

Clinical Assessment and Performance Tasks in Depression: a Comparison of Amitriptyline and Trazodone

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Depression, anxiety and psychomotor performance were assessed in 20 depressed patients during double-blind treatment with amitriptyline or trazodone. There was no difference in onset of antidepressant or anxiolytic action. No decrement or improvement on computerised tasks was found. Dry mouth was significantly more frequent and severe with amitriptyline.

The tricyclic antidepressants remain the yardstick against which newer remedies are compared, although they can cause troublesome side-effects, particularly those resulting from cholinergic blockade. Moreover, in overdose and in certain forms of heart disease they are toxic, and cardiac arrhythmias are a special cause for concern. There is a need to develop new drugs which are as effective as the tricyclics but which do not have their drawbacks, and trazodone is a candidate for inclusion in this category.

Trazodone, a triazolopyridine derivative, was first synthesised in 1966; chemically it is 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1, 2, 4-triazolo-[4, 3-a] pyridin-3(2H)-one hydrochloride. Trazodone has an unusual pharmacological profile since it has both agonist and antagonist activity in the cerebral serotonin-mediated pathways, it reduces the sensitivity of central beta-adrenoreceptors, and in animals there are no substantial anticholinergic or cardiotoxic effects characteristic of tricyclic antidepressant drugs (Al-Yassiri *et al*, 1981). Clinical studies are consistent with this last finding (Gershon & Newton, 1980; Van de Merwe *et al*, 1984).

The present study was undertaken to establish if there are important differential effects on intellectual function, on psychomotor function, or in the speed of onset of antidepressant action of amitriptyline (AMT) as compared with trazodone (TZ).

Method

In a double-blind parallel-group comparison of AMT and TZ, patients in whom primary depressive illness was diagnosed were recruited. Inclusion criteria required the presence of depressed mood out of proportion to the environmental situation, and disabling depressive symptoms (e.g. disturbed affect, loss of interest and energy, and pessimistic thought content) in numbers above those found in the normal population. Furthermore, patients included were those who, in the opinion of the prescribing physician, required treatment with antidepressant drugs.

The patients were aged 18-80 years, suffered from a current episode of depressive illness of less than 18 months' duration, and were in satisfactory physical health. Patients were excluded if they were suffering from other psychiatric disorder (organic or functional), if they had received electroconvulsive therapy (ECT) in the previous three months, if their current episode was severe enough to warrant ECT, if they had received adequate doses of antidepressants in the past seven days (according to the manufacturer's recommendations), if they required other psychotropic drugs (other than small doses of benzodiazepines at night only), or if they were pregnant. In the event, six patients (three in each treatment group) received benzodiazepines at night. Informed consent was obtained from patients before they were accepted for the study, and ethical approval was obtained before any patient was started on treatment.

Following one week on placebo (single-blind phase), patients with a score of 17 or more on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) were allocated to three weeks of active treatment according to a predetermined randomisation which was stratified for age (above or below 50) and sex.

After the placebo week, active medication was given as matched capsules of AMT (25 mg) or TZ (50 mg). Between days 8 and 14, the daily doses of AMT and TZ were 75 mg and 150 mg respectively, administered in divided doses twice daily, with the larger portion of the dose taken in the evening. Between days 15 and 21, increased doses of 150 mg and 300 mg respectively were administered. Thereafter, a flexible dosage regimen applied according to the patients' clinical response: the maximum allowable doses for AMT and TZ were 200 mg and 400 mg respectively. Only one patient improved substantially on placebo, and was not entered into the analysis.

On entry to the study, a full clinical assessment was made and the following scales were completed: the HDRS Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), the States of Anxiety and Depression scales (SAD; Bedford *et al*, 1976), the Newcastle Diagnostic Scale (Carney *et al*, 1965), and an overall Severity of Illness scale (1, normal - not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, severely ill; 6, among the most severely ill patients).

On days 8 (first day of active treatment), 12, 15 and 29, the same psychometric assessments were administered,

except that the MADRS was omitted on day 12. Also administered was a Global Improvement Scale with respect to the start of active medication (0, not assessed; 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse).

A battery of computerised performance tasks of known sensitivity – consisting of simple and choice reaction times, a tracking task and an arithmetic test (McManus *et al.*, 1983) – was administered at entry and on days 1, 3, 4, 8 (placebo period), 12, 15, 22 and 29 (double-blind treatment period).

Patients were assessed twice on each test at each visit, except on the first occasion, when each test was administered three times to allow for a learning effect. For the purpose of statistical analysis, the mean score on each day was considered.

Subjective reports on total sleep duration and the perceived quality of sleep were assessed, using the relevant two questions from the St Mary's Hospital Sleep Questionnaire (Ellis *et al.*, 1981), on each of the first 15 days of the study (seven days on placebo, eight days on active treatment).

A checklist for pre-existing events was completed before treatment started, with side-effects being monitored on days 8, 12, 15 and 19. Patients were asked both an open-ended question, "Have you had any problems which you think might be due to the tablets?", and subsequently about specific side-effects. For the specific questions, the clinician rated the frequency and severity of nine side-effects (dry mouth, blurring of vision, constipation, nausea, vomiting, headaches, drowsiness, dizziness and tremors) on all occasions except days 1, 3 and 4. The ratings of severity were 'mild', 'moderate', and 'severe', and the ratings of frequency were 'some of the time', 'most of the time', and 'all of the time'.

The statistical analysis was carried out using univariate and multivariate techniques. Analyses of individual variables across a number of testing days were by analysis of variance with both within-subject and between-subject factors, implemented using the MANOVA technique. Analyses of results on particular testing days were by the unpaired *t*-test. Simultaneous analysis of several dependent variables on a number of testing days was by multivariate analysis of variance using the MANOVA technique.

Results

Ten patients were allocated to each treatment group. The groups did not differ significantly in terms of age (AMT – mean 49.2 years, s.d. 23.2; TZ – mean 45.6 years, s.d. 14.4), sex (AMT – 4 male, 6 female; TZ – 3 male, 7 female), in-patient/out-patient status (AMT – 3 in-patients, 7 out-patients; TZ – 4 in-patients, 6 out-patients), type of depression as rated on the Newcastle score (AMT and TZ – 5 reactive and 5 endogenous each), or severity of illness as judged by the 17-item HDRS (AMT – 29.9, s.d. 2.9; TZ – 27.1, s.d. 3.1). Three patients did not complete the study due to side-effects (2 patients on AMT complained of dry mouth and drowsiness; 1 patient on TZ complained of

headache); these patients' results were not included in the analysis.

Clinical rating scales

The separate clinical rating scales showed high correlations one with another (range 0.550–0.911), and factor analysis revealed two separate independent dimensions: 'Depression' represented well by the MADRS (loading 0.828), and 'Anxiety', represented by the anxiety scale of the SAD (loading 0.909). Only these scales will therefore be reported here.

Statistical analysis used *a priori* comparisons to assess change during the placebo period, and at days 12–29 relative to the placebo period. Differences between drugs were assessed by examination of the interactions between drug type and these comparisons. The MADRS (Fig. 1(a)) showed no evidence of improvement during the placebo period ($P > 0.1$), and then a significant improvement at day 15 ($P < 0.001$) and at day 29 ($P < 0.001$). Tests for interactions of drug and contrasts showed no significant differences ($P > 0.1$) between either of the drugs at any time.

Analysis of the anxiety scale of the SAD (Fig. 1(b)) showed a significant improvement even during the placebo period ($P < 0.01$), and then further improvements by day 15 ($P < 0.01$) and day 29 ($P < 0.001$). Interactions of drug and contrasts showed that the trazodone group was significantly less anxious at day 12 ($P < 0.01$), although this difference had disappeared by days 15 and 29.

Performance tests

A priori contrasts were used to assess learning effects during days 1–4, the stability of the baseline during days 4–8, and then change relative to the baseline during days 12–29. Analysis of performance on all of the four tasks showed a similar pattern of results, and only reaction time and addition tasks are shown in Fig. 1(d) and (e). Highly significant learning effects were present during days 1–4 ($P < 0.001$) for all tasks (except simple reaction time). In all tasks the baseline was stable over days 4–8, and no tasks showed evidence for significant improvement at days 12–29 relative to baseline. None of the tasks showed any statistically significant evidence for differences between the two drugs, during learning, baseline or drug-treatment phases of the study.

Sleep

Quality and duration of sleep were assessed by *a priori* comparisons of sleep during the placebo and the active period, and linear trends within each of these periods, and their interaction with drug type. Sleep quality (Fig. 1(g)) improved significantly during treatment with the active drug ($P < 0.001$), but there were no differences between the two drugs. Sleep duration (Fig. 1(h)) increased on amitriptyline, but not on trazodone, although the effect did not reach statistical significance.

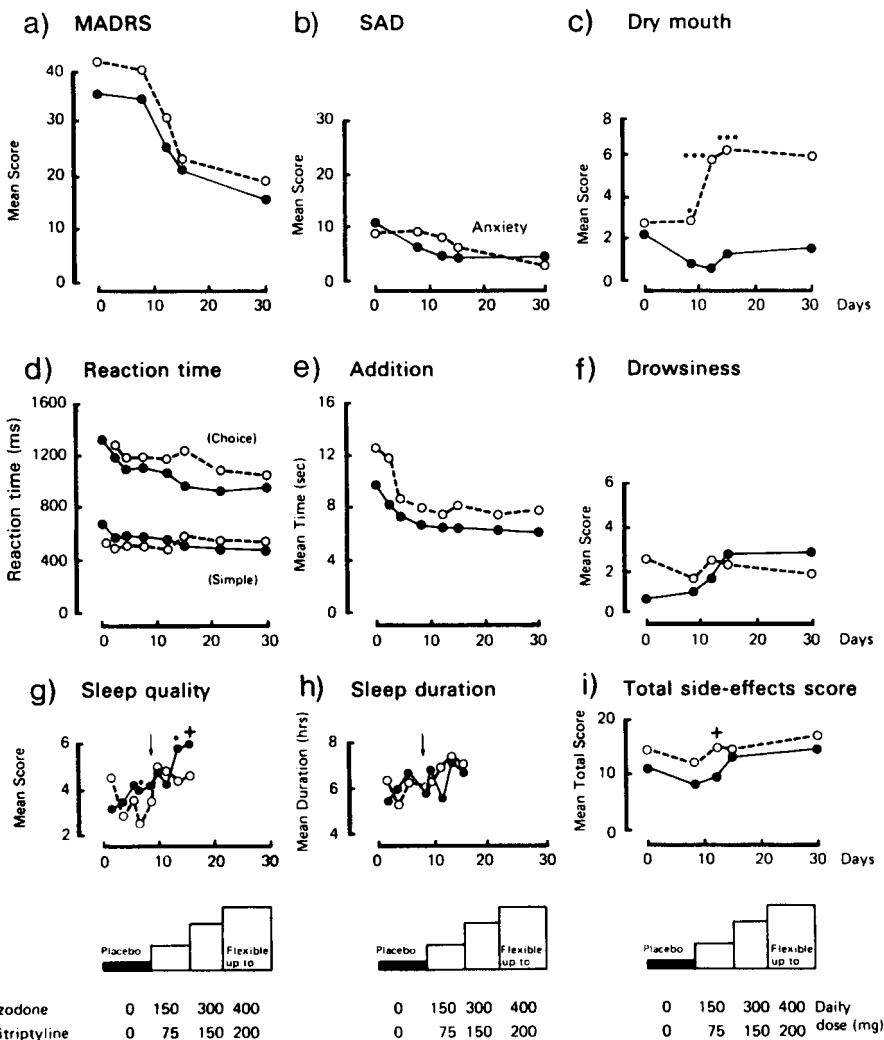


FIG. 1 Results of the assessment of antidepressant (MADRS) and anxiolytic (sAD) activities, performance tests (reaction time and addition tasks), sleep quality and sleep duration, and side-effects (dry mouth, drowsiness and total side-effect score) for patients receiving AMT (○) or TZ (●). + $P < 0.1$; · $P < 0.05$; ··· $P < 0.001$; ↓ start of active treatment.

Side-effects

Side-effects were assessed by means of a composite score for each side-effect, calculated by multiplying ratings of severity and frequency. The nine side-effects were considered separately, and were also combined in a single overall score. 'Dry mouth' showed a significant increase during active treatment ($P < 0.02$) (Fig. 1(c)), but a highly significant interaction with drug treatment ($P < 0.005$) showed that this effect was only present in those treated with amitriptyline. Drowsiness (fig. 1(f)) also showed a significant effect of active treatment ($P < 0.05$), but there was no significant difference between the drugs ($P > 0.1$).

Nausea, blurred vision, vomiting, dizziness, constipation, headache, and tremor showed no significant differences either between active and inactive treatments, or between the two drugs. The total side-effects score (Fig. 1(i)) showed a slight tendency to increase during active treatment ($P < 0.1$), but there was no significant difference between the two drugs.

Discussion

The patients allocated to AMT and TZ were well matched, and no serious difference in the groups

developed as regards dosage change or discontinuation of active treatment. Both drugs had a significant effect in reducing symptoms of depression, but there was no substantial difference between the two treatment groups. However, with a relatively small number of patients, the sensitivity of the measurements may not have been sufficient to provide adequate statistical power to detect differences between the active treatments.

Patients receiving TZ showed an earlier remission of anxiety, which confirms previous reports (Al-Yassiri *et al*, 1983). This is an important subjective improvement in the patient's response and may provide an indication for the use of this drug in the high proportion of depressed patients who also are anxious.

Both drugs improved sleep quality, but a trend for increased duration of sleep was noted with AMT only, a finding similar to that of Montgomery *et al* (1983). Since both drugs cause drowsiness, it is interesting that only AMT caused an increase in duration of sleep, despite the fact that TZ had an early anxiolytic effect (an effect frequently associated with soporific action).

The absence of significant differences on the psychomotor tests is unlikely to be due to an inappropriate bluntness of the tests themselves, since the tests have been shown (McManus *et al*, 1983) to be sensitive to the effects of benzodiazepine and of alcohol. In addition, each of the measures shows clear learning effects within the present study. Nevertheless, even during the period of frank clinical improvement (days 15–29), performance on the psychomotor tasks remained substantially impaired.

The symptoms of blurred vision, constipation, nausea, vomiting, headache, dizziness, and tremor appeared not to be induced by either drug, although drowsiness seemed to be a product of both, and dry mouth an effect of AMT only. Drowsiness is the most frequent side-effect that has been reported for TZ in previous studies (Brogden *et al*, 1981).

In conclusion, the results of the present study fail to suggest an important difference in the onset of antidepressant activity between AMT and TZ. However, the anticholinergic effect of dry mouth was more frequent and severe in the AMT group than in the TZ group.

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