixed-symptom subgroups) by their PANSS composite scores for the subgroup analysis (Kay, 1991; Mattson *et al*., 1997; Cavallaro *et al*., 2001), which was calculated by subtracting the negative-symptom subscale score from the positive-symptom subscale score obtained at baseline. A patient with a score of <-3 was included in the negative-symptom group, and those with scores of $>+3$ were included in the positive-symptom group. The mixed-symptom group included patients who had PANSS composite scores between -3 and +3. Effectiveness and changes in the scores for the depression factor in the PANSS five-factor model developed by Lindenmayer *et al*. (1994) were assessed and compared for each of the three groups during the acute and maintenance treatment phases by a paired *t*-test. Defining response as a ≥20% reduction in baseline PANSS total scores, we performed a one-way analysis of variance (ANOVA) on the clinical characteristics of early, late, and non-responders (early: at week 2; late: at 1 year). The amisulpride dosage prescribed for the three groups was evaluated by a repeated-measures ANOVA based only on the observed cases. Measures of safety including the DIEPSS, the LUNSERS, and the laboratory test results were analyzed using a paired *t*-test including changes at each treatment phase. All tests were performed using two-tailed probabilities with a significance level set at 0.05.

RESULTS

Subject characteristics

In total, 134 patients were enrolled, but five patients were excluded from the ITT analysis because they withdrew before the post-baseline evaluation. The baseline demographic and clinical characteristics are presented in Table 1. The mean age was 33.4 years, and the mean age at onset was 26.6 years. About 72% of patients were hospitalized. The mean duration of illness was 82.1 months. The mean baseline total scores for the PANSS (80.8 ± 17.0) and the CGI-S (4.36 ± 1.0) showed a relatively wide range of baseline symptom severity.

No significant differences existed in most baseline demographic and clinical characteristics among the positive-symptom, negative-symptom, and mixed-symptom groups (Table 1). The paranoid schizophrenia subtype was the most common in all three groups, although the undifferentiated subtype was also common in the negative-symptom groups. The scores for the total PANSS, PANSS general subscale, CGI-S, GAF, total SWN, and DAI were very similar in the three groups; the exceptions to this homogeneity were the scores on the PANSS positive and negative scores.

DOI: 10.1002/hup

Table 1. Baseline clinical and demographic characteristics of the subjects

	Total ($n=129$)	Positive-symptom group ($n=26$)	Negative-symptom group ($n=52$)	Mixed-symptom group ($n=51$)
Demographic variables				
Gender, male/female, *n*	63/66	11/15	26/26	26/25
Age, years	33.4 ± 9.3	31.6 ± 7.7	34.1 ± 9.5	33.6 ± 9.8
Education, years	12.5 ± 2.9	12.5 ± 2.5	12.5 ± 2.9	12.6 ± 3.1
Past history variables				
Age at onset of symptoms, years	26.6 ± 8.0	24.5 ± 6.5	26.7 ± 8.0	27.7 ± 8.8
Hospitalization at enrollment, y/n, *n*	93/36	17/9	40/12	36/15
Frequency of hospitalization, *n*	2.9 ± 3.3	2.7 ± 1.8	3.5 ± 4.7	2.4 ± 1.6
Duration of illness, months	82.1 ± 80.8	87.6 ± 81.8	88.4 ± 85.7	72.9 ± 75.9
Antipsychotic medication history, y/n, *n**	117/12	22/4	51/1	44/7
Schizophrenia subtypes, *n**				
Paranoid type	80	22	25	33
Disorganized type	2	0	2	0
Undifferentiated type	40	3	21	16
Residual type	7	1	4	2
Baseline symptom variables				
PANSS total score	80.8 ± 17.0	78.7 ± 17.3	80.4 ± 15.8	82.4 ± 18.3
Positive subscale score***	19.8 ± 5.8	24.0 ± 5.7	16.4 ± 4.2	21.2 ± 5.3
Negative subscale score***	21.7 ± 6.1	16.0 ± 4.9	25.0 ± 5.2	21.2 ± 5.3
General subscale score	39.2 ± 8.4	38.3 ± 8.2	39.0 ± 8.0	40.0 ± 9.0
CGI-S score	4.36 ± 1.04	4.58 ± 1.17	4.27 ± 0.97	4.33 ± 1.03
GAF score	43.1 ± 13.6	42.9 ± 14.8	44.4 ± 12.8	41.8 ± 14.0
SWN total score	72.7 ± 14.9	75.8 ± 18.4	71.3 ± 15.2	72.5 ± 12.6
DAI score	1.2 ± 5.0	1.2 ± 4.9	1.5 ± 4.6	0.9 ± 5.4

PANSS, Positive and Negative Symptom Scale; CGI-S, Clinical Global Impression—Severity; GAF, Global Assessment of Function; SWN, Subjective Well-being under Neuroleptics; DAI, Drug Attitude Inventory.
*$p < 0.05$.
**$p < 0.001$.
***$p < 0.005$.

The numbers of patients who fully completed the trial by week 8 and month 12 were 101 (78.3%) and 72 (55.8%), respectively. No significant differences in completion rates were observed among the positive-symptom, negative-symptom, and mixed-symptom groups (Table 2).

Prescribed dose of amisulpride

The prescribed doses in the observed cases for the 12-month period are summarized in Figure 1. The mean amisulpride starting dose in all patients was 313.2 (± 178.7) mg/day, with a rapid increase in the mean dose at week 1 (505.8 ± 218.2 mg/day), which was maintained at week 8 (508.6 ± 261.5 mg/day) and month 12 (501.4 ± 283.5 mg/day). In general, the dosage in the positive-symptom group tended to be higher than that in the other groups, but a repeated-measures ANOVA did not show a significant difference ($F = 1.849$, $p = 0.165$).

Effectiveness measures

Effectiveness in total patients. The effectiveness during acute and maintenance treatment phases in all patients and in the three subgroups is summarized in Table 3. All effectiveness measures, including the primary measures of the total PANSS and subscale scores, improved significantly during the acute treatment phases. In particular, in addition to psychiatric symptoms, the patients' subjective well-being (mean change in SWN = 5.6 ± 17.3) and attitude (2.5 ± 5.5) toward amisulpride clearly improved during the acute treatment phase. During the maintenance treatment phase, amisulpride led to further improvement in most aspects of the effectiveness measures. Significant decreases were observed in the total (−2.7 ± 11.2, $p = 0.007$), negative (−1.2 ± 4.2, $p = 0.002$), and general (−1.1 ± 5.6, $p = 0.035$) scores of the PANSS during the maintenance treatment phase, but no further improvement in positive symptoms occurred (−0.5 ± 3.2, $p = 0.081$). Additionally, improvements in most secondary measures including the CGI, GAF, and total SWN (with the exception of the DAI) continued during the maintenance treatment phase.

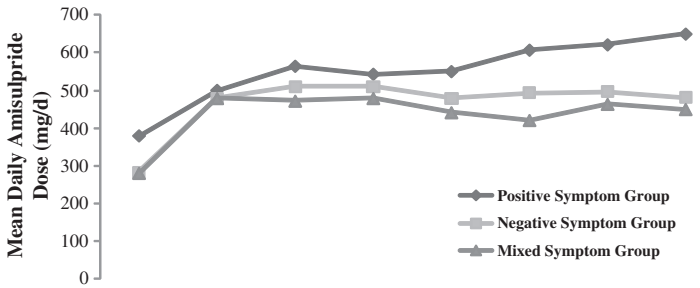
Comparison of effectiveness among the positive-symptom, negative-symptom, and mixed-symptom groups. The positive-symptom group showed a clear evidence of effectiveness during the acute phase. The total PANSS score decreased significantly from 78.7 (± 17.3) to 60.5 (± 5.7) during the acute phase and remained stable during

DOI: 10.1002/hup

Table 2. Completion rate and reasons for withdrawing in the total and the three symptom groups

	Total ($n = 129$)	Positive-symptom group ($n = 26$)	Negative-symptom group ($n = 52$)	Mixed-symptom group ($n = 51$)
Acute treatment phase				
Number of completed subjects (%)[a]	101 (78.3)	20 (76.9)	38 (73.1)	43 (84.3)
Reasons for withdrawing, n[a]				
Loss during follow-up	7	1	5	1
Lack of effectiveness	5	3	0	2
Adverse event[b]	4	0	2	2
Protocol violation	4	0	2	2
Withdrawal of consent	8	2	5	1
Total	28	6	14	8
Maintenance treatment phase				
Number of completed subjects (%)[a]	72 (55.8)	14 (53.8)	29 (55.8)	29 (56.9)
Reasons for withdrawing, n[a]				
Loss during follow-up	10	2	4	4
Lack of effectiveness	6	1	1	4
Adverse event[b]	3	1	1	1
Protocol violation	6	1	2	3
Withdrawal of consent	4	1	1	2
Total	29	6	9	14

[a]No statistical significance.
[b]Adverse events were agitation, nausea, akathisia, and muscle rigidity in acute treatment phase, and breast engorgement, toxic hepatitis, and tardive dyskinesia in maintenance treatment phase.



Subgroup	Baseline	Week 1	Week 2	Week 4	Week 8	Week 16	Week 32	Month 12
Positive Symptom Group	378.6	500	564.3	542.9	550	607.1	621.4	650
Negative Symptom Group	282.8	479.3	510.3	510.3	479.3	493.1	496.6	481
Mixed Symptom Group	279.3	479.3	472.4	479.3	441.4	420.7	463.8	450

Repeated measures ANOVA with planned comparisons (repeated type), $F = 1.849$, $p = 0.165$ for the tests between the doses of the three groups.

Figure 1. Changes in the daily doses of amisulpride prescribed at each visit

the maintenance period. Similar patterns were observed in the PANSS positive and general subscales but not in the negative subscale. The negative-symptom group showed acute effectiveness in all PANSS symptom subscales, and further improvement in the PANSS negative subscale score (-1.5 ± 3.8) occurred during the maintenance phase. Significant improvements in the mixed-symptom group occurred during both the acute and maintenance phases in all PANSS symptom subscales. Improvement in the CGI-S and GAF scores only occurred during the acute treatment phase in the positive-symptom group. The negative and mixed group achieved a statistical improvement in these symptoms during the acute and maintenance phases. Total SWN scores improved significantly only during the acute phase in the general-symptom group (7.1 ± 18.0, $p = 0.015$), whereas DAI scores improved only during the acute treatment phase in the positive-symptom (3.5 ± 5.2, $p = 0.007$) and mixed-symptom (2.9 ± 5.9, $p = 0.003$) groups.

Scores for the depressive factor in the PANSS five-factor model improved significantly during the acute treatment phase (12.6 ± 3.5 to 9.8 ± 3.5, $p < 0.001$) but not during the maintenance phase (9.8 ± 3.5 to 9.6 ± 3.5, $p = 0.361$) in all patients. A similar pattern was observed in the positive-symptom, negative-symptom, and mixed-symptom groups. In terms of

DOI: 10.1002/hup

Table 3. Changes in the PANSS and other clinical scale scores during the acute and maintenance treatment phases

	Total patients ($n=129$)			Positive-symptom group ($n=26$)			Negative-symptom group ($n=52$)			Mixed-symptom group ($n=51$)		
		Change (mean ± SD)			Change (mean ± SD)			Change (mean ± SD)			Change (mean ± SD)	
	Baseline	Acute	Maintenance	Baseline	Acute	Maintenance	Baseline	Acute	Maintenance	Baseline	Acute	Maintenance
PANSS scores												
Total	80.8 ± 17.0	−17.9 ± 21.5**	−2.7 ± 11.2*	78.7 ± 17.3	−18.2 ± 21.7**	−1.3 ± 16.4	80.4 ± 15.8	−13.9 ± 20.8**	−2.7 ± 10.2	82.4 ± 18.2	−21.8 ± 21.7**	−3.5 ± 9.0*
Positive subscale	19.8 ± 5.8	−5.3 ± 6.5**	−0.5 ± 3.2	24.0 ± 5.7	−7.7 ± 8.2*	0.0 ± 5.4	16.4 ± 4.2	−2.7 ± 4.9**	−0.5 ± 2.2	21.2 ± 5.3	−6.6 ± 6.3**	−0.73 ± 2.5*
Negative subscale	21.7 ± 6.1	−3.7 ± 6.5**	−1.2 ± 4.2*	16.0 ± 4.9	−1.5 ± 5.1	0.2 ± 5.3	25.0 ± 5.2	−4.0 ± 7.0**	−1.5 ± 3.8*	21.2 ± 5.3	−4.6 ± 6.4**	−1.5 ± 3.9*
General subscale	39.2 ± 8.4	−8.8 ± 10.8**	−1.1 ± 5.6*	38.3 ± 8.2	−8.6 ± 10.1**	−1.5 ± 6.9	39.0 ± 8.0	−7.1 ± 10.7**	−0.7 ± 5.9	40.0 ± 9.0	−10.6 ± 11.2**	−1.2 ± 4.7
CGI-S	4.4 ± 1.0	−1.2 ± 1.3**	−0.3 ± 0.7**	4.58 ± 1.17	−1.31 ± 1.38**	−0.23 ± 0.86	4.27 ± 0.97	−1.02 ± 1.20**	−0.27 ± 0.63*	4.33 ± 1.03	−1.26 ± 1.29**	0.26 ± 0.72*
GAF	43.1 ± 13.6	18.8 ± 19.0**	3.2 ± 8.9**	45.0 ± 13.6	16.6 ± 16.3**	0.6 ± 7.5	45.1 ± 13.2	15.4 ± 16.6**	4.4 ± 10.1*	42.5 ± 14.4	22.9 ± 4.0**	4.0 ± 8.1*
SWN score	72.7 ± 14.9	5.6 ± 17.3*	2.3 ± 11.3*	73.4 ± 17.7	3.8 ± 14.4	4.4 ± 12.1	71.5 ± 16.4	4.8 ± 18.2	1.1 ± 10.6	72.5 ± 13.1	7.1 ± 18.0*	2.5 ± 11.6
DAI score	1.2 ± 5.0	2.5 ± 5.5**	−0.6 ± 3.3	0.7 ± 4.8	3.5 ± 5.2*	−0.7 ± 3.0	1.8 ± 4.5	1.6 ± 5.2	0.6 ± 3.2	0.9 ± 5.5	2.9 ± 5.9*	−0.5 ± 3.6

PANSS, Positive and Negative Symptom Scale; CGI-S, Clinical Global Impression—Severity; GAF, Global Assessment of Function; SWN, Subjective Well-being under Neuroleptics; DAI, Drug Attitude Inventory.
*$p<0.05$.
**$p<0.001$.
***$p<0.005$.

demographic variables, the only significant difference among early, late, and non-responders related to the number of hospitalizations at enrollment ($p=0.012$), as presented in Table 1. Early responders scored significantly higher at baseline in their total, positive, and general scores on the PANSS and CGI-S, and obtained lower GAF scores than did others.

Safety profile

During the entire study period, 88 (68.2%) of 129 patients reported at least one adverse event. Hyperprolactinemia (54, 41.9%) was reported to be the most common adverse event, followed by akathisia (25, 19.4%), Parkinsonism (20, 15.5%), weight gain (11, 8.5%), dysarthria/dystonia (10, 7.8%), blurred vision (9, 7.0%), sedation (9, 7.0%), and sialorrhea (9, 7.0%). Frequently reported adverse events in the acute treatment phase were hyperprolactinemia (47, 36.4%), akathisia (21, 16.3%), and Parkinsonism (18, 14.0%); frequently reported adverse events in the delayed treatment phase included hyperprolactinemia (42, 41.6%), Parkinsonism (10, 9.9%), and weight gain (10, 9.9%). Most adverse events occurred during the acute treatment phase; with the exception of hyperprolactinemia, its related adverse events, and weight gain, the rates of other events decreased during the delayed treatment phase. Total scores on the LUNSERS, excluding the red-herring items, decreased significantly during the acute treatment phase (44.1 ± 26.6 at baseline: a change of -11.5 ± 26.6, $df=118$, $p<0.001$) and did not improve during the maintenance phase (-0.04 ± 18.0, $df=118$, $p=0.980$). A similar pattern was also observed for all LUNSERS subscales. The mean total score on the DIEPSS was 2.0 ± 2.5 at baseline, indicating a low rate of extrapyramidal symptoms. A significant improvement in DIEPSS scores was observed during the maintenance phase (-0.7 ± 1.6, $df=122$, $p<0.001$ at 12 months) but not during the acute phase (-0.4 ± 2.6, $df=122$, $p=0.078$). The mean body weight and BMI (kg/m^2) at baseline were 64.7 ($\pm$ 14.2) kg and 23.8 ($\pm$ 4.1) kg, respectively. Weight gain was observed during both the acute treatment (1.3 ± 4.5 kg, $t=2.724$, $df=88$, $p=0.008$) and maintenance (1.2 ± 5.9 kg, $df=89$, $p=0.027$) phases. BMI also increased according to a pattern similar to that followed by body weight during both treatment phases in the prominent-negative group. Results of laboratory tests (i.e., aspartate aminotransferase, alanine aminotransferase, cholesterol, and non-fasting glucose) did not indicate any changes except with respect to serum prolactin levels. At baseline, the mean serum prolactin level of all patients was 42.7 ng/mL, which increased significantly to 92.7 ng/mL at 8 weeks

DOI: 10.1002/hup

(50.0 ± 58.9, $df = 95$, $p < 0.001$) and then decreased significantly to 73.3 ng/mL at month 12 (-17.7 ± 49.3, $df = 69$, $p < 0.001$).

DISCUSSION

This prospective study demonstrated the effectiveness of amisulpride in a heterogeneous population of patients with schizophrenia under natural clinical conditions over 1 year. In addition to an improvement in positive and negative symptoms during the acute treatment phase, this study suggests that long-term maintenance treatment with amisulpride would improve the negative symptoms substantially especially in the predominantly negative-symptom and mixed-symptom groups, whereas the positive symptoms remained stable during the maintenance phase. Additionally, amisulpride can increase effectiveness in terms of global functioning, subjective well-being, and attitudes concerning antipsychotic treatment.

Acute and long-term effectiveness

During the acute treatment phase, an improvement occurred in all primary treatment effectiveness measures in all patients. This result is in accordance with those of another study and a meta-analysis (Möller *et al*., 1997; Leucht *et al*., 2005) that reported a rapid onset of action in a population treated with amisulpride. The acute effectiveness was not different from those of previous well-designed double-blind 4–12-week clinical trials, which reported that amisulpride is as effective as risperidone, haloperidol, and flupenthixol for treating positive symptoms (Möller *et al*., 1997; Puech *et al*., 1998; Wetzel *et al*., 1998; Peuskens *et al*., 1999; Hwang *et al*., 2003) with additional effects on negative symptoms compared with haloperidol and risperidone (Möller *et al*., 1997; Peuskens *et al*., 1999).

Efficacy for negative symptomatology is increasingly viewed as critical in the treatment of schizophrenia (Möller *et al*., 1994), as it is associated with functional and social outcomes (Ho *et al*., 1998). The effectiveness of amisulpride for negative symptoms has been specifically demonstrated through short-term or mid-term treatment in subjects with predominantly negative symptoms (Boyer *et al*., 1995; Loo *et al*., 1997; Speller *et al*., 1997; Olié *et al*., 2006). These studies, however, did not show the long-term effectiveness of amisulpride for negative or residual symptoms in heterogeneous patients (Tandon *et al*., 2000). Our results may provide evidence of the effectiveness of maintenance treatment for negative symptoms after recovery from an acute exacerbation. Negative symptoms have been further differentiated into primary and secondary negative symptoms (Carpenter *et al*., 1988). Because improvements in secondary negative symptoms, such as the control of positive symptoms and depressive features, or a lower liability for extrapyramidal symptoms, are more likely to be present during the acute treatment phase with antipsychotics (Speller *et al*., 1997), the effectiveness of maintenance treatment for the negative symptoms identified in this study implies the efficacy of amisulpride for primary negative symptoms, which is in accordance with a previous study (Danion *et al*, 1999). This speculation may be also supported by two additional findings in this study. Delayed improvement in negative symptoms was observed in the negative-symptom and mixed-symptom groups but not in the positive-symptom group. Depressive symptoms improved only during the acute phase in all three subgroups and in all patients. The guidelines issued by the Committee for Medicinal Products for Human Use (CHMP) for the treatment of schizophrenia explicitly state that efficacy for negative symptoms should be demonstrated in specifically designed studies including patients selected for persistent predominantly negative symptoms (CHMP, 1998) to rule out a primary beneficial effect on positive symptoms that causes a secondary improvement in the negative symptom score.

To evaluate the effectiveness of amisulpride for positive and negative symptoms, previous well-designed clinical trials carefully screened subjects using stricter inclusion and exclusion criteria than the ones used in this study. For example, to enroll patients into the positive-symptom predominant group, the inclusion criteria used by Mortimer *et al*. (2004) were a Brief Psychiatric Rating Scale score of 36 or higher and a PANSS positive score higher than the PANSS negative score; the criterion for the negative-symptom-predominant group used by Olié *et al*. (2006) was a PANSS negative score that was 6 points greater than the positive score. Although we separated the subjects using rather loose criteria to mirror an authentic clinical setting, a similar pattern of results was observed when we divided our subjects using the criteria of Mortimer *et al*. (2004) and Olié *et al*. (2006).

This 1-year study showed that amisulpride was associated with improvement in total SWN scores during all treatment phases. Schimmelmann *et al*. (2005) emphasized that in an acute sample. SWN response may be predominantly related to an improvement in positive symptoms, whereas later in treatment, negative symptoms become more relevant to SWN. In this study, improvements in negative symptoms may have resulted from a patient's feeling of subjective well-being related to amisulpride during the maintenance treatment phase. However, this possibility could

DOI: 10.1002/hup

not be definitely established because SWN is a broad measure of subjective distress, and experience is negatively correlated with symptoms including anxiety (Karow *et al*., 2005) and with antipsychotic-inducing side effects (Lambert *et al*., 2003; Schimmelmann *et al*., 2005). SWN is also positively correlated with life satisfaction and quality of life (Lambert *et al*., 2003; Ponizovsky *et al*., 2003), social functioning (Lambert *et al*., 2007), and drug adherence (Lambert *et al*., 2003). This study also showed that drug attitude and adherence and global functioning improved significantly during the 12-month treatment with amisulpride. Similar results were obtained in previous long-term open studies (Colonna *et al*., 2000; Kahn *et al*., 2008) in which amisulpride was associated with a significantly greater improvement in the GAF than was haloperidol and with a comparable improvement in the Quality of Life Scale.

In summary, this study showed that the substantial improvement in schizophrenic symptoms, global functioning, and subjective experience during the acute treatment phase continued throughout the 12-month maintenance treatment phase.

Pattern of prescribed amisulpride doses

One of the special characteristics of amisulpride is that it has a large recommended therapeutic dosage range (50–1200 mg/day), and dosage individualization is justified because of the unique receptor profile for treating both positive and negative schizophrenic symptoms. These findings and recommendations were established in a preclinical study (Di Giovanni *et al*., 1998; Xiberas *et al*., 2001) and well-designed multiple fixed-dose clinical trials (Puech *et al*., 1998; Müller *et al*., 2002), although these results are known to differ from those of clinical practice in many aspects, such as the use of highly selected patients and specialized protocols. Treatment decisions during routine care must consider not only other medical information but also cultural, economic, and psychological aspects (Linden, 1994). This study described the amisulpride dosage pattern prescribed by clinicians in real-life heterogeneous patients. It also showed that clinicians have a tendency to prescribe higher daily amisulpride doses for the positive-symptom group than the negative-symptom and mixed-symptom groups. Clinicians initially prescribed a small dose of amisulpride to both groups and then rapidly increased the dose to about 500 mg/day for all groups after 1 week and maintained this dosage during the 12-month treatment. Primary negative symptoms in patients with remitted positive symptoms can be effectively treated with lower amisulpride doses (50–300 mg/day) (Wetzel *et al*., 1998), but higher amisulpride doses may be necessary to treat negative symptoms in patients with acutely exacerbated schizophrenia (Möller *et al*., 1997; Wetzel *et al*., 1998). In this study, the negative-symptom group also showed a mild degree of positive symptoms (16.4 on the positive-symptom subscale). In an 8-week observational naturalistic study of inpatients with schizophrenia, Linden *et al*. (2004) reported that the initial mean daily dose and that at week 8 were 361 and 550 mg/day, respectively, which was very similar to the results in this study. They also reported that the sum of the PANSS positive scale, but not of the negative scale, at the start of treatment significantly contributed to the variance in the maximum amisulpride dose over the entire course of treatment. On the basis of a clinical trial with four fixed doses of amisulpride (100, 300, 800, and 1200 mg/day), Müller *et al*. (2002) reported that the estimated optimum dose for negative symptoms such as anergia was 584 mg/day; they suggested that amisulpride doses in the range of 400–650 mg were most appropriate for the treatment of negative symptoms in patients with an acute exacerbation of schizophrenia. Although the results in this study need to be further confirmed by a study with a large population, it may give clinicians tips for selecting the amisulpride dose in a real clinical situation.

Tolerability

Seven patients discontinued treatment with amisulpride because of an adverse event, which does not appear to be more problematic than the results of previous trials (Sechter *et al*., 2002; Mortimer *et al*., 2004; Kahn *et al*., 2008).

The proportion of patients who reported at least one adverse event throughout the entire treatment period was 68.2%, which is similar to the proportion found in several mid-term or long-term European trials (Colonna *et al*., 2000; Sechter *et al*., 2002; Mortimer *et al*., 2004). Hyperprolactinemia and its related adverse events were encountered most frequently and were more common in our trial than in Western trials of amisulpride (McKeage and Plosker, 2004). The percentage of patients reporting weight gain also increased gradually throughout the entire study period. However, EPS (akathisia, Parkinsonism, and dysarthria), autonomic nervous system adverse events (blurred vision, constipation, gastrointestinal disturbances, and dry mouth), and sedation and sleep disturbances occurred primarily during the acute treatment phase and decreased during the maintenance phase. Moreover, according to various scales, reported adverse events, and laboratory exams, amisulpride demonstrated a good safety profile throughout the long-term treatment.

DOI: 10.1002/hup

Some limitations of this study include the lack of a control group, open-label, flexible dose, and relatively loose definitions for the positive-symptom, negative-symptom, and mixed-symptom-dominant groups. Additionally, the relatively brief durations of the illnesses of participants and the lack of predefined criteria for depression and EPS to be used for the exclusion of secondary negative symptoms raise questions about whether the observed improvement in negative symptoms was primary. Nevertheless, this long-term study provides clinically relevant data about amisulpride dosage patterns and its effectiveness for positive and negative symptoms in the acute and long-term treatment phases of a heterogeneous patient population having schizophrenia with varying degrees of symptom severity.

CONCLUSION

This study demonstrated the effectiveness of amisulpride for treating acute and 12-month phases of schizophrenia under natural conditions. The negative-symptom and mixed-symptom-predominant patients group showed significant improvement of the negative symptom and global functioning during the maintenance period. Amisulpride demonstrated a good safety profile throughout the treatment.

CONFLICT OF INTEREST

Dr. Ahn has received research grants or served as a lecturer for Janssen, Pfizer, Otsuka, GlaxoSmithKline, Servier, Lundbeck, Eli Lilly, Lundbeck, and AstraZeneca. Dr. Chul-Eung Kim has received honoraria from Janssen, Eli Lilly, Pfizer, Sanofi-Aventis, Otsuka, AstraZeneca, Organon, GlaxoSmithKline, and Lundbeck. Dr. Seok has received an award from AstraZeneca. Tae-Youn Jun, MD, PhD, has served as a consultant for, on the speakers bureau of, and/or received research support from Korean branches of AstraZeneca, Janssen, Eli Lilly, Pfizer, Sanofi-Aventis, Otsuka, Organon, GlaxoSmithKline, Eisai and Lundbeck, Bukwang and Whanin Pharma. Co. Ltd. He was also supported by the Ministry of Health, Welfare and Family Affairs, Republic of Korea (A050047). Dr. Yong Sik Kim has received grants, research support, and/or honoraria from Novartis, Janssen, Eli Lilly, Pfizer, Sanofi-Aventis, Otsuka, AstraZeneca, Organon, GlaxoSmithKline, and Servier, and was also supported by the second stage Brain Korea 21 Project. All other authors have no conflicts of interest.

ACKNOWLEDGEMENT

This study was supported by a grant from Sanofi-Aventis Korea.

REFERENCES

Ahn YM, Lee KY, Kim C, Kim J, Kang D, Jun T, *et al*. 2009. Changes in neurocognitive function in patients with schizophrenia after starting or switching to amisulpride in comparison with the normal controls. *J Clin Psychopharmacol* **29**: 117–123.

Boyer P, Lecrubier Y, Puech AJ, Dewailly J, Aubin F. 1995. Treatment of negative symptoms in schizophrenia with amisulpride. *Br J Psychiatry* **166**: 68–72.

Carpenter WT, Heinrichs DW, Waqman AM 1988. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* **145**: 578–583.

Cavallaro R, Mistretta P, Cocchi F, Manzato M, Smeraldi E. 2001. Differential efficacy of risperidone versus haloperidol in psychopathological subtypes of subchronic schizophrenia. *Hum Psychopharmacol* **16**: 439–448.

CHMP. 1998. *Note for Guidance on the Clinical Investigation on Medicinal Products in the Treatment of Schizophrenia*. London: EMEA.

Colonna L, Saleem P, Dondev-Nouvel L, Rein W. 2000. Long-term safety and efficacy of amisulpride in subchronic or chronic schizophrenia. Amisulpride Study Group. *Int Clin Psychopharmaol* **15**: 13–22.

Danion J, Rein W, Fleurot O, Amisulpride Study Group. 1999. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. *Am J Psychiatry* **156**: 610–616.

Day JC, Wood G, Dewey M, *et al*. 1995. A self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. *Br J Psychiatry* **166**: 650–653.

Di Giovanni G, Di Mascio M, Di Matteo V, Esposito E. 1998. Effects of acute and repeated administration of amisulpride, a dopamine D2/D3 receptor antagonist, on the electrical activity of midbrain dopaminergic neurons. *J Pharmacol Exp Ther* **287**: 51–57.

Ho BC, Nopoulos P, Flaum M, Arndt S, Andreasen NC. 1998. Two-year outcome in first-episode schizophrenia: predictive value of symptoms for quality of life. *Am J Psychiatry* **155**: 1196–1201.

Hwang TJ, Lee SM, Sun HJ, Lin HN, Tsai SJ, Lee YC, *et al*. 2003. Amisulpride versus risperidone in the treatment of schizophrenic patients: a double-blind pilot study in Taiwan. *J Formos Med Assoc* **102**: 30–36.

Hwang SS, Chang JS, Lee KY, Kim SH, Ahn YM, Kim YS. 2009. Causal model of insight and psychopathology based on the PANSS factors: 1-year cross-sectional and longitudinal revalidation. *Int Clin Psychopharmacol* **24**:189–198.

Inada T 1996. *Evaluation and Diagnosis of Drug-induced Extrapyramidal Symptoms: Commentary on the DIEPSS and Guide to Its Usage*. Seiwa Shoten Publishers: Tokyo, Japan.

Jung HY, Kim JH, Ahn YM, Kim SC, Hwang SS, Kim YS. 2005. Liverpool University Neuroleptic Side-effect Rating Scale (LUNSERS) as a subjective measure of drug-induced parkinsonism and akathisia. *Hum Psychopharmacol* **20**: 41–45.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IPM, *et al*. 2008. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* **371**: 1085–1097.

Kapur S, Seeman P. 2001. Does fast dissociation from the dopamine D_2 receptor explain the action of atypical antipsychotics? A new hypothesis. *Am J Psychiatry* **158**: 360–369.

Karow A, Moritz S, Lambert M, Schoder S, Naber D. 2005. PANSS syndromes and quality of life in schizophrenia. *Psychopathology* **38**: 320–326.

Kay SR. 1991. *Positive and Negative Syndromes in Schizophrenia: Assessment and Research*. Brunner/Mazel: New York.

Kerwin R. 2000. From pharmacological profiles to clinical outcomes. *Int Clin Psychopharmacol* **15**(Suppl 4): S1–S4.

Kim SW, Shin IS, Kim JM, Yoo JA, Ahn YM, Kwon JS, *et al*. 2007. A validation study of the Korean version of the Subjective Well-being under Neuroleptic Treatment Scale—Short Form. *Korean J Psychopharmacol* **18**: 221–230.

Lambert M, Schimmelmann BG, Karow A, Naber D. 2003. Subjective well-being and initial dysphoric reaction under antipsychotic drugs—concepts, measurement and clinical relevance. *Pharmacopsychiatry* **36**(Suppl 3): 181–190.

Lambert M, Naber D, Eich FX, Schacht M, Linden M, Schimmelmann BG. 2007. Remission of severely impaired subjective wellbeing in 727 patients with schizophrenia treated with amisulpride. *Acta Psychiatr Scand* **115**: 106–113.

Leucht S, Busch R, Hamann J, Kissling W, Kane JM. 2005. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. *Biol Psychiatry* **57**: 1543–1549.

Linden M 1994. Therapeutic standards in psychopharmacology and medical decision-making. *Pharmacopsychiatry* **27**(Suppl 1): 41–45.

Linden M, Scheel T, Xaver EF. 2004. Dosage finding and outcome in the treatment of schizophrenic inpatients with amisulpride. Results of a drug utilization observation study. *Hum Psychopharmacol* **19**: 111–119.

Lindenmayer JP, Bernstein-Hyman R, Grochowski S. 1994. A new five factor model of schizophrenia. *Psychiatr Quart* **65**: 299–322.

Loo H, Poirier-Littre MF, Theron M, Rein W, Fleurot O. 1997. Amisulpride versus placebo in the medium-term treatment of the negative symptoms of schizophrenia. *Br J Psychiatry* **170**: 18–22.

Martin S, Ljo H, Peuskens J, Thirumalai S, Siudicelli A, Fleurot O, *et al*. 2002. A double-blind, randomized comparative trial of amisulpride versus olanzapine in the treatment of schizophrenia: short-term results at two months. *Curr Med Res Opin* **18**: 355–362.

Mattson DT, Berk M, Lucas MD. 1997. A neuropsychological study of prefrontal lobe function in the positive and negative subtypes of schizophrenia. *J Genet Psychol* **158**: 487–494.

McKeage K, Plosker GL. 2004. Amisulpride: a review of its use in the management of schizophrenia. *CNS Drugs* **18**: 933–956.

Meisenzahl EM, Schmitt G, Günder G, Dresel S, Frodl T, la Fougère J, *et al*. 2008. Striatal D2/D3 receptor occupancy, clinical response and side effects with amisulpride: an iodine-123-iodobenzamide SPET study. *Pharmacopsychiatry* **41**: 169–175.

Möller HJ. 2003. Amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. *Prog Neuropyshopharmacol Biol Psychiatry* **27**: 1101–1111.

Möller HJ, van Praag HM, Aufdembrinke B, Bailev P, Barnes TR, Beck J, *et al*. 1994. Negative symptoms in schizophrenia: considerations for clinical trials. Working Group on Negative Symptoms in Schizophrenia. *Psychopharmacology (Berl)* **115**: 221–228.

Möller HJ, Boyer P, Fleurot O, Rein W. 1997. Improvement of acute exacerbations of schizophrenia with amisulpride: a comparison with haloperidol. PROD-ASLP Study Group. *Psychopharmacology (Berl)* **132**: 396–401.

Mortimer A 2009. Update on the management of symptoms in schizophrenia: focus on amisulpride. *Neuropsychiatr Dis Treat* **5**:267–277.

Mortimer A, Martin S, Loo H, Peuskens J, SOLIANOL Study Group. 2004. A double-blind, randomized comparative trial of amisulpride versus olanzapine for 6 months in the treatment of schizophrenia. *Int Clin Psychopharmacol* **19**: 63–69.

Müller MJ, Wetzel H, Eich FX, Rein W, Puech A, Benkert O, Amisulpride Study Group. 2002. Dose-related effects of amisulpride on five dimensions of psychopathology in patients with acute exacerbation of schizophrenia. *J Clin Psychopharmacol* **22**: 554–560.

Olié JP, Spina E, Murray S, Yang R. 2006. Ziprasidone and amisulpride effectively treat negative symptoms of schizophrenia: results of a 12-week, double blind study. *Int Clin Psychopharmacol* **21**:143–151.

Peuskens J, Bech P, Möller HJ, Bale R, Fleurot O, Rein W. 1999. Amisulpride vs. risperidone in the treatment of acute exacerbations of schizophrenia. Amisulpride Study Group. *Psychiatry Res* **88**: 107–117.

Ponizovsky AM, Grinshpoon A, Levav I, Ritsner MS. 2003. Life satisfaction and suicidal attempts among persons with schizophrenia. *Compr Psychiatry* **44**: 442–447.

Puech A, Fleurot O, Rein W. 1998. Amisulpride, and atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. The Amisulpride Study Group. *Acta Psychiatr Scand* **98**: 65–72.

Sanofi-Aventis. Solian: summary of product characteristics [online]. Available at URL: http://emc.medicines.org.uk [Accessed 2007 Feb].

Schimmelmann BG, Moritz S, Karow A, Schafer I, Bussopulos A, Golks D, *et al*. 2005. Correlates of subjective well-being in schizophrenic patients treated with atypical antipsychotics. *Int J Psych Clin Pract* **9**: 94–98.

Sechter D, Peuskens J, Fleurot O, Rein W, Lecrubier Y, Amisulpride Study Group. 2002. Amisulpride vs. risperidone in chronic schizophrenia: results of a 6-month double-blind study. *Neuropsychopharmacology* **27**: 1071–1081.

Speller JC, Barnes TR, Curson DA, Pantelis C, Alberts JL. 1997. One-year, low-dose neuroleptic study of in-patients with chronic schizophrenia characterized by persistent negative symptoms. Amisulpride v. haloperidol. *Br J Psychiatry* **171**: 564–568.

Tandon R, DeQuardo JR, Taylor SF, McGrath M, Jibson M, Eiser A, *et al*. 2000. Phasic and enduring negative symptoms in schizophrenia: biological markers and relationship to outcome. *Schizophr Res* **45**: 191–201.

Weiden PJ, Aquila R, Emanuel M, Zygmunt A. 1998. Long-term considerations after switching antipsychotics. *J Clin Psychiatry* **59**(Suppl 19): 36–49.

Wetzel H, Grűnder G, Hillert A, Philipp M, Gattaz WF, Sauer H, *et al*. 1998. Amisulpride versus flupentixol in schizophrenia with predominantly positive symptomatology—a double-blind controlled study comparing a selective D2-like antagonist to a mixed D1-/D2-like antagonist. The Amisulpride Study Group. *Psychopharmacology (Berl)* **137**: 223–232.

Xiberas X, Martinot JL, Mallet L, Artiqes E, Canal M, Loc'h C, *et al*. 2001. In vivo extrastriatal and striatal D2 dopamine receptor blockade by amisulpride in schizophrenia. *J Clin Psychopharmacol* **21**: 207–214.

Yi JS, Ahn YM, Shin HK, An SK, Joo YH, Kim SH, *et al*. 2001. Reliability and validity of the Korean version of the Positive and Negative Syndrome Scale. *J Korean Neuropsychiatr Assoc* **40**: 1090–1105.

Yoon BH, Bahk WM, Lee KU, Hong CH, Ahn JK, Kim MK, *et al*. 2005. Psychometric properties of Korean version of Drug Attitude Inventory (KDAI-10). *Korean J Psychopharmacol* **16**: 480–487.

DOI: 10.1002/hup