INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY, VOL. 9: 55–59 (1994)

A PILOT PLACEBO-CONTROLLED STUDY OF TRAZODONE AND BUSPIRONE IN ALZHEIMER'S DISEASE

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SUMMARY

The pharmacological management of behavioural symptoms in Alzheimer's disease is limited by the dearth of effective agents in this area. The purpose of this study was to determine whether trazodone or buspirone are helpful in the treatment of behavioural disturbance in AD. Ten patients meeting NINCDS criteria for AD with behavioural complications were administered trazodone (up to 50 mg tid), buspirone (10 mg tid), and placebo in a 12-week double-blind, crossover design. Outcome measures were the Brief Psychiatric Rating Scale (BPRS), the Dementia Mood Assessment Scale (DMAS), and the Buschke Selective Reminding Task. The data were analysed by ANOVA. Compared to placebo, trazodone produced a small but significant reduction in BPRS and DMAS scores ($p < 0.05$), indicating improvement in behaviour but no change in cognitive measures. In contrast, buspirone has no significant effect on either behavioural or cognitive measures compared to placebo. The results of this pilot study suggest a beneficial role for trazodone, but not buspirone, in the treatment of behavioural disturbance in AD. Further studies using a wider range of doses of trazodone in more behaviourally disturbed AD patients should now be initiated in an attempt to replicate and expand on this preliminary finding.

KEY WORDS—Pilot study, clinical trial, trazodone, buspirone, Alzheimer's disease.

Behavioural complications such as agitation, depression, psychosis and anxiety are commonplace in Alzheimer's disease (AD), and result in much disability and distress for caregiver and patient (Zarit and Zarit, 1983). Unfortunately, pharmacological interventions in this area tend to be empirically based, unpredictable in terms of response rate, and can often result in problematic side-effects (Sunderland and Silver, 1988).

There is an accumulating body of evidence pointing to the existence of a significant serotonergic deficit in AD (Cross *et al.*, 1984, 1986; Palmer *et al.*, 1987; Middlemiss *et al.*, 1986; Bowen *et al.*, 1989). While the clinical correlates of 5-HT abnormalities in AD are unclear, some of the behavioural symptoms, notably depression and agitation, may be linked to the presence of a serotonergic lesion (Zubenko and Moosy, 1988; Zweig *et al.*, 1988; Palmer *et al.*, 1988; Nyth and Gottfries, 1990). Furthermore, given the emerging evidence supporting a role for 5-HT in learning and memory (Altman and Normile 1986), abnormalities in this system may also be relevant to the cognitive disturbances in AD.

Trazodone, a heterocyclic antidepressant with mixed 5-HT agonist/antagonist properties (Maj *et al.*, 1979), and buspirone, a novel anxiolytic with 5-HT1A agonist activity (Hoyer, 1986), have anecdotally been reported to improve behavioural symptoms in dementia patients (Simpson and Foster, 1986; Colenda, 1988; Greenwald *et al.*, 1986; O'Neill *et al.*, 1986). The purpose of this study was to examine, in a pilot fashion and under controlled conditions, whether trazodone or buspirone could improve behavioural disturbance in a group of carefully characterized outpatients with AD.

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0885–6230/94/010055–05$07.50

Received 24 November 1992
Accepted 29 March 1993

METHODS

Ten patients (mean age 67.6 ± 7.24 years, seven males, three females, mean duration of illness 4.85 ± 2.39 years, mean GDS score (Reisberg *et al.*, 1982) 4.4 ± 0.97) were included in this study. All patients met NINCDS criteria for AD (McKhann *et al.*, 1984), and were experiencing behavioural complications, defined in this instance as the presence of either agitation, depression, psychosis or anxiety of such a degree as to interfere with the patient's or caregiver's quality of life. Prior to entry into the study, all patients scored ≥4 on one of the BPRS items, and had a total BPRS score of ≥30. All subjects were free of neuroleptics or benzodiazepines for at least 2 weeks prior to commencing the study.

Patients were randomly assigned to receive either trazodone, up to 150 mg a day, buspirone 30 mg a day, or placebo, in a double-blind fashion, counterbalanced for order. With buspirone, patients started on 10 mg tid, whereas with trazodone, patients were commenced on 50 mg a day, increasing in 50 mg increments every 2 days as tolerated up to a maximum dose of 150 mg a day. Each treatment phase lasted 4 weeks, and there was no intervening washout period.

Behavioural disturbance was assessed using the Dementia Mood Assessment Scale (DMAS) (Sunderland *et al.*, 1988) and the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) at the end of each treatment phase. Cognition was evaluated using a modified (six-word) selective reminding task (Buschke, 1973). Side-effects were recorded using the NIMH Side-Effect Scale.

Data analysis

The data were analysed by ANOVA comparing endpoint assessments for each of the drug conditions with placebo.

RESULTS

Trazodone treatment resulted in a small but significant decrease in the total BPRS scores (Fig. 1) and in the total DMAS and 18–24-item DMAS scores (Fig. 2) compared to placebo.

In contrast, there was no change on behavioural measures following buspirone. The overall improvement in behaviour on trazodone does not appear to have been an antidepressant effect, since there was no specific decrease in the 17-item DMAS, which reflects depression in this patient population (Fig. 2).

Both the free recall and the new learning measures on the selective reminding task showed no significant change following either buspirone or trazodone compared to placebo.

All patients tolerated 30 mg of buspirone a day. However, a number of patients were unable to tolerate 150 mg of trazodone because of excessive sedation; thus the mean dose of trazodone for the 10 subjects was 120 ± 35 mg a day.

DISCUSSION

In spite of an extensive anecdotal literature on the usefulness of trazodone and buspirone in behaviourally disturbed dementia patients, this is the first attempt to examine the efficacy of these serotonergically active agents under controlled conditions in AD. Trazodone, in doses up to 150 mg a day, resulted in only a modest improvement in disturbed behaviour, whereas buspirone, at what would be considered to be therapeutic antianxiety doses in this age group, showed no beneficial effects.

The pharmacological mechanism through which trazodone achieves its therapeutic effect is unclear. Trazodone's 5-HT antagonist properties may be particularly relevant in this regard, in view of the hyperresponsive behavioural effects of meta-chlorophenylpiperazine (m-CPP), a 5-HT agonist and metabolite of trazodone, in AD patients (Lawlor *et al.*, 1989).

The size of the drug effect seen in this study was modest and of doubtful clinical significance. However, methodological issues such as low dosage and potential carryover effects may have mitigated against a more robust effect for trazodone.

The results of this pilot study support the initiation of larger controlled trials using higher doses of trazodone. Such studies should explore the efficacy of this agent in treating a wide range of disturbed behaviours in these patients, and help determine whether trazodone's utility relates specifically to AD or in a more general fashion to all dementia patients, irrespective of the underlying diagnosis or neurobiology.

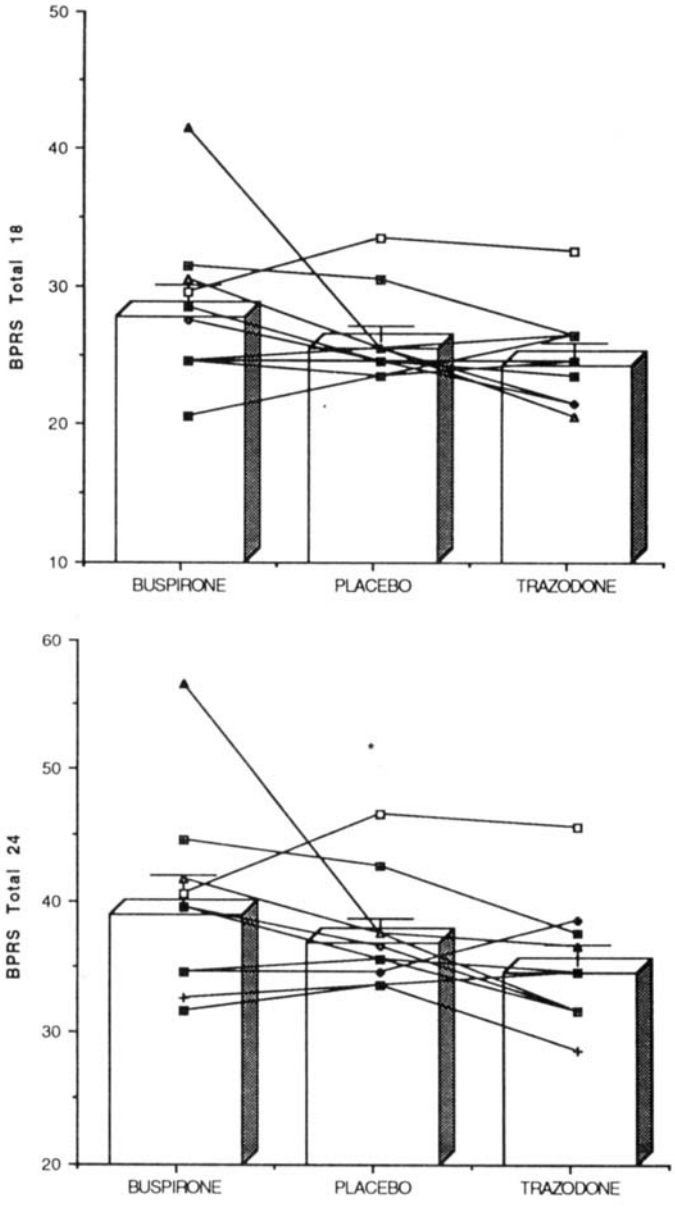

Fig. 1 Effect of trazodone and buspirone on BPRS scores. * $p < 0.05$, trazodone vs placebo. Data expressed as mean ± SEM

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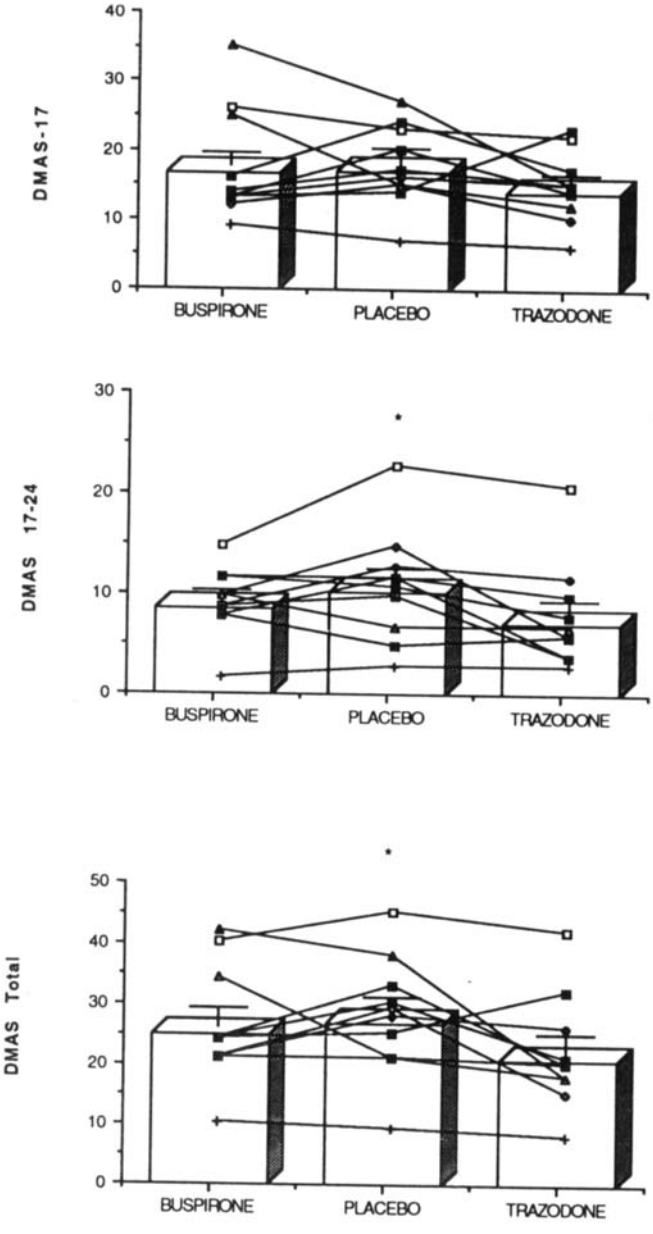

Fig. 2 Effect of trazodone and buspirone on DMAS scores. * $p<0.05$, trazodone vs placebo. Data expressed as mean ± SEM

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