

Amineptine treatment of persistent catatonic symptoms in schizophrenia: a controlled study

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Background: Data on the treatment response of enduring catatonic phenomena accompanying chronic schizophrenia are few and far between. The aim of this study was to explore the therapeutic effects of add-on amineptine, a dopamine agonist antidepressant in chronic catatonia occurring in schizophrenia. **Method:** Fifteen subjects with DSM-IV schizophrenia presenting with persistent catatonic features underwent a 15-week, double-blind, placebo-controlled cross-over trial; they were treated for 6 weeks each with amineptine and a placebo, with a 3-week wash-out period in between. The primary outcome measures were the sum scores of the Bush-Francis Catatonia Rating Scale and the Modified Rogers Scale. Changes in other aspects of psychopathology and extrapyramidal side effects (EPS) constituted the secondary outcome measures. **Results:** Amineptine augmentation of antipsychotic treatment had no appreciable effect on either of the catatonia ratings. Apart from a statistically significant but clinically negligible improvement in the negative symptom scores, there were no changes in the psychopathology and EPS ratings. **Conclusion:** The lack of a therapeutic effect of the dopamine agonist amineptine on persistent catatonic signs and symptoms suggests that the dopamine system may not have a decisive role in the pathophysiology of chronic catatonic syndrome arising in the context of schizophrenia.

Keywords: catatonia, schizophrenia, amineptine

After decades of neglect by mainstream psychiatry, catatonia has made a remarkable comeback over the past two decades (for reviews, see Fink & Taylor, 2003; Caroff et al., 2004). The recent upsurge of interest in catatonia is due, in part, to the serendipitous finding that benzodiazepines (BZD) can effectively, although transiently, suspend acutely arising catatonic stupor (Rosebush & Mazurek, 2010). Chronically persistent catatonia associated with schizophrenia, however, remains a neglected research topic generating only a few publications over recent years (Hoffler et al., 1995; Bush et al., 1997; Cohen et al., 2005; Ungvari et al., 2005/2010; Wong et al., 2007).

While the use of benzodiazepines (BZD), particularly lorazepam, in acute stupor has generated a sizeable body of research (Rosebush, 2004), the treatment of persistent catatonic phenomena accompanying chronic psychoses, primarily schizophrenia ("chronic catatonia"), has received very little attention (Ban, 1990; Bush et al., 1997). BZDs showed no therapeutic effect in chronic catatonia in the only controlled study

published to date: long-standing symptoms of simple and complex mannerisms, posturing, grimacing, stereotypes and blocking were resistant to a 15-week trial of 6 mg/day lorazepam in this random-assignment, placebo-controlled, double-blind, cross-over trial (Ungvari et al., 1999). Before this lorazepam study, all participating chronically ill, catatonic schizophrenia patients underwent another placebo-controlled 15-week trial with the anticholinergic antiparkinson drug, benzhexol (max. dose 6 mg/day) added to their ongoing antipsychotic regime. This was done for two main reasons. The first was to test the therapeutic value of benzhexol in chronic catatonia because reports had suggested that anticholinergic antiparkinson drugs could improve catatonic schizophrenia (Hirschberg, 1964; Winter & Grosse, 1979; Franz et al., 1994). These brief papers, buried in the vast schizophrenia literature, have not received any attention in the modern literature, even in comprehensive reviews of the subject (Fink & Taylor, 2003; Rosebush & Mazurek, 2010). The second reason for running a benzhexol trial was

the possible elimination of extrapyramidal side effects (EPS), particularly akinesia, akathisia and Parkinson syndrome that could mimic catatonic phenomena before subjecting the patients to lorazepam. Contrary to expectations, benzhexol had no appreciable effect on catatonia as rated by the Bush-Francis Catatonia Rating Scale (BFCRS; Bush et al., 1996).

In a quest for other treatment options for chronic catatonic schizophrenia, amineptine augmentation seemed to be a logical choice. First, as add-on medications, antidepressants have the potential to improve the overall mental state of chronic schizophrenia patients even if depressive symptoms are absent (Singh et al., 2010). Second, amineptine increases dopamine transmission in the central nervous system. As all chronic catatonic patients in this series of trials presented with hypo-akinetic syndromes, although not with frank stupor, that suggested a hypodopaminergic state, just the right target for an antidepressant with dopamine-enhancing action.

Amineptine is derived from tricyclic antidepressants. Its main mode of action in vivo and in vitro is the inhibition of dopamine uptake in both D1 and D2 receptor sites (Bonnet et al., 1987). Amineptine is reportedly effective in amotivational depressive states associated with psychomotor retardation (Deniker et al., 1980). Although amineptine has proved to be fast-acting and efficacious (Deniker et al., 1980), its side-effect profile (rare but severe hepatotoxicity and acneiform eruptions) and addictive potential (Prieto et al., 1994) have restricted its widespread use.

The aim of this study was to explore the therapeutic effect of amineptine on the catatonic syndrome associated with chronic schizophrenia. To tease out the possible anti-catatonic effect of amineptine, in addition to the standardized BFCRS, various aspects of psychopathology and EPS were simultaneously rated.

METHOD

Subjects

Over an 18-month period, a comprehensive review of the psychiatric, medical and social status of all chronically ill inpatients in a 170-bed long-term rehabilitation facility (Shatin Hospital, Hong Kong) was undertaken by the author with the help of a multidisciplinary team. Diagnoses were assigned according to DSM-IV (APA, 1994) by the author, who had been responsible for the day-to-day management of all patients. Of the 170 patients, 135 were diagnosed with DSM-IV schizophrenia; 18 patients who presented

with the persistent and prominent catatonic features to warrant the subtype diagnosis of catatonic schizophrenia were selected for the study. During previous trials with lorazepam and benzhexol, 3 patients were discharged to other types of residential care, leaving 15 subjects for the current study.

None of the 15 subjects had an ongoing serious medical condition, a history thereof or significant alcohol or substance abuse. Their mental states had been stationary at least for a year and in most cases for many years. Over the years these treatment-resistant subjects received several combinations of antipsychotic treatment with first and second-generation antipsychotic drugs without appreciable treatment response. During the 15-week trial, only 50 mg/day of chlorpromazine equivalent (CPZeq) antipsychotic medication was allowed in case of agitation or the worsening of psychotic symptoms; otherwise, the pre-existing drug regime was unchanged.

Assessment instruments

Aspects of psychopathology, catatonia and EPS were evaluated with the following standardized rating scales: the Brief Psychiatric Rating Scale (BPRS; Wernner et al., 1988), Hamilton Depression Rating Scale (HDRS; Williams, 1988), Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983), Clinical Global Impression (CGI; Guy, 1976) for psychopathology, Simpson-Angus Extrapyramidal Side Effect Scale (SAS; Simpson & Angus, 1970), Abnormal Involuntary Movement Scale ([AIMS; Munetz & Benjamin, 1988), for EPS and the BFCRS, and the Modified Rogers Scale (MRS; McKenna et al., 1991) for catatonia.

Study design and procedures

The study had a placebo-controlled, double-blind, crossover design that lasted for 15 weeks; 6 weeks add-on 200 mg/day of amineptine and an identical-looking placebo, interspersed with a 3-week wash-out period during which the subjects took their standard antipsychotic medication only. Eight patients were started on amineptine, 7 began the study on the placebo. Assessments were made four times: at baseline and at the ends of week 6, week 9 and week 15. The same three raters, all qualified psychiatrists with considerable clinical and research experience, scored psychopathology, EPS and catatonia on each occasion independently and blind not only to the medication status of the subjects but also to the overall

Table 1. Basic socio-demographic and clinical data for the study sample

	Amineptine/Placebo	Placebo/Amineptine
Age (years)	52.3±14.6	47.4±11.0
Sex		
Male	6	5
Female	2	2
Age of onset (years)	24.8±14.8	21.1±5.5
Age at first hospitalization (years)	28.4±16.1	22.0±5.8
Current antipsychotic dose (CPZeqmg/day)	181.3±263.5	428.6±285.6
Length of antipsychotic treatment (years)	19.3±13.1	23.9±11.1

Table 2. Clinical ratings at baseline and week (mean±sd)

<i>Instruments</i>	Amineptine		Placebo	
	Baseline	week 6	Baseline	week 6
BPRS	28.0±6.7	26.2±7.3	29.3±8.0	27.8±6.0
HRDS	4.5±3.4	4.3±2.7	4.6±3.8	4.8±2.5
SANS	97.2±12.1	93.9±12.0	94.5±12.6	97.4±10.9
CGI	6.4±0.6	6.5±0.5	6.4±0.6	6.4±0.6
BFCRS	16.2±4.7	14.4±3.2	14.5±4.2	14.9±4.3
MRS	19.6±4.2	18.3±3.2	20.1±4.4	19.0±3.9
SAS	2.0±2.2	2.5±1.7	2.6±2.7	2.2±0.8
AIMS	5.6±5.6	7.0±5.1	5.7±5.3	6.6±5.7

BPRS=Brief Psychiatric Rating Scale; HRDS=Hamilton Depression Rating Scale; SANS=Scale for Assessment of Negative Symptoms; CGI=Clinical Global Impression; BFCRS=Bush-Francis Catatonia Rating Scale; MRS=Modified Rogers Scale; SAS=Simpson-Angus Scale; AIMS=Abnormal Involuntary Movement Scale

study design. The raters worked in a different setting and were not involved in the subjects' routine clinical management.

Statistical analysis

The statistical analysis was performed with the SSPS statistical package, Version 10. Depending on the distribution of variables, the t-test, Mann-Whitney U-test, and Fisher's exact test were used to compare basic demographic and clinical information between the drug and placebo groups. A paired t-test was used to determine the differences between baseline scores for all clinical measurements. Split plot analysis of variance (ANOVA) was used to test the carry-over, period and treatment effects.

Ethical considerations

The study protocol was approved by the Ethics Committee of the Chinese University of Hong Kong and that of Shatin Hospital. All patients signed a consent Form and, in keeping with Chinese cultural traditions, available relatives were also informed about the trials.

RESULTS

Basic socio-demographic and clinical characteristics of the 15 subjects meeting the criteria of catatonic schizophrenia according to DSM-IV are shown in Table 1. The baseline and post-trial values of the comprehensive set of rating scales are presented in Table 2. A cursory glance at the Tables reveals that the chronically

ill, late middle-aged subjects had prominent psychotic symptomatology, severe catatonic syndrome and a poor level of overall functioning. No significant differences were found between the amineptine/placebo and the placebo/amineptine groups ($p > 0.1$; t-test, Mann-Whitney U-test and Fisher's exact test), and neither were any differences between the baseline scores for any of the clinical rating scales ($p > 0.35$, t-test). No significant treatment effects were found for any of the clinical measurements ($p > 0.05$; F-test) except for a weak treatment effect for the SANS composite score ($p = 0.02$; $df = 1.13$; $F = 7.74$). No treatment-emergent side effects were observed or reported by the subjects.

DISCUSSION

Apart from a weak statistically significant but clinically negligible improvement in the negative symptoms, there was no change on any of the rating scales. A slight improvement in the negative symptoms of schizophrenia on antidepressant treatment is a well-known phenomenon, although its pathomechanism is still uncertain (Singh et al., 2010). This study confirmed an earlier report that amineptine could reduce the severity of negative symptoms in some patients with schizophrenia (Volterra et al., 1990).

Following the therapeutic failure of lorazepam and benzhexol, amineptine augmentation was also unsuccessful in improving persistent catatonic signs and symptoms occurring in chronic schizophrenia. This finding seems to replicate the results of earlier studies that found that schizophrenia characterized by prominent catatonic features is particularly resistant to antipsychotic drugs (Fish, 1964; Astrup, 1979; Ban, 1990; Beckmann et al., 1992).

The main limitation of the study is its relatively small sample size, which might be partially offset by its strengths including the clinically homogenous sample, the independent assessment of catatonia, psychopathology and EPS with a comprehensive set of rating scales, the random assignment, double-blind cross-over design and the use of experienced clinicians as raters.

On the basis of one relatively small-scale treatment response study it would be premature to make assumptions about the pathomechanism of chronic catatonia. The complete lack of response to the dopamine agonist amineptine and also to lorazepam (Ungvari et al., 1999) and benzhexol suggest, however, that cholinergic-dopaminergic imbalance, dysfunction in GABA-dopamine interrelations or a hypodopaminergic

state – all of which have been implicated in the pathogenesis of acute catatonia (Taylor & Fink, 2003; Caroff et al., 2004) – may not play a decisive role in the development of the motor manifestations of chronic catatonia. Further, larger scale, comprehensive studies involving sophisticated neuroimaging techniques are needed to elucidate the pathophysiology of the fascinating psychomotor phenomena of transient (acute) and enduring (chronic) catatonia.

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Tartós kataton tünetek kezelése szkizofréniában amineptinnel: kontrollált vizsgálat

Kérdésfelvetés: A krónikus szkizofréniát kísérő, tartósan fennálló kataton tünetek kezeléséről kevés adat áll rendelkezésre. A jelen közlemény célja az amineptin, egy dopamin rendszert stimuláló antidepresszáns terápiás hatásának vizsgálata krónikus kataton szkizofréniában. **Módszer:** A 15 hetes, kettős vak, cross-over vizsgálatban 15, DSM-IV szerint diagnosztizált krónikus kataton szkizofrén beteg vett részt. A betegek 6-6 hét amineptin és placebo kezelésben részesültek a fennálló antipszichotikus terápia kiegészítéseképpen, 3 hetes wash-out periódussal elválasztva. A kataton tünetek változását a Brief Psychiatric Rating Scale és a Modified Rogers Scale segítségével regisztráltuk. A pszichopatológia egyéb aspektusainak és az extrapiramidális mellékhatások változásait ugyancsak standardizált becslőskálákkal követtük. **Eredmények:** Amineptin hozzáadása az antipszichotikus kezeléshez nem befolyásolta a kataton tüneteket. Eltekintve a negatív tünetcsoport statisztikusan szignifikáns, de klinikailag nem számottevő csökkenésétől, az egyéb pszichopatológiai és extrapiramidális tünetek változatlanok maradtak a vizsgálat során. **Következtetés:** A dopamin agonista amineptin terápiás hatástalansága tartósan fennálló kataton szkizofréniában azt sugallja, hogy a dopamin rendszernek nem valószínű, hogy jelentős szerepe lenne a szkizofréniához csatlakozó krónikus fennálló kataton tünetek patofiziológiájában.

Kulcsszavak: katatónia, szkizofréniában, amineptin