Letters to the Editor

Sirs,

Moclobemide and amitriptyline, alone or in combination, in therapy resistant depression

Treatment resistant depression is of major concern to most practising physicians and its management at some point often includes the combination of antidepressants. Although psychiatrists are reluctant to use such combinations due to the report of serious adverse events with some of them, the combination of amitriptyline with a MAO-inhibitor has been shown to be effective and well tolerated (Razani *et al*., 1983; Schmauss *et al*., 1986; van Oefele *et al*., 1986). Combined with amitriptyline, moclobemide was well tolerated in healthy volunteers (Amrein *et al*., 1992). In order to demonstrate the good tolerability and safety of the combination moclobemide/amitriptyline in hospitalised patients with therapy resistant depression and to evaluate if the combination treatment is more efficacious and has a faster onset of action than monotherapy, we performed a randomised, double-blind, three-armed, single-centre trial.

Fifty-nine in-patients (46 F, 13 M), aged 43 $\pm$ 12 years (range 18–69) fulfilling the DSM-III R criteria of Major Depressive Episode (MDE) were studied. The patients scored a mean of 41 $\pm$ 7 on the MADRS and were resistant to treatment with at least 2 separate antidepressants. The patients were selected for 4 weeks treatment with moclombemide (M) or amitriptyline (A) separately or combined (MA). M was administered at a dosage ranging from 200 to 600 mg/d, while A was administered at an increasing dosage to a maximum of 280 mg/d.

When evaluating the onset of action globally, a non-significant trend towards a faster onset of action was noted for the combination group. Worth noting is the fact that drop-outs in the amitriptyline and combination group were mainly caused by a switch to (hypo)mania (5 in the A-group and 4 in the MA-group), while a majority of patients in the moclobemide-group (at least 4) dropped out for lack of efficacy. Our data suggest that moclobemide in monotherapy is an effective treatment for therapy resistant depression. It is better tolerated and seems to have a more gentle onset of action compared to amitriptyline and the combination treatment. However, the relatively low number of patients studied makes the finding of statistically significant differences in efficacy highly improbable.

The combination treatment-group showed a tendency towards increasing agitation, predicting an imminent switch to (hypo)mania or improvement in mood. In our opinion, this reserves the combination treatment to hospitalised patients only, at least at the very beginning of therapy. Taking into account the trend in favour of a more rapid onset of action of the combination, there seems to exist some basis for the use of this combination in resistant, severely depressed,

Table 1 MADRS score evolution (Patients Evaluable for Efficacy; score $\pm$ st.dev.)

	Day 1	Day 6	Day 10	Day 14	Day 21	Day 28
Amitriptyline ($n = 19$)	39.16 ($\pm$ 5.10)	28.16 ($\pm$ 9.56)	22.47 ($\pm$ 5.10)	18.31 ($\pm$ 9.82)	13.31 ($\pm$ 7.75)	15.54 ($\pm$ 11.93)
Moclobemide ($n = 19$)	41.26 ($\pm$ 8.22)	29.63 ($\pm$ 11.19)	21.06 ($\pm$ 12.73)	17.59 ($\pm$ 10.51)	13.57 ($\pm$ 13.77)	7.20 ($\pm$ 7.11)
Combination ($n = 20$)	41.80 ($\pm$ 6.08)	31.65 ($\pm$ 9.56)	22.11 ($\pm$ 11.35)	15.71 ($\pm$ 12.64)	12.33 ($\pm$ 13.66)	8.92 ($\pm$ 8.38)

hospitalised patients. Signs of increasing agitation must however be anticipated, and indicate prompt reassessment of the antidepressant treatment.

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Sirs,

Intermittent withdrawal program of neuroleptics with sulpiride in remitted schizophrenic outpatients

Long-term neuroleptic treatments are at high risk for neuroleptic-associated tardive syndromes. Furthermore, inadequate high dose treatment might prevent patients from returning to their former employment because of behavioral inactivity induced by neuroleptics. Consequently, there has been increasing interest in developing viable clinical management alternatives to long-term, high-dose neuroleptic drug maintenance and prophylaxis. One approach is the use of continuous medication at doses considerably below those traditionally viewed as therapeutic (Heresco-Levy *et al.*, 1993). Others have attempted to reduce cumulative neuroleptic doses by administering medication only during episodes of symptom exacerbation (Herz *et al.*, 1991). The present study was performed to explore the usefulness of a neuroleptic withdrawal program in remitted schizophrenics using gradual intermittent treatment with the selective D2 receptor blocker, sulpiride.

Forty-six remitted schizophrenic outpatients (their maintenance chlorpromazine equivalents: 265.6 ± 163.5 mg) were given gradual drug reduction and then switched to one tablet of sulpiride 200 mg/day at night. Twenty-two patients gave informed consent to participate in this intermittent neuroleptic withdrawal program (Trial group). Other patients continued to take sulpiride 200 mg/day (Continuous group). An abrupt withdrawal group (their maintenance chlorpromazine equivalents: 258.8 ± 186.2 mg) was used as a retrospective placebo group (Placebo group). Final number of patients on the Trial, Continuous and Placebo group was 19, 15 and 13, respectively. The three groups were virtually identical with respect to age and sex of the subjects, onset age, years after onset the disease, number of hospitalization and remission periods before the beginning of the trial (Table 1). The gradual intermittent withdrawal program consisted of five steps (drug intake every

Table 1. Background of Subjects. Values are expressed as the mean $\pm$ SD

	Number	Age	Sex		Onset age	Years after onset of the disease	Number of hospitalization	Remission period (years)
			Male	Female				
Trial group	19	42.3 ± 12.9	14	5	26.5 ± 9.7	15.7 ± 12.5	3.3 ± 3.1	3.0 ± 5.0
Continuous group	15	36.9 ± 12.3	11	4	24.8 ± 5.6	13.3 ± 8.7	2.5 ± 2.0	4.0 ± 5.6
Placebo group	13	39.4 ± 10.0	9	4	26.8 ± 6.9	13.9 ± 8.3	3.8 ± 2.4	7.7 ± 8.5

