A CONTROLLED TRIAL OF CAVODIL (PHENIPRAZINE) IN DEPRESSION

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In reviewing controlled trials using mono-amine oxidase inhibitors in the treatment of depression it is soon obvious that workers vary as to whether they consider "depression" as a symptomatic mood change in diverse conditions or as a disease entity. Where the latter occurs, a variety of classifications of depressive illnesses appear, and that most widely used is the broad separation between endogenous and reactive depressions. Other points to note are the authors' definition of improvement, and particularly whether this refers to one aspect of the mental state only and whether the patient left hospital before receiving any treatment other than the drug.

Thus although there was significant improvement in the trial by Rees *et al.* (1961) "only 3 of the 20 patients improved sufficiently with the drug to be discharged from hospital, and 13 patients received E.C.T. subsequently".

In the trial of Middlefell *et al.* (1960) the results of a preliminary double blind controlled study were conflicting, and in the ordinary clinical trial, the nature of the control of which is not clear, significant improvement occurred in female but not in male patients.

Hutchinson *et al.* (1960) in their trial found no significant improvement with regards to total conditions, but a significant action on insomnia and early waking.

There was significant improvement in depression in the Joshi trial (1961) but depression was treated as a symptom, and only thirteen of the fifty-three patients were diagnosed as endogenous depression. Furthermore it is not clear whether improvement was sufficient for discharge in each case.

Thus of the controlled trials with statistical analysis which suggest that mono-amine oxidase inhibitors are efficacious in endogenous depression only that of Kiloh *et al.* (1960) with iproniazid together with a follow-up study by the same authors, provides reliable evidence.

Against this is a negative trial of the same drug by Rees *et al.* (1960) and negative trials of other mono-amine oxidase inhibitors, Harris *et al.* (1960) on phenelzine and a recent controlled trial of nialamide by Affleck *et al.* (1961) in which the drug was compared with chlorpromazine and "neither the short-term nor the long-term difference between treatment groups was statistically significant".

There have been no previous published controlled trials of Cavodil (B-phenylisopropyl hydrazine, pheniprazine) in the treatment of endogenous depression comparing the effect of the drug with placebo.

A comparative uncontrolled trial of mono-amine oxidase inhibitors, Ayd (1960), suggested that Cavodil was the most rapidly effective and also possessed

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the lowest effective dose ; however the overall efficacy compared with the other drugs cannot be reliably assessed from this trial.

Dally *et al.* (1961) carried out a comparative trial of several mono-amine oxidase inhibitors including Cavodil as well as imipramine (Tofranil) using the patients as their own controls and the efficacy of iproniazid as a standard. The result showed that of patients responding fully to iproniazid considerably less than 40% did as well with Cavodil. In both of these comparative trials, however, cases were not exclusively endogenous depressions.

Another trial by Bates *et al.* (1961) on chronic depressives (37/63 endogenous depression) comparing the effects of phenelzine, iproniazid, nialamid and Cavodil showed Cavodil, 12 mg. daily, to be statistically of less value than the other three drugs.

A more recent study by Oakley (1961) compared the effects of Cavodil with Tofranil (imipramine) (using 24 mg. daily of Cavodil for the first fortnight and subsequently 12 mg. daily for two weeks) on female in-patients suffering from endogenous depression. The results showed no significant difference between the two drugs, but patients who received E.C.T. were excluded from the analysis of results.

The Trial

Fifty-five patients participated in a double blind controlled trial of Cavodil used in a dose of 12–18 mgm. daily for two weeks. Previous studies suggest that the onset of any improvement with mono-amine oxidase inhibitors takes place within 10–14 days, Rees *et al.* (1960) Middlefell *et al.* (1960), Hutchinson *et al.* (1960), Dally *et al.* (1961), Bates *et al.* (1961).

The diagnosis was made by at least two psychiatrists who saw cases independently and further assessed them during the trial at weekly intervals, when various aspects of the mental state were examined and any improvement in each was charted.

TABLE I

A Controlled Trial of Cavodil

	Endogenous Depression		All Depressions		Reactive Depression	
	Improved	Not Improved	Improved	Not Improved	Improved	Not Improved
Cavodil... ...	4	9	8	11	4	2
Placebo... ...	9	14	9	20	0	6
	36		48 (12+36)		12	

Seven patients were eliminated (schizophrenia 3, puerperal depression 1, reactive depression 1, endogenous depression 2).

"Improved" in this trial referred to any one or more aspects of the mental state and the results did not indicate significant improvement in any respect. The four patients who improved were discharged without subsequent treatment.

The results showed no significant improvement, whether the cases are considered together or when endogenous depressions are separated. If reactive depressions are separated the numbers are small and suggest a trend for improvement.

Side effects. No side effects were encountered in this trial using 12–18 mgm. daily.

The drug has been withdrawn from the market by the manufacturers because it can cause a reversible red-green colour-vision disturbance (personal communication) and some cases of fatal jaundice have been reported, Holdsworth *et al.* (1961).

Summary

There is little published evidence from controlled trials that mono-amine oxidase inhibitors have any place in the treatment of endogenous depression.

A double-blind controlled trial of Cavodil in 48 depressed patients is reported and the results show no significant improvement in cases given the drug as compared with placebo. 36 patients suffering from endogenous depression showed no significant improvement and it is concluded that Cavodil is not indicated in this condition.

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