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Combination therapy with amisulpride and antidepressants: Clinical observations in case series of elderly patients with psychotic depression

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ABSTRACT

Psychotic depression is classified as a clinical subtype of major depressive disorder. The combination of an antidepressant with an antipsychotic agent has been demonstrated to be efficacious for the treatment of psychotic depression. However, in elderly patients with psychotic depression, little information is available on the efficacy of such combinations. Therefore, we have evaluated combination treatment for 5 weeks with amisulpride and antidepressants in non-demented elderly patients with psychotic depression. Eleven patients were treated with either citalopram 20–40 mg/day ($n=5$) or mirtazapine 30–60 mg/day ($n=6$), and amisulpride 75–100 mg/day for 5 weeks. Clinical status was evaluated at baseline and after 3 and 5 weeks using the Brief Psychiatric Rating Scale (BPRS), the Hamilton Depression Rating Scale—17 items (HDRS) and the Clinical Global Impression Scale (CGI-S). In 5 of the 11 patients there was remission of depression, while in another 5 patients there was partial remission of depression and in one patient there was no remission. Finally, there was resolution of psychotic symptoms in all the patients involved. One patient developed tremor and rigidity but insisted on continuing with the drug since her psychopathology has improved considerably after the addition of amisulpride to antidepressant treatment. In conclusion, some of the elderly patients with psychotic depression may benefit from the combination of amisulpride and antidepressant pharmacotherapy.

1. Introduction

Psychotic depression is classified as a clinical subtype of major depressive disorder according to DSM-IV TR (APA, 2000). Patients with this psychopathology differ from those with non-psychotic depression in certain sociodemographic characteristics, family history, neurobiological variables, clinical symptoms, neuropsychological profile and response to pharmacological treatments. They are more likely to relapse and generally have a poorer clinical course (Bassiony et al., 2002; Jeste et al., 2005a; Lykouras et al., 1986; Politis et al., 2004; Rothschild, 2003; Schatzberg and Rothschild, 1992; Schatzberg, 2003). The prevalence of geriatric psychotic depression is 20%–45% in hospitalised patients and 3.6% in outpatients (Jeste et al., 2005a; Meyers, 1992).

Combination of an antidepressant with an antipsychotic agent is considered the most appropriate first-line treatment for the management of old-age psychotic depression (Alexopoulos et al., 2004). However, in elderly patients with psychotic depression, little information is available on the efficacy of such combinations. A randomised controlled trial by Mulsant et al. (2001) compared the efficacy of nortriptyline plus perphenazine vs. nortriptyline plus placebo in 36 patients aged 50 or older with psychotic depression, in which the response rates (defined as resolution of both depression and psychosis) did not differ significantly between the two groups (50% and 44% respectively).

Since elderly psychotic patients are more sensitive to extrapyramidal side-effects, atypical antipsychotics seem to be a safer choice of treatment compared to classical antipsychotics. (Friedman, 2003; Jeste et al., 2005b; Katona, 2001). In addition, these patients may be more susceptible to drug interactions and changes in metabolism. The atypical antipsychotic amisulpride (Leucht, 2004) is not metabolised by the liver and is therefore a good candidate for treatment of the elderly (Hamon-Vilcot et al., 1998; Legangneux et al., 2000). This drug has been shown to be efficacious in dysthymic (Bellino et al., 1997), psychotic (Möller et al., 2005) elderly patients and in the treatment of behavioural disturbances of patients with moderate to severe Alzheimer's disease (Mauri et al., 2006). However, in a recent study it was proposed that adverse effects offset advantages in the efficacy of

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; APA, American Psychiatric Association; BPRS, Brief Psychiatric Rating Scale; CGI-S, Clinical Global Impression Scale; DSM, Diagnostic and Statistical Manual of Mental Disorders; ECG, electrocardiogram; HDRS, Hamilton Depression Rating Scale—17 items; MMSE, Mini Mental State Examination; NIMH, National Institute of Mental Health; SAS, Simpson–Angus Scale.

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atypical antipsychotics for the treatment of psychosis, aggression and agitation in patients with Alzheimer's disease (Schneider et al., 2006).

The aim of our 5-week study was to observe the efficacy and safety of combination treatment with amisulpride and antidepressant treatment in elderly patients with psychotic depression.

2. Method

2.1. Subjects

Forty-five elderly outpatients with unipolar depression and mood-congruent psychotic symptoms were interviewed. Two psychiatrists independently administered the Structured Clinical Interview for DSM-IV Axis I Disorders Patient's Edition to each subject. Subjects with a history of substance dependence or current abuse, or with neurological disease were excluded. Of the initial 45 patients interviewed, 28 were excluded (20 suffering from dementia and 8 suffering from a neurological disease) and six were not included as they refused to provide written informed consent. All patients before entering this study gave their written informed consent. The remaining eleven patients (4 males and 7 females) were aged from 65 to 87 years (mean:75.6± 7.9 years) and fulfilled consensus criteria for the treatment of psychotic depression in the elderly (Alexopoulos et al., 2004). Cognitive function was assessed using the Mini Mental State Examination (MMSE, Folstein et al., 1975). All subjects had MMSE score >26 at inclusion.

Patients and doctors participated in the study were masked to antidepressants selection. Each of the eleven patients was randomised to treatment either with citalopram or mirtazapine. We gave each patient an identification number and then we generated from the computer a randomizer form. After 4–6 weeks of application of each of these two antidepressants (citalopram 20–40 mg/day and mirtazapine 30–60 mg/day) without any improvement of the patients' psychotic symptoms, adjunctive pharmacotherapy with amisulpride was implemented at a starting dose of 75 mg/day and adjusted according to clinical status. The dosage of the antidepressant treatment at first and of the antipsychotic treatment later on, was gradually titrated according to each patient's clinical condition. Monotherapy with antidepressant was chosen as a first step to combination treatment of antidepressant and amisulpride since there are reports of antidepressant monotherapy with positive treatment outcomes both in elderly and younger patients suffering from psychotic depression (for a review see Mulsant et al., 2001).

2.2. Symptom ratings

The Brief Psychiatric Rating Scale (BPRS, Ventura et al., 1993), the Hamilton Depression Rating Scale—17 items (HDRS, Hamilton, 1960) and the Clinical Global Impression Scale (CGI, NIMH, 1976a) were assessed at baseline of the combination therapy and after 3 and 5 weeks. Adverse events, routine laboratory test results and changes in body weight were recorded and extrapyramidal symptoms were evaluated with the Simpson–Angus Scale (Simpson and Angus, 1979), Barnes Akathisia Scale (Barnes, 1989) and the Abnormal Involuntary Movement Scale (AIMS, NIMH, 1976b). ECG, blood pressure and heart rate were also monitored during the study. A patient was judged to be a full responder if he/she experienced full resolution of both depressive symptoms (final total HDRS score of 10 or below) and psychotic symptoms [final scores of 1 (none) or 2 (doubtful) for BPRS items regarding suspiciousness (item 11), hallucinatory behaviours and statements (item 12), and unusual thought content (item 15)] (Mulsant et al., 2001). Non-response was defined as persistence of both significant depressive symptoms (HDRS score of 15 and above) and psychotic symptoms [scores on BPRS items 11, 12 or 15 of 3 (mild) or higher]. Patients who were neither full responders nor non-responders (i.e. they had residual depressive or psychotic symptoms) were classified as partial responders (Mulsant et al., 2001).

2.3. Brief description of cases

All patients who participated in the study presented with delusional ideas while patient nos. 2, 7, 10 and 11 experienced agitation as well. For a more detailed look for the demographics of the patients, medications used, the dosages, responses to medications and side-effects see Table 1.

3. Results

All patients completed the 5-week procedure. The mean dose of amisulpride at the end of the study was 85.6± 13 mg/day (range 75–100).

Concomitant medication included antihypertensive drugs (n=6), aspirin (n=2), lorazepam (n=3, range: 1–2 mg/day) and bromazepam (n=1, daily dosage: 1.5 mg/day). The percentage reduction in score with respect to baseline after 3 weeks was 21.6% for the BPRS, 24.5% for the HDRS and 38% for the CGI; after 5 weeks of treatment, the percentage reduction was 36% for the BPRS, 53% for the HDRS and 67% for the CGI. In five of the 11 patients (45,4%) there was full remission of depression (HDRS≤10), while in another 5 patients (45,4%) there was partial remission of depression (HDRS=11–14) and in one patient there was no remission (HDRS=15) (9%). Finally, there was resolution of psychotic symptoms in all the patients involved. No statistically significant change in overall cognitive function MMSE score was observed.

No clinically adverse effects or abnormalities related to ECG, heart rate or blood pressure were reported. At study endpoint, the mean change in weight was 0.018±0.64 kg [range (−1)–(+1) kg]. No patient complained of sedation or sleep problems. One patient experienced extrapyramidal symptoms (rigidity and tremor). The patient was

Table 1
Epidemiological and clinical characteristics of the sample

			BPRS		HDRS		CGI		Amisulpride	Antidepressant	
Subject	Sex	Age	Baseline	5-week	Baseline	5-week	Baseline	5-week	(mg/day)	(mg/day)	Side effects
1	Female	77	30	20	20	11	4	2	100	C 20	–
2	Female	65	37	21	21	10	5	1	100	C 30	–
3	Male	65	33	20	25	12	4	2	100	M 30	–
4	Female	69	30	21	27	15	4	2	75	C 40	–
5	Female	77	34	22	26	11	5	2	75	C 30	–
6	Female	68	31	22	26	12	4	2	75	M 30	–
7	Female	87	34	22	24	13	5	2	75	M 30	–
8	Male	85	32	24	22	11	4	2	100	M 30	–
9	Female	84	33	21	17	10	5	1	75	C 20	Tremor
10	Male	78	35	20	22	9	5	1	75	M 45	–
11	Male	77	38	20	23	9	6	1	100	M 60	–

BPRS = Brief Psychiatric Rating Scale, HDRS = Hamilton Depression Rating Scale, CGI = Clinical Global Impression Scale.
C = citalopram, M = mirtazapine.