two more patients by the end of September 1976, giving a total over 27 months of 17 patients accepted into the trial out of a total of 35 specially referred. Of the 18 who did not fulfil the trial criteria, 16 were offered treatment: 13 were taken on, two declined, and one defaulted. Reasons for exclusion from the trial are shown in the table.

*The Newcastle experience*—TAK and HAMcC selected suitable patients from their high urban case load of outpatient referrals and admissions. But to complete the series the criterion of three months without previous antidepressant treatment could not be firmly adhered to throughout. In the nine months from January to September 1976 20 patients entered the trial in Newcastle upon Tyne.

*Reasons for rejection of specially referred patients from the trial*

| | No of patients | |
|---|---|---|
| Found to have been on an antidepressant in previous three months | | 3 |
| Tricyclics not indicated: | | 10 |
| Acute situational anxiety (agoraphobia) | 2 | |
| Appropriate psychological reaction to stress | 1 | |
| Marital/personality problems and crises | 3 | |
| Impotence | 1 | |
| Acute melancholia requiring immediate ECT | 1 | |
| On monoamine oxidase inhibitor and unwilling to change | 1 | |
| Not depressed | 1 | |
| Tricyclics contraindicated: | | 2 |
| Severe obesity with mild cardiac failure | 1 | |
| Recent coronary thrombosis, cardiac insufficiency, diabetes mellitus and gross obesity | 1 | |
| Other reasons: | | 3 |
| Spontaneous recovery before seen | 1 | |
| On a shoplifting charge | 1 | |
| Technical fault in videotape equipment[4] | 1 | |
| Reiected | | 18 |
| Accepted for the trial | | 17 |
| Total referrals for the trial | | 35 |

## Comment

From the late 1950s through the '60s the treatment of depressive illness by psychiatrists was at its peak. Thereafter the numbers of depressed patients under care and treatment by psychiatrists began to decline. At first, probably as a result of successful treatment as outpatients, the number of patients with depression in hospitals fell by 10% in England and Wales between 1963 and 1971.

At the Crichton Royal between 1968 and 1976 outpatient referrals of patients given one of the ICD depressive diagnoses fell by 47%, while admissions for depression fell by 31%. In Newcastle, at St Nicholas Hospital, over the same eight years, admissions for depression fell by 22%. The reduction in referrals with depressive disorders is probably a combined effect of the increasing use of antidepressants by general practitioners and a reduction of re-referrals of recurrent manic depressive psychoses owing to the increasing use of lithium in secondary prevention.

This observation has considerable implications for clinical research in psychiatry when, as in our experience, a clinician can now attract only 10 suitable untreated depressives in a year for a drug trial with broad selection criteria. Were Leff's reasonable case for eliminating polar prognostic groups to be adopted,[5] the single-handed clinician could well take 10 years or more to collect two series of 25 depressed patients adequate for a drug effect comparison. The lesson is clear: psychiatrists can henceforth pursue drug trials in depressive illness only under two conditions: firstly, in collaborative multicentre investigations; secondly, by moving out of the wards and outpatient departments and attaching to one or more general practices, for it is here that the untreated depressive now presents.


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# Drug dependence caused by dihydrocodeine

The development of tolerance and physical dependence with repeated use is a characteristic feature of all the opiate and opioid drugs, and the possibility of developing psychological dependence on their effects is one of the major limitations of their clinical use.

Eddy *et al*[1] reported that dihydrocodeine was an effective analgesic, which, however, never seemed to attain the potency of morphine. At its optimal dose of 30 mg little respiratory depression occurred and there were no other side effects of significance other than drowsiness. Increasing the dose to 60 mg increased the analgesia only slightly but did cause the appearance of morphine-like side effects and respiratory depression. It is extremely likely that dihydrocodeine is metabolised in a similar fashion to codeine—that is, by N-demethylation, o-demethylation, and conjugation. Codeine itself can undergo d-demethylation to morphine. Although this is usually a minor pathway, with increased ingestion it does become important. In addition, possibly o-demethylation might be a more favoured pathway in those who become addicted to dihydrocodeine.

## Case reports

*Case 1*—A 30-year-old housewife who complained of headache was given three months' supply of dihydrocodeine. She returned to her doctor after two months asking for a further supply. Over six months she had increased her dose to 60 mg four or five times a day, from one tablet taken as necessary originally. She was continually drowsy and lost her job. In a fit of depression she took 30 dihydrocodeine tablets and was admitted to hospital with constricted pupils. Two days later she began a course of psychiatric rehabilitation.

*Case 2*—A 49-year-old company director who had pain at the site of an old thoracotomy wound was given dihydrocodeine, 30 mg twice daily. Six months later he had increased the dosage to 60 mg four times a day. He admitted to his general practitioner one year later that he had irritability, sweating, anxiety, palpitations, and insomnia on withdrawal of the dihydrocodeine. Despite attempts to wean him from the drug he has continued to take 60 mg three times a day and 120 mg at night for three years.

*Case 3*—A 23-year-old engineering student was given a supply of dihydrocodeine tablets, 30 mg to be taken as required because of a strained muscle. At vacation time he was given three months' supply, and after this was over he was noticeably drowsy with constricted pupils. On questioning he admitted that he found taking dihydrocodeine pleasurable. On drug withdrawal he became restless and irritable and could not sleep. At that time he was taking 90 mg four times a day.

*Case 4*—A 26-year-old artist with a history of drug misuse had started taking dihydrocodeine, 60 mg at night time, because it facilitated sleep. After four months he was taking 90 mg four times a day for the agreeably drowsy sensation it caused. At this time he developed signs of acute peptic ulceration. His pupils were constricted and he was severely constipated. He was referred to a psychiatrist.

*Case 5*—A 50-year-old insurance broker with severe osteoarthritis was given dihydrocodeine, 60 mg thrice daily. He felt more relaxed after taking the tablets, and the dose before bed time helped him to sleep. After four months he had increased his dose to 90 mg four times daily and he was finding it difficult to cope with his job. A severe respiratory tract infection necessitated a home visit by his general practitioner, and he was found to have constricted pupils and severe difficulty in respiration. The patient confessed that he was taking 120 mg thrice daily.

## Discussion

Although dihydrocodeine is useful as an analgesic, addiction may occur, with severe physical and psychological results on abrupt withdrawal. Our five cases illustrate the risk of physical dependence on this drug.

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