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The Newcastle Chronic Depression Study: Results of a Treatment Regime

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A trial is described of new therapeutic approaches in treatment-resistant chronic depression. Phenelzine, L-tryptophan and lithium ("5HT–cocktail") was used as the major pharmacological strategy, and a regime aimed at reducing vanadium concentrations was added in the second part of the trial. Patients were randomly assigned to cognitive behaviour therapy in addition. All but 1 of the patients who ultimately entered the trial were unipolar depressives; 2 bipolar patients were withdrawn in the initial drug-free period because of the development of mixed affective states. Eleven of 20 patients showed an improvement to less than 50% of their initial scores on the Hamilton Rating Scale for Depression, and all those who improved did so in the first 6 weeks. Cognitive behaviour therapy did not seem to influence the response, but it is recognized that the short duration of therapy may be inadequate in these circumstances. It is suggested that intensive drug treatment is a necessary preliminary in management and may allow the effective use of rehabilitation aimed at the secondary handicaps of chronic depression.

Introduction

Although chronic depression has not attracted a great deal of attention, it is a source of considerable psychiatric morbidity, and occurs in a proportion of the new long-stay patients. It has been estimated that up to 20% of depressives do not recover (Lundquist, 1945; Beck, 1976). In one of the best published studies, Winokur and Morrison (1973) followed a group of 225 mainly unipolar depressives over a period of 2 to 20 years and showed that 25–30% of female depressives developed a chronic state, and that 10% of male depressives did so. Astrup (1979) reported a chronicity rate of 5% in patients with pure manic-depressive illness. Despite the size of the problem, there have been few systematic studies on the subject (Weissman and Klerman, 1977).

Chronically depressed patients consume large amounts of psychiatric time and resources, and pose diagnostic and therapeutic challenges. As a result of the chronicity and the treatment-resistant nature of their condition, they are often labelled "psychoneurotic", "hysterical" or even "malingering"—labels which reflect their doctors' frustration rather than accurate psychopathological assessment, and which explain why they are often given inadequate antidepressant trials,

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or inappropriately treated with minor tranquillisers (Weissman and Klerman, 1977).

The potential therapeutic strategies available for these patients have expanded considerably over the past few years (Eccleston, 1984) and we suggest that this condition may be successfully treated (Barker and Eccleston, 1984). An expression of interest by the Department of Psychiatry in Newcastle upon Tyne to Consultant Psychiatrists in the Northern Region resulted in a high referral of such patients. A decision was made to assess the patients in some detail and to offer vigorous treatment.

Method

All patients thus referred were seen by one of the authors (D.E.), and although all were offered treatment, only those who fulfilled the Research Diagnostic Criteria for definite or probable major depressive illness (Spitzer *et al.*, 1977), had been depressed for at least 2 years, had failed to respond to recognized treatment regimes (Shaw 1977) and were under 65 years old were entered into the trial.

Assessment

On admission the patients were assessed on an observer rating of severity of depression (Hamilton Rating Scale for Depression (HAM-D), Hamilton, 1960) and the patients were asked to complete the Beck Depression Inventory (BDI) (Beck, 1961) and the Rosenberg mood self-rating scale (Rosenberg, 1965). They were also asked to rate the severity of their mood on a 10-point scale (0 = most severe depression imaginable, 10 = normal). the Nurses Observation Scale for Inpatient Evaluation (Honigfeld *et al.*, 1966) was completed during the first week of admission. Each item on the NOSIE was awarded a positive or negative score and the total summed. The greater the negative score, the more depressed the patient. A non-depressed individual would score in excess of 15. The patients were also allocated a score on the Newcastle Rating Scale (Carney *et al.*, 1965). The Vocabulary and Similarities Subscale of the WAIS (Wechsler, 1955) were administered to each patient to exclude any gross impairment of verbal functioning which might preclude engagement in cognitive therapy. The Digit-Symbol Substitution Test Subscale of the WAIS (DSST) was measured as an assessment of psychomotor speed. All these measures were repeated after a drug-free "washout" period of at least 2 weeks. Each week, the NOSIE, Rosenberg, 10–point mood self-rating and DSST were remeasured.

The BDI and HAM-D were administered at 6 weeks and 12 weeks following the start of treatment.

Treatment

All patients who successfully completed the washout period were given a

combination of drugs originally used by Loudon and Eccleston in Edinburgh (unpublished observations) and designed to be targeted on 5HT mechanisms. The combination was phenelzine 45 mg per day (given as 30 mg in the morning and 15 mg at lunchtime), L-tryptophan 1 g b.d. and lithium carbonate at a dose sufficient to achieve a plasma level of between 0·5–0·8 mmol/l (Barker and Eccleston, 1984).

After 6 weeks on the "5HT–cocktail" a second drug regime was added. This second combination was designed to lower both total plasma vanadium and the proportion of the pentavalent vanadate ion (Naylor and Smith, 1981*a*; Naylor and Smith, 1981*b*). To achieve this, patients were placed on a diet low in vanadium, and were given the chelating agent sodium calcium EDTA 1 g t.d.s., to reduce the amount of vanadium available for absorption. To alter the ionic state of plasma vanadium, the reducing agent ascorbic acid was given at a dose of 1 g. t.d.s. The "5–HT cocktail" and the "low vanadium regime" were continued together over the next 6 weeks to the end of the trial period.

All other psychotropic medication, except for nocturnal short-acting benzodiazepines, were specifically excluded.

In addition to these physical treatments, patients were randomly allocated to treatment with cognitive behavioural therapy. This consisted of twice weekly sessions over the first 3 weeks followed by 9 weekly sessions (a total of 15 hours over 12 weeks).

Results

The epidemiological data are fully described in a previous paper (Scott *et al.*, 1986).

Twenty-five patients fulfilled the entry criteria and were judged suitable for the trial. During the washout period, 2 patients deteriorated into a severe mixed affective state requiring other therapeutic intervention and had to be withdrawn from the trial. During the first 6 weeks 1 patient became severely retarded and required emergency ECT with which he made a good clinical recovery. One patient improved dramatically over the first 3 weeks of treatment and was discharged home. Unfortunately, she was lost to follow up over the next 12 weeks but is known to have remained well. Another patient improved during the first 6 weeks of active treatment and was discharged, but again it was not possible to continue monitoring her progress because of the distance from Newcastle. Thus full data are available on 20 patients. Of these, 7 required a modification of the basic drug regime. They are analysed separately as being in the "paratrial". Three of the 7 required the addition of a major tranquilliser because of the development of paranoid symptoms. The other 4 "paratrial" patients needed a reduction of the dose of phenelzine because of intolerable side-effects.

The total group of 20 patients had a mean HAM-D of 23·2 (SD ± 6·6). This did not change significantly after the washout period (mean = 23·4, SD ± 6·9). The mean BDI score on admission was 38·3 (SD ± 11·4). At the end of the washout period, the mean BDI had fallen to 34·4 (SD ± 12·1). This small change is statistically significant ($t = 2{\cdot}82$, $p = 0{\cdot}01$).

However, it is probably more appropriate to analyse the "trial" and "paratrial" patients separately.

Trial Patient n = 13; 7 female, 6 male

These patients all received the treatment regime outlined previously. The mean age was 43 (range 30–60). Eleven fulfilled RDC criteria for definite major primary depression, and 2 for probable. Five scored less than 6 on the Newcastle Rating Scale (i.e. "neurotic") and 8 scored over 6 (i.e. "endogenous").

Observer rating of mood

HAM-D: The mean HAM-D on entry was 23·0 (SD ± 7·4) and at the end of the washout it had not altered significantly. At 6 weeks, the mean HAM-D had dropped by a highly significant amount. There was no further change at 12 weeks (Fig. 1).

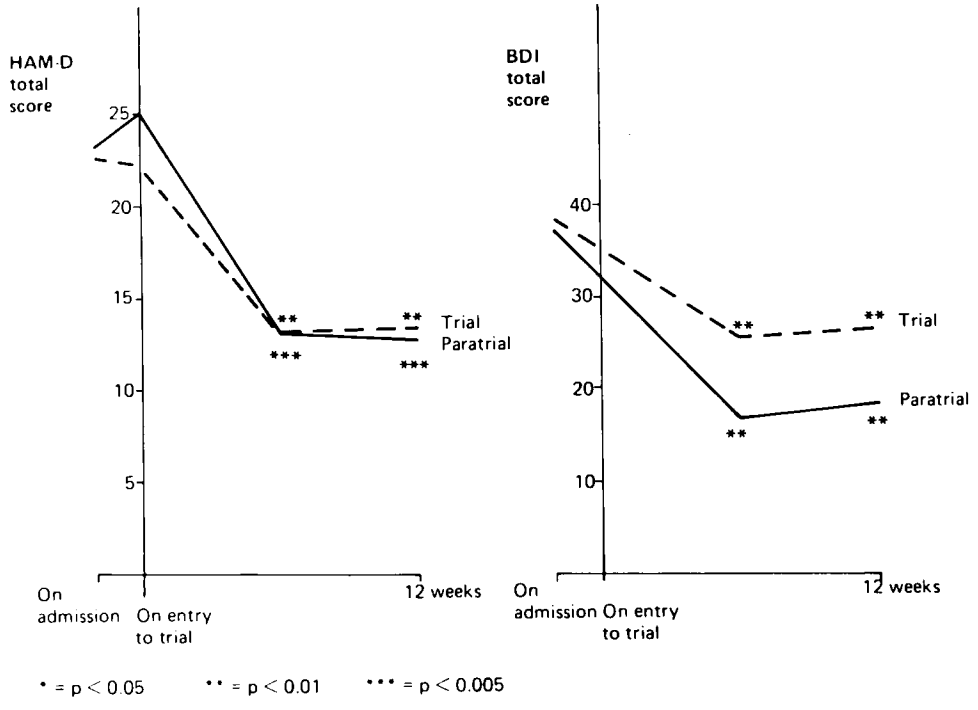

FIG. 1. Changes in Hamilton rating scale for depression (Ham-D) and Beck depression inventory (BDI) scores in trial and paratrial groups

Self-rating of mood

BDI: On admission the patients were significantly depressed. This fell slightly by the end of the washout period although the change is not significant. However,

there was a highly significant change by 6 weeks ($t = 3{\cdot}37$, $p = 0{\cdot}006$). As with the HAM-D, there was no further change in the next six weeks (Fig. 1).

Rosenberg: There is no change from the baseline assessment until 5 weeks when a small clinical (although statistically significant, $p = 0.02$) change begins and increases to week 7. After this the scores seem to level at between 4 and 5 (of a maximum of ten) (Fig. 2).

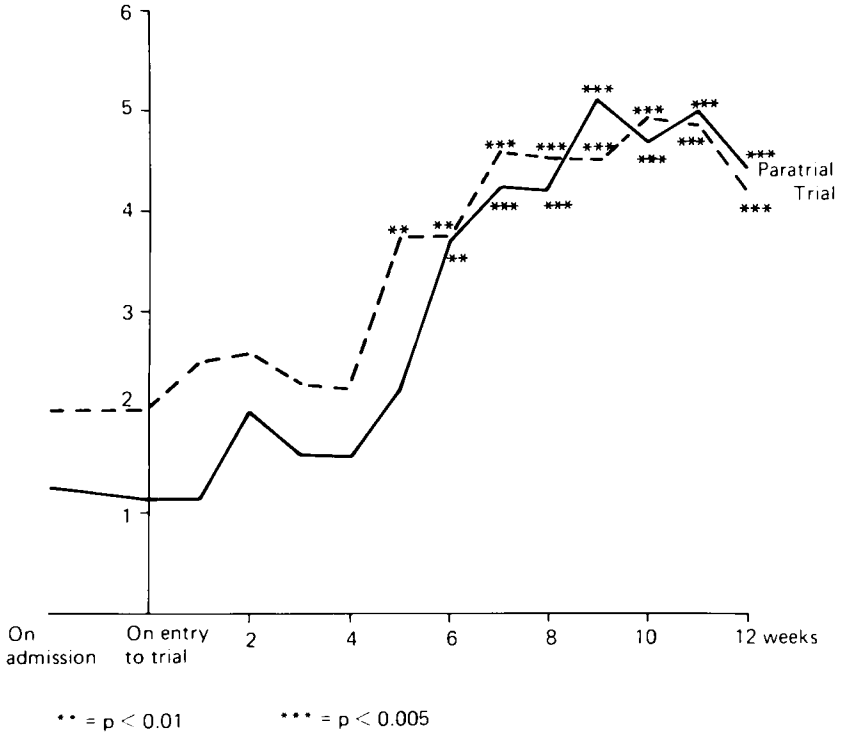

FIG. 2. Changes in self rating on Rosenberg scale in trial and paratrial groups

Ten point mood rating

Although there is a trend towards a gradual improvement in self-rating of mood, the change is small and does not reach statistical significance (Fig. 3).

Observer rating of behaviour

NOSIE: There is a slow improvement in NOSIE scores over the first 6 weeks but this does not attain statistical significance until the sudden change at 6 weeks. The improvement appears to be maintained over the second 6 weeks with little further improvement. There is a curious unexplained drop at 10 weeks which occurred in 2 patients and was of sufficient degree to influence the mean score considerably. (Fig. 4).

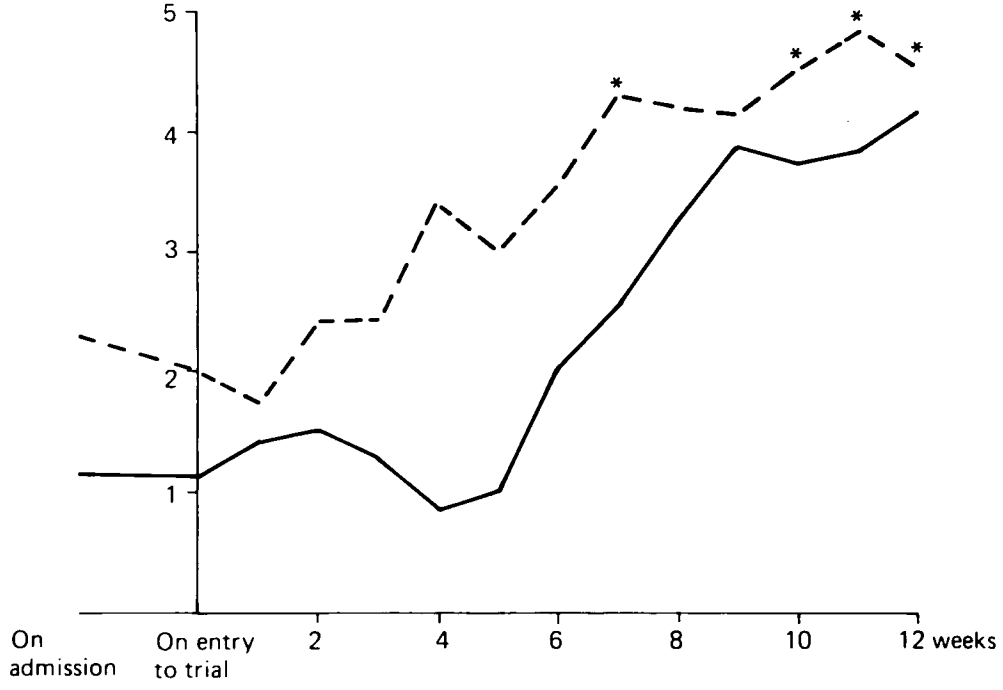

FIG. 3. Changes in self rating of mood (ten point score) in trial and paratrial groups

Measures of psychomotor speed

DSST: The change in number of items completed on DSST in a fixed interval of time showed a gradual increase, reaching statistical significance at 6 weeks ($p=0.01$) and becoming highly significant following this ($p=0.0001$) (Fig. 5).

Paratrial patients (n=8) 7 female 1 male

The mean age was 50 (range 39–60). Six were classified as definite primary major depressive, the other one reaching criteria for probable major primary depression. Only 1 was classified as "neurotic" on the Newcastle Rating Scale, all the others scoring in the "endogenous" range.

Observer rating of mood

The mean HAM-D on admission was 23·4 (SD ± 5·2) and this had not changed after the "washout" period. At 6 weeks the mean HAM-D had dropped significantly ($t=4·9$, $p=0·003$) but at 12 weeks had remained unchanged (Fig. 1).

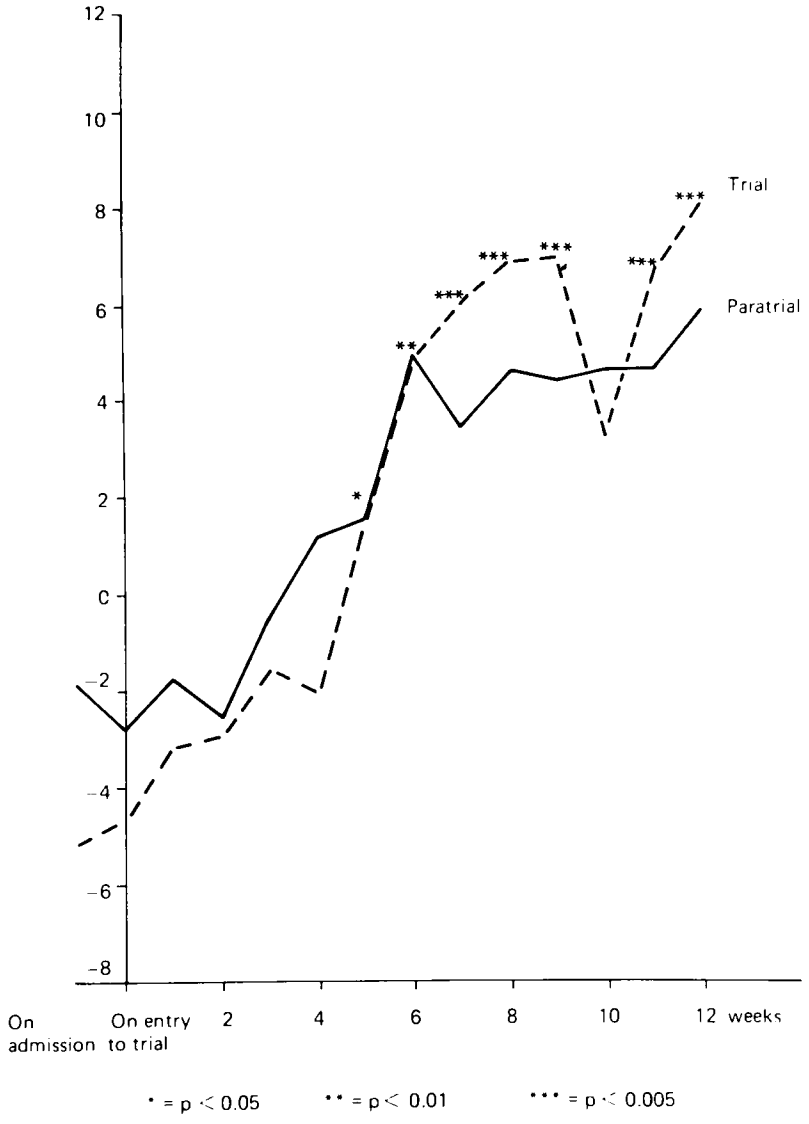

FIG. 4. Changes in NOSIE ratings in trial and paratrial groups

Self-rating of mood

BDI: On admission the patients scored themselves as moderately severely depressed and this assessment did not change following withdrawal of drugs. After 6 weeks of active treatment the mean score had fallen significantly ($t=4{\cdot}17$, $p=0{\cdot}006$) but there was no further change at 12 weeks (Fig. 1).

Rosenberg: There was no change in self-rating on the Rosenberg until 6 weeks when a statistically significant change from baseline was noted ($t=2{\cdot}87$, $p=0{\cdot}01$). This change appeared to level out in the second 6-week period (Fig. 2).

Mood: Using the self-scoring of mood out of 10, there was no significant change from baseline throughout the period. Although a trend towards improvement was noted, this did not reach levels of statistical significance (Fig. 3).

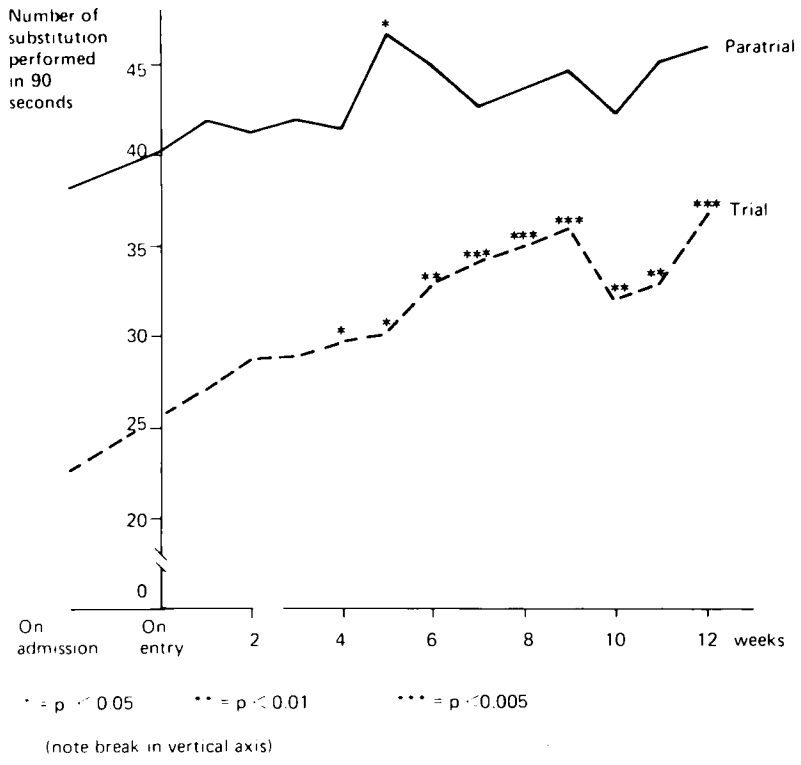

FIG. 5. Changes in digit-symbol substitution subtest of WAIS (DSST) in trial and paratrial groups

Observer rating of behaviour

NOSIE: Although a trend towards improvement over the first 6 weeks was clearly discernible, with no further improvement in the next 6 weeks, the small number of the sample does not permit a definite statement to be made. Levels of statistical significance were not reached (Fig. 4).

Psychomotor speed

DSST: Throughout the 12-week period there was no change in this measure of retardation. The baseline measure was significantly higher than that of the trial group, suggesting the groups differed in degree of psychomotor retardation (Fig. 5).

Cognitive therapy

The outcome for those receiving CBT in addition to the drug combinations described was not significantly different from that of patients receiving physical treatments alone. Two patients dropped out of CBT after developing paranoid delusions or being unable to engage in the therapy session. The other patients completed 15 sessions of CBT during the trial and 3 of them continued with further sessions after the trial had ended.

Side-effects

A wide range of side-effects occurred during the treatment period resulting in modification of the treatment regime in 4 patients, by a reduction of phenelzine. These serious side-effects were due to cardiovascular problems in particular, with a combination of dizziness and weakness being the major reason in 3, and the onset of cardiac dysrhythmia and congestive cardiac failure requiring discontinuation of phenelzine in the fourth patient. Other symptoms such as ankle oedema and muscle jactitation were seen although these were not severe enough to necessitate withdrawal of the patients from the treatment regime. Tremor was noted in 4 patients and was of the type seen typically on treatment with lithium even though plasma levels were within the therapeutic range.

Discussion

There are several obvious criticisms of this trial which need to be answered, and which influence the interpretation of the results. The numbers are relatively small, and this is the result of several factors. The chronic nature of the condition meant that the patients remained in hospital for considerable periods of time, up to 12 months in some cases. This reflects the gross secondary handicaps developed during prolonged illness, requiring intensive rehabilitation. As a result, the "turnover" rate of the patients was low, and either a longer period of research, or a greater availability of resources would be necessary to investigate the problem more fully.

Because of the severe distress the patients were experiencing it was not felt ethical to withhold active treatment in any case. As a result there is no placebo control group. It was not felt acceptable to use alternative treatment as an "active control drug" since the patients had all undergone conventional antidepressant strategies without success. It might be argued that any improvement observed was due simply to transfer to another unit. We can answer this only by pointing to the lack of improvement during the initial drug-free washout period, when any "honeymoon" effect might be expected to occur. Given the long period of previous active treatments before the entry to the trial, we felt it was justified to regard the patients as acting as their own controls.

It might be said that the patients do not represent true depressive illness, and that the chronicity is a reflection of misdiagnosis. While it is true that many of the patients had previously been regarded as "personality disordered", this label was applied only after the onset of the chronic episode, and usually could not be substantiated by vigorous examination of the history (Scott *et al.*, 1986). The patients all fulfilled clinical and research criteria of depression. It would seem that we have demonstrated the truth of Weissman and Klerman's comment that chronic depression leads to inaccurate diagnostic labelling (Weissman and Klerman, 1977).

In previous pilot studies (Louden and Eccleston, unpublished observations) using the combination of L-tryptophan and phenelzine first advocated for its efficiency by Coppen (Coppen *et al.*, 1963) it was found that the improvement in

depressive symptomatology, which was often quite dramatic, did not persist for more than a few weeks, but that if lithium carbonate was added the improvement was sustained. Phenelzine and L-tryptophan are targeted on 5HT mechanisms (Eccleston, 1981). The effect of lithium is elusive since its role has been suggested to be on Na/K ATPase (Naylor *et al.*, 1973; Hesketh *et al.*, 1977). However a rapid response in patients previously unresponsive to tricyclic antidepressants has been described (De Montigny *et al.*, 1981; Heninger *et al.*, 1983) in patients when lithium carbonate is added.

The low vanadium regime has been advocated by Naylor (1981*a*, 1981*b*) who hypothesized genetic defects in the control of the sodium pump in manic depressive psychosis. In this respect he sees vanadium as an ingested inhibitor of Na/K ATPase in individuals with this defect. In our series no clinical effect could be demonstrated by such a regime, but this may not contravene the initial hypothesis which is related to bipolar illness.

Side-effects of dizziness and weakness led to reduction of drug dosage in 3 patients, and the development of serious cardiovascular side-effects required discontinuation of phenelzine in 1 patient. Otherwise side-effects, although a problem, were not sufficiently severe to require withdrawal.

Thus, we were able to produce modest, though statistically significant improvement in mood state and behaviour. In essence, the patients shifted from severe depression to a moderate level, allowing the appropriate application of other rehabilitative treatments which had previously been ineffective because of the patients' inaccessibility and inability to engage in treatment. Those patients who required modification of the drug regimes because of the development of paranoid symptoms or side-effects showed a level of response much the same as those who remained on the original drug regime.

On the HAM-D, BDI and NOSIE, those patients who showed an improvement seemed to do so in the first 6 weeks and this improvement did not progress further. This finding held true for both trial and paratrial patients. Whether the introduction of the vanadium regime actually inhibited further improvement produced by the "5HT cocktail", or that this was reducing anyway, is not known.

An interesting observation was that patients were often reported to be improving but did not admit to this themselves. This is demonstrated by the improvements shown on the HAM-D and NOSIE scores by 6 weeks, although the changes in self-rating were much more modest and occurred during the second 6-week period. This presumably reflects different criteria of improvement since both the HAM-D and the NOSIE are clinical scales relying heavily on behaviour assessment, and this may change before the patients' cognitions and assessment of mood begin to improve. However, the BDI, which is concerned with assessing depressive cognitions, showed improvement between entry and 6 weeks.

Weissman and Akiskal (1984) suggest that the practical, problem-solving approach of CBT is likely to be more effective in chronic depression than other forms of psychotherapy. However, results so far on the use of CBT with chronically depressed outpatients (Fennel and Teasdale, 1982; Harpin *et al.*, 1982) have been disappointing. In our study, we faced the further problem of conducting CBT in an in-patient setting which has many additional difficulties and limitations (Shaw, 1981). These problems along with the severity and prolonged nature of the

illness, the generalized hopelessness and the chronic low self-esteem of these patients left us with the impression that 15 sessions of CBT, with or without additional physical treatments, are unlikely to be sufficient.

Drug treatment can only be seen as a primary therapy directed at relieving the underlying mood disorder, and cannot be naively expected to produce complete recovery in patients with chronic depression. However, it seems that chronically depressed patients are unlikely to benefit from non-pharmacological therapies until their mood state can be shifted, and indeed, their lack of responsivity can serve to alienate them from their therapists, producing hostility and a sense of therapeutic nihilism in both parties. We would suggest that in many such patients it is possible to produce improvements by using vigorous and sometimes complex pharmacology in combination with other rehabilitation. However, the number of patients who did not respond to treatment reminds us that chronic depression remains a serious clinical problem.

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