Medication and Physical Therapies

Carbamazepine and Haloperidol Versus Placebo and Haloperidol in Excited Psychoses: A Controlled Study

Carbamazepine is a well-known anticonvulsant with special advantages for temporal lobe epilepsy. Recently it was reported that carbamazepine has potential for the treatment of mania. Carbamazepine plus haloperidol versus placebo plus haloperidol were studied in excited psychoses in a controlled double-blind design. Twenty-three patients completed five weeks of carbamazepine-haloperidol therapy, while 20 patients were given placebo-haloperidol therapy. Scores on the Brief Psychiatric Rating Scale showed superior improvement in the group that received carbamazepine plus haloperidol. This benefit was clear for both excited schizophrenia and mania. No unusual toxicity was observed from the combination of the two drugs.

These results have materially changed the clinical practice at the authors' hospital, where carbamazepine is now cautiously but realistically viewed as an alternative for lithium carbonate prophylaxis failures or high-risk lithium carbonate-treated patients with severe polyuria or preexisting kidney disease. It is important not to make etiologic assumptions because of the possible efficacy of carbamazepine for some psychoses. Those patients who showed dramatic improvement with carbamazepine therapy did not share a common clinical diagnosis and could not be defined as a specific group with a predictable positive response to carbamazepine treatment.

Klein E, Bental E, Lerer B, et al. Arch Gen Psychiatry 41:165-170, 1984.
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Memory Test Performance Under Three Different Waveforms of ECT for Depression

The most frequently held reservation about electroconvulsive therapy (ECT) is the risk of memory impairment of which some 64% of patients complain, although systematic measures of memory have usually failed to support these claims. Nevertheless it has been shown that ECT can produce retrograde amnesia for events immediately preceding the shock and occasionally for much longer periods — from months to years before the ECT treatment. However, the evidence for anterograde amnesia following ECT remains inconclusive, and any measurable impairment usually disappears within a week or two of treatment.

In this study, 38 patients suffering from severe depression were given a course of ECT in one of three waveforms. These were high-energy sine wave (HS), high-energy pulse (HP), and low-energy pulse (LP). The patients were assigned to one of these treatments on a double-blind basis. The patients were given a battery of memory tests before ECT began, after three treatments, at the termination of treatment, and two weeks following the last treatment. The marked improvement in both verbal and nonverbal memory scores was attributed to the lifting of the patients' depression. No significant differences were found in the memory scores of the three groups at any point.

The results of this study suggest that memory impairment is associated with depression but that when the depression is treated with ECT memory function improves; the specific ECT waveform does not seem to have a differential effect on memory.

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Dexamethasone in Electroconvulsive Therapy: Efficacy for Depression and Post-ECT Amnesia

Memory loss and intellectual changes are prominent side effects of electroconvulsive therapy (ECT) which occur in some patients. Indeed, memory loss and cognitive confusion are often cited to justify a reluctance to use ECT, even though it has been shown to be more effective than standard pharmacological methods for treating many depressed patients.

This study was designed to confirm reports that dexamethasone prevents the post-ECT amnestic syndrome. Dexamethasone, as compared with placebo in this double-blind study, failed to prevent the memory deficiency that typically accompanies ECT ($n = 48$ patients treated for DSM-III diagnosed major depressive disorder). Rather, administering the drug was associated with attention ($p < 0.02$) and short-term memory ($p < 0.003$) difficulties in both bilateral and unilateral ECT patients. Bilateral ECT plus dexamethasone patients demonstrated significantly less improvement ($p < 0.05$) in their depression (measured by the Hamilton Depression Scale) compared with bilateral ECT plus placebo patients. These depression differences were not seen among unilateral ECT patients.

Horne RL, Pettinati HM, Menken M, et al. Biol Psychiatry 19:13-27, 1984.
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Absolute Bioavailability of Imipramine: Influence of Food

Imipramine hydrochloride (IMI) has a limited and highly variable bioavailability after oral ingestion. This may be due in part to intrinsic anticholinergic activity, slowing gastrointestinal motility and possibly drug absorption and in part to differences among individuals in hepatic first-pass extraction of IMI. High first-pass hepatic extraction, or "presystemic" elimination, occurs with a number of drugs after oral ingestion. When such drugs are ingested with food, systemic bioavailability may increase. The mechanism of increased bioavailability during food ingestion is not well defined, but it may be related to altered splanchnic or hepatic blood flow.

The authors administered IMI to 12 healthy volunteers on three occasions in random sequence: 12.5 mg IV, 50 mg orally after an overnight fast, and 50 mg orally 30 minutes after eating a standardized breakfast. IMI concentrations were measured by gas-liquid chromatography using nitrogen-phosphorus detection and pharmacokinetic and bioavailability parameters determined by iterative nonlinear least-squares regression analysis. After IV administration, the mean kinetic variables were: volume of distribution, 21.01/kg; total clearance, 12.8 mL/min per kg; and elimination half-life, 21.2 hours. The mean absolute bioavailability of IMI in the fasting state was 43.6%. When IMI was administered after a standardized meal, absolute bioavailability was 44.1%. After oral administration, the time to peak IMI level was not changed by concurrent food ingestion (2.8 vs 3.2 hours after administration), and the peak IMI concentration did not differ (35 vs 30 ng/mL). Thus, concurrent food ingestion has no effect on the absolute bioavailability of IMI, peak concentration achieved, or the time to peak concentration.

Abernethyl DR, Divoll M, Greenblatt DJ, et al. Psychopharmacology 83:104-106, 1984.
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Disulfiram Implantation: A Dose-Response Trial

Alcoholic volunteers (n = 120) were assigned at random to receive an 800-mg, 1200-mg, or 1600-mg subcutaneous disulfiram implant, and they were followed for two years. Although all three groups showed increased sobriety following implantation, there was no significant dose-response relationship. Also there were no significant differences among the groups in the incidence of disulfiram-ethanol reaction.

Previous studies in this series had concluded that there is a psychological deterrent aspect in the effectiveness of the disulfiram implant procedure, and possibly the magnitude of that aspect outweighed any differential pharmacologic deterrence associated with the three implant doses. It is also possible that only a certain quantity of disulfiram is required, and that any additional amount would have no beneficial effect. It is interesting to note that a nonparametric assessment of the direction of change for each of 11 questionnaire items showed that changes in 10 of the 11 were in a direction that would indicate some rehabilitation. This finding is consistent with the concept that the disulfiram implant effectively alters the drinking behavior of the alcoholic. Although these findings support previous conclusions that disulfiram implantation is effective in keeping the alcoholic abstinent or in reducing his drinking, they are not consistent with the idea of a pharmacologically mediated deterrent component. If such a component represented a major part of the effectiveness of disulfiram implantation, one would expect a correlation between the implant dose and subsequent drinking behavior.

Wilson A, Blanchard R, Davidson W, et al. J Clin Psychiatry 45:242-247, 1984.
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Within-Individual Variation in Steady State Plasma Levels of Different Neuroleptics and Prolactin

Clinical experience suggests that although one neuroleptic is probably no more effective than any other in treating groups of schizophrenics, some individual patients appear to respond better to one drug than to another. However, it is not yet possible to match particular neuroleptics with particular schizophrenics in terms of symptom profiles. There are many reasons for an individual's response to a given drug. Pharmacokinetic factors include poor absorption, large first-pass metabolism, and rapid metabolism to inactive metabolites, which will lower the steady state plasma levels. With less drug exerting its effect at the site of action, there may be less clinical efficacy. It is well known that there is a large variation among individuals in the pharmacokinetics of neuroleptic drugs, but so far within-individual variation for different neuroleptics (that is, variation in the pharmacokinetics of different neuroleptics given to the same patient) has not been examined in detail.

In this study, 11 chronic schizophrenic men were given, serially, oral pimozide, fluphenazine, and flupenthixol; the two latter were also administered intramuscularly as decanoates in oil. Oral haloperidol was given before and after each drug. Analysis of variance of the steady state plasma levels of the several neuroleptics showed considerable within-individual variation in such levels, probably due to differences in absorption and metabolism and also in the two routes of administration. These findings suggest that if a patient fails to respond to one neuroleptic, there may be good pharmacokinetic reasons for switching to another that belongs to a different group, or for using a different route of administration for the same neuroleptic. This study also showed that the previous administration of one neuroleptic may affect the steady state level of another. The several neuroleptics produced different effects on plasma prolactin levels.

McCreadie RG, Mackie M, Wiles DH, et al. Br J Psychiatry 144:625-629, 1984.
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