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Efficacy of amisulpride in treating primary negative symptoms in first-episode psychosis: a pilot study

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Objective Negative symptoms are debilitating and associated with poor role functioning and reduced quality of life. There is a paucity of research on antipsychotic efficacy against the primary negative symptoms, particularly in first-episode psychosis (FEP). We undertook a prospective, open-label pilot trial to investigate the use of amisulpride in the treatment of young people with FEP characterised by primary negative symptoms.
Method Twelve male and two female first-episode patients with primary negative symptoms (aged 16–26) were commenced on low-dose amisulpride (mean 250 mg/day) and followed-up over a 6-month period. Primary outcome measures were the Scale for the Assessment of Negative Symptoms (SANS), the Quality of Life Survey (QLS) and their respective subscales.
Results For the 12 completers there was a statistically significant improvement in SANS summary score ($p = 0.036$), Affective Flattening subscale global score ($p = 0.046$), QLS total score ($p = 0.021$), QLS subscales of Instrumental Role ($p = 0.018$) and Intra-psychic Foundations ($p = 0.009$) from baseline to week 24.
Conclusions Amisulpride appears to be associated with less severe negative symptoms and improved quality of life. Generalisabilty of the findings is limited by the small sample size and open-label design of our study, however the positive findings suggest that further controlled trials are warranted. Copyright © 2006 John Wiley & Sons, Ltd.

KEY WORDS — primary; negative symptoms; schizophrenia; first-episode; atypical antipsychotic

INTRODUCTION

Negative symptoms of psychosis include affective flattening, apathy, anhedonia, speech impoverishment and social withdrawal (Andreasen, 1985). A differentiation has been made between primary and secondary forms (Mayerhoff *et al*., 1994), where the former are seen as a core part of the illness, while the latter are seen as a response to other factors, including positive psychotic symptoms, anxiety, depression, social deprivation, substance use and extrapyramidal side effects (EPSE; Carpenter *et al*., 1988). Negative symptoms in FEP have been associated with a poorer course (Liddle, 1987a, 1987b; Liddle and Barnes, 1990), therefore effective treatment of primary negative symptoms during the early phase of psychotic illness is an important strategy in improving global outcome.

A number of studies have assessed the incidence of negative symptoms in FEP. Edwards *et al*. (1999) found that secondary negative symptoms in a first episode population are unstable during the first year of illness; with over half their sample having moderate levels at some stage during the follow-up period. Gerbaldo *et al*. (1994) reported that primary negative symptoms affect approximately 40% of cases within the first 5 years of illness, while Malla *et al*. (2002) determined that moderate levels of primary negative symptoms within a non-affective sample were present in 26.8% of their cohort, although they did not control for positive symptoms.

The efficacy of amisulpride in treating primary negative symptoms has been assessed in seven trials.

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All studies compared amisulpride with either placebo or conventional antipsychotics in patients with chronic psychosis. Besides a dose-finding study (Boyer *et al*., 1995), there are three short-term studies: a comparison with placebo (Paillère-Martinot *et al*., 1995); a comparison with fluphenazine (Pichot *et al*., 1988); and an add-on study with fluoxetine (Bogetto *et al*., 1995). There are two medium-term placebo-controlled studies of 3 months (Danion *et al*., 1999) and 6 months (Loo *et al*., 1997), as well as a long-term study, over 12 months (Speller *et al*., 1997). A meta-analysis of relevant studies found that amisulpride was superior to placebo but not to typical antipsychotics (Leucht *et al*., 2002).

Interestingly, pooled data from three of the placebo-controlled trials (Paillère-Martinot *et al*., 1995; Danion *et al*., 1999; Loo *et al*., 1997) found that response to amisulpride was related to, duration of disease. In those unwell for less than 2 years 63.2% responded, compared with 40.4% in those unwell for 2–5 years, 34.3% in those unwell for 5–10 years and 17.9% in those unwell for more than 10 years (Lecrubier *et al*., 2001). This suggests that chronicity is an important treatment factor, reinforcing the need for early intervention.

There is no research, to date, on the use of amisulpride (or any other antipsychotic) in first-episode patients with primary negative symptoms. We undertook a pilot trial to investigate the use of amisulpride in the treatment of young people with FEP with primary negative symptoms. We hypothesised that low-dose amisulpride treatment would be associated with improvement in both negative symptoms, as measured by the SANS (Andreasen, 1981), and overall functioning, as measured by the QLS (Heinrichs *et al*., 1984).

METHOD

Subjects

Patients were recruited from the Early Psychosis Prevention and Intervention Centre (EPPIC; McGorry *et al*., 1998). Sixteen patients were eligible; 14 patients consented to participation (12 male, 2 female; mean age 21.79 years, range 16–26 years) and were changed to low-dose amisulpride; 12 patients completed the 12-week trial. Two participants withdrew: one at Week 2 who requested and restarted olanzapine and one at Week 8 due to disclosure of longstanding non-adherence. Their follow-up data were, therefore, not included in statistical analysis. All participants had a current diagnosis of schizophrenia (residual type) and no other current diagnoses.

The inclusion criteria for the study were: age of onset for first psychotic episode between 15 and 30 years; diagnosis of schizophrenia spectrum disorder; a negative symptom score of at least three on two or more of four SANS global subscales persisting over the previous month (excluding attention); positive symptoms rated three or below on the Brief Psychiatric Rating Scale (BPRS; Lukoff *et al*., 1986) over the previous month; a depression score of six or less on the Calgary Depression Scale (CDS; Addington *et al*., 1993); medication compliance of at least 4 weeks. Exclusion criteria included: a diagnosis of affective psychosis or psychosis due to a general medical condition; a co-morbid diagnosis of major depression; significant drug abuse; a significant co-existing physical condition including extrapyramidal side effects; a severe intellectual disability; pregnant or lactating.

The two patients who withdrew from the study were excluded from further analyses, leaving a sample of 12 patients. All patients lived with their family in a house or flat; eight patients were born in Australia. One patient was working full-time, seven were unemployed and four were students. The average duration of untreated psychosis was 25.58 weeks (range: 1–104 weeks). All patients were on antipsychotic medications at study entry: six on olanzapine, two on risperidone, two on quetiapine and two on zuclopenthixol decanoate. The average number of antipsychotic medications to achieve remission of positive symptoms prior to the trial was 1.75 (Mdn = 1.50, $SD = 0.89$); treatment of negative symptoms was not a therapeutic focus before trial entry. The mean chlorpromazine-equivalent maximum dose over the 2-week period prior to the trial was 314.08 mg/day (range 134–675 mg/day) and the mean number of weeks on that dose was 9.78 (Mdn = 8, $SD = 8.758$, min = 2, max = 32).

Measures

Diagnoses were ascertained at baseline using the Structured Clinical Interview for Diagnosis (SCID-IV; First *et al*., 1996). Corroborative information was gathered from relatives and clinical files. The 24-item BPRS was used to assess positive symptoms and the SANS was used to assess negative symptoms. The CDS was used to measure depressive symptoms and was chosen because items are less likely to be confounded by negative symptoms (Malla *et al*., 2002).

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Additional assessment tools were used during the trial to assess psychopathology and general functioning. The Schedule for the Deficit Syndrome (SDS; Kirkpatrick *et al*., 1989) was used to categorise patients into those with and without the deficit syndrome (i.e. those with and without high levels of primary negative symptoms of greater than 12 months duration). The SDS is not designed for use as a scale, but as a diagnostic instrument, and is a problematic measure of change in treatment trials (Kirkpatrick *et al*.). Side effects were assessed weekly using the UKU Side Effect Rating Scale (Lingjaerde *et al*., 1987). The QLS was used to assess the impact of the illness on overall functioning and subjective depression was assessed using the Beck Depression Inventory (BDI; Beck *et al*., 1961). Finally, medication compliance was measured with the Medication Adherence Rating Scale (MARS; Thompson *et al*., 2000). Clinicians and patients were also asked to rate their subjective perception of current compliance on a five-point Likert scale.

The Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 1997) was used to measure premorbid intellectual functioning in all participants at baseline.

Procedure

Individuals were screened via the Treatment Resistance Early Assessment Team (TREAT; Edwards *et al*., 2002), a group of senior clinicians assisting in the early identification and treatment of patients at EPPIC who are experiencing a prolonged recovery from their first psychotic episode. Patients identified through their treating team were presented for review at TREAT, where their eligibility was ascertained; they were then formally assessed by the research assistant (RA). Eligible patients entered a 4-week screen to exclude those with co-morbid depression, positive symptoms and non-enduring negative symptoms; no patients were judged to have EPSE. Those not excluded were judged to have primary negative symptoms. Patients were further classified into those with and without the deficit syndrome.

The study had a 12-week treatment phase and a 24-week follow-up period. Participants were started on amisulpride 100 mg/day, with a clinically judged increase to 200 mg/day by week 3 and 300 mg/day at week 6 if there was no improvement in negative symptoms. At commencement there was a 1-week cross-titration with previous oral therapy; for those on depot, amisulpride was initiated when the next depot was due. If an exacerbation of positive symptoms occurred the dose of amisulpride was adjusted accordingly (up to a maximum dose of 800 mg/day). All other aspects of their management remained constant.

Participants were followed-up weekly for 12 weeks by their treating team and the RA. Completers were those still receiving amisulpride treatment (irrespective of dose) at 12 weeks. The RA reviewed all the participants, 6 months after commencing amisulpride. All measures were completed at baseline, 12 weeks and 24weeks. In addition, the UKU was completed on a weekly basis, and the BPRS-E, the SANS, the CDS and the BDI were completed fortnightly. The QLS and the SDS were completed monthly.

DATA ANALYSIS

Data analysis was based on the 12 completers. Non-parametric analyses were used, as data were not normally distributed. A series of Wilcoxon Signed Ranks tests were employed to compare baseline scores to scores obtained at weeks 12 and 24. When the outcome variable was categorical, McNemar's test was used to examine change over time.

Domain scores, a summary score and a total score were derived from the SANS. Domain scores are based on the sum of global and item scores for each of the five subscales while the summary score is based on the summation of the five global domain items. The summary score is recommended by the author on the scale as the preferred measure of overall severity of symptoms (American Psychiatric Association, 2000).

RESULTS

Twenty-seven (24 male, 3 female) of the 331 clients registered to the service between October 2002 and April 2004 (approximately 8.2%) were identified as possible recruits and began the screening process. These figures are comparable to the 9.2% identified as the incidence of first episode patients with moderate levels of general negative symptoms by Edwards *et al*. (1999) using the same process. Sixteen (14 male, 2 female) of the 331 clients were assessed to have primary negative symptoms (4.8%) and were approached for inclusion in the trial. This figure is also comparable to Edwards et al's 3.8%. The other 11 patients (10 male, 1 female; mean age 22.54 years, range 18–28 years) were omitted based on the exclusion criteria mentioned.

Participants were registered with the service for an average of 33.4 weeks (range: 16.3–61.4) before consent. The mean dose of amisulpride during the

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trial was 250 mg/day (Mdn = 200 mg/day, *SD* = 131.43 mg/day, min = 100 mg/day, max = 600 mg/day); dose range was not governed by side effects. Table 1 summarises the clinical data for baseline, 12-week and 24-week time points for all completers ($N = 12$).

There was a significant decrease in SANS summary score from baseline to week 24 ($Z = -2.102$, $p = 0.036$), indicating an improvement in negative symptoms at 6 months. There was also a significant decrease in the mean Avolition subscale global score from week 12 to week 24 ($Z = -2.11$, $p = 0.035$), indicating a decrease in apathetic symptoms during the follow-up phase of the trial. Finally, there was a significant decrease in the mean Affective Flattening subscale global score between baseline and week 24 ($Z = -1.99$, $p = 0.046$), indicating an increase in emotional reactivity at 6 months.

For the QLS, there was a significant increase in the mean total score between baseline and week 24, ($Z = -2.32$, $p = 0.021$), reflecting improved global life quality. A significant improvement was also found on the Instrumental Role subscale (relating to role functioning and subjective satisfaction with it) between baseline and week 24 ($Z = -2.37$, $p = 0.018$). Similarly, there was a significant improvement in the intra-psychic Foundations subscale, including items relating to anhedonia, avolition and emotional responses ($Z = -2.59$, $p = 0.009$), for the same time period.

There was a significant decrease in the mean total BDI score from baseline to week 12, ($Z = -2.29$, $p = 0.022$), and from baseline to week 24, ($Z = -2.09$,

Table 1. Clinical data collected over the 24 week period

	Baseline			12 weeks			24 weeks		
	M	Mdn	*SD*	*M*	Mdn	*SD*	*M*	Mdn	*SD*
BPRS									
Total score[a]	33.58	33.5	3.75	31.50	30.00	5.45	30.67	30.00	4.81
Psychotic subscale[b]	5.25	4.00	1.96	4.75	4.00	1.76	4.50	4.00	1.17
SANS									
Summary score[d]	12.58	12.50	1.89	12.25	13.00	3.19	10.83[e]	12.00	3.67
Total score	53.67	55.00	10.82	49.33	51.50	13.38	46.25	51.50	17.50
Affective flattening/blunting	18.08	18.00	6.50	15.08	14.50	6.71	14.92[f]	17.50	9.96
Alogia	7.00	7.00	3.52	5.58	5.00	2.87	5.67	5.50	3.31
Avolition/apathy	10.33	11.00	3.52	11.08	12.00	3.03	9.25[e]	9.50	3.41
Anhedonia/asociality	16.50	17.00	2.35	15.58	15.50	3.20	15.42	15.50	4.36
Attention	1.50	0.50	1.78	1.50	0.00	2.24	1.00	0.00	1.48
BDI									
Total score	6.42	5.50	4.76	3.83[4]	2.50	4.47	3.92[f]	3.50	4.01
% with score 5 or greater		66.67%			33.33%			25.00%	
CDS									
Total score	1.42	1.00	1.38	1.17	1.00	1.47	0.83	0.00	1.19
% with score 5 or greater		8.30%			0.00%			0.00%	
SDS									
% with a deficit syndrome		50.00%			41.70%			41.70%	
QLS[c]									
Total score	2.70	2.71	0.47	2.95	2.81	0.85	3.13[f]	2.95	0.77
Interpersonal relations	2.50	2.44	0.51	2.77	2.44	0.98	2.85	2.56	1.10
Instrumental roles	2.69	2.25	1.13	3.04	2.25	1.44	3.23[f]	2.75	1.26
Intrapsychic foundations	2.70	2.79	0.52	2.90	3.00	0.84	3.18[g]	3.56	0.79
Common objects & activities	3.54	4.00	0.99	3.67	3.75	1.05	3.88	3.75	0.93
MARS									
Total score	6.58	6.50	2.07	8.00[h]	8.00	1.48	8.00[f]	9.00	2.09

[a]Based on average scores on a scale from 1 to 7, with higher scores indicating better functioning.
[b]Includes suspiciousness, hallucinations, unusual thought content and conceptual disorganisation.
[c]On a scale from 0 to 6, with higher scores indicating better functioning.
[d]Summary score based on the sum of the five global items from the SANS.
[e]$p < 0.05$ from Week 12 to Week 24.
[f]$p < 0.05$ from Baseline to Week 24.
[g]$p < 0.01$ from Baseline to Week 24.
[h]$p < 0.05$ from Baseline to Week 12.

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$p = 0.036$), indicating a decrease in subjective levels of low mood during the trial period.

With the MARS, there was a significant increase in scores from baseline to week 12, ($Z = -2.21$, $p = 0.027$) and from baseline to week 24, ($Z = -2.28$, $p = 0.023$), indicating an increase in willingness to adhere to medication treatment over the trial period. Subjective and clinical ratings indicated that all completers were compliant during the trial period, and no patient experienced significant side effects, as measured by the UKU. Ten completers were still compliant with amisulpride treatment at 6 months.

Six of the 12 participants were classified as having the deficit syndrome based on scores on the SDS at baseline, and five at weeks 12 and 24. No significant differences across time were noted for the SDS, BPRS and the CDS.

The mean WTAR Predicted Full Scale IQ (FSIQ) for the sample ($N = 14$) was 83.79 ($SD = 15.49$, min = 53, max = 112), indicating a sample with a low average IQ. Three clients had a WTAR Predicted FSIQ less than 70 (i.e. FSIQ scores of 53, 67 and 69).

DISCUSSION

In our study, a mean amisulpride dose of 250 mg/day over 6 months resulted in a significant decrease in primary negative symptoms, confirming our hypothesis. Secondary confounders were excluded during screening and therefore cannot explain negative symptom improvement. This improvement is consistent with Leucht *et al*.'s (2002) interpretation of other amisulpride studies. To our knowledge this is the first study to test the efficacy of an antipsychotic for primary negative symptoms in individuals with FEP. An improvement in primary negative symptoms during a first-episode psychosis is very encouraging as was the early and sustained response. Given the findings of Lecrubier *et al*. (2001), it may be the optimum time for treatment, paralleling the argument for early intervention for positive symptoms.

The hypothesis that low-dose amisulpride would improve overall functioning in first episode psychosis was also confirmed. This finding mirrored the improvement in SANS results, with quality of life and general functioning increasing as negative symptoms decreased. The previous studies mentioned did not include quality of life measures, raising the question as to whether any improvement in negative symptoms translated into real-world benefit—especially given the low effect sizes Leucht *et al*. (2002) found. Our study suggests that improvement in primary negative symptoms and quality of life are positively correlated and that treating negative symptoms results in significant improvement in global life quality, role functioning and subjective satisfaction with it, as well as in avolition and anhedonia.

Interestingly, there was significant improvement in the BDI scores over the 24 weeks, despite no significant changes in the objectively scored CDS. While objective baseline CDS scores indicated no patient had clinically significant depression, subjective baseline BDI scores indicated a level of mild depressive pathology. The CDS was specifically chosen as the objective measure because of the limited degree to which depressive items on the scale covary with negative symptoms (Malla *et al*., 2002). Eight of the BDI's 13 items, however, appear to have overlapping symptomatology between negative and depressive symptoms. As such, any change in these items may reflect an improvement in negative symptoms of depression or psychosis. Since patients were not objectively depressed during the study, it is possible that our cohort were subjectively reporting an improvement in primary negative symptoms.

As expected, we found no differences over time on the BPRS psychotic subscale, the CDS and the SDS. The BPRS psychotic subscale was used to measure levels of positive symptoms at all time points, and given the minimal levels at baseline no further improvement was expected. The same reasoning holds true for the CDS. Finally, as noted previously, the SDS has been suggested for use as a diagnostic tool rather than as a measure of change during a trial period, therefore significant changes over a 24-week period were not expected. Although the incidence of the deficit syndrome was relatively high within our cohort (50% at baseline), this only equates to 1.8% of the FEP patients registered in the service during the trial period.

The major limitation in our study was the small sample size recruited and the subsequent limited statistical analyses. Edwards *et al*. (1999) noted that the prevalence of primary negative symptoms is low in first episode psychosis. Moreover, they suggested that there is an inherent instability in negative symptoms in the first 12 months of the illness. Both of these identified impediments hindered the detection of suitable study participants. The anticipated low recruitment led to the omission of a control group and left the study open-label introducing a further limitation. The low mean IQ within the cohort may have acted as a confounding factor contributing to the high levels of negative symptoms at baseline, although this would not explain any subsequent improvement.

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Given the small sample size in the present study more research is needed before firm conclusions can be reached regarding the role of amisulpride in the treatment of primary negative symptoms in FEP. However, participants in our study began to show functional improvement within 6 months of low-dose amisulpride treatment—an improvement at an average of 33.4 weeks in a specialised FEP service and 1.75 other antipsychotic treatments had only minimal impact on by study entry. We suggest that a randomised controlled trial of low-dose amisulpride versus treatment as usual be undertaken to confirm the findings and to determine whether the results found in the current study are actually related to the use of amisulpride and not to other treatment factors. Given the difficulties in recruiting suitable participants for this type of research, it is also suggested that multi-site trials be utilised to increase the sample yield. Further positive results would provide a powerful driving force in addressing negative symptoms at an early point in a patient's illness and reinforcing therapeutic optimism.

Our finding of an incidence of 8.2% of primary negative symptoms in a first-episode cohort was similar to the 9.2% incidence reported by Edwards *et al*. (1999) on a cohort from the same centre. These figures differ however from the generally accepted incidence among a more chronic clinical sample—20–25% (Kirkpatrick *et al*., 2006). This suggests that the underlying cause is progressive not static and that there is a deepening of primary negative symptoms with chronicity. It also raises the possibility of treatment to slow or even reverse the evolution of negative symptoms and of prophylaxis to prevent progression. Since Lecubrier (2001) demonstrated that negative symptom response to amisulpride was inversely related to chronicity, treatment early in a patient's illness would appear to be paramount.

To our knowledge this is the first study assessing the pharmacological treatment of primary negative symptoms in first episode psychosis and provides a positive first step. Statistically significant decreases in negative symptoms and increases in overall functioning were found in a sample of 12 patients diagnosed with first episode psychosis treated with low-dose amisulpride. Given the difficulties in recruiting our cohort, it is suggested that a multi-site randomised controlled trial of low dose amisulpride versus treatment as usual be undertaken to determine whether the results found in the current study are related to the use of amisulpride treatment. Confirmation of our results should provide a powerful driving force in addressing negative symptoms at an early stage and accelerating the search for more effective agents.

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