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Prediction of therapeutic uses of psychotherapeutic drugs from experiences with normal volunteers

One of the great paradoxes with psychotherapeutic drugs is that we are caught in a circular trap. We know the pharmacologic properties of sedatives and stimulants so well that we can identify some of these (largely those that are nontherapeutic) in normal subjects and make reasonably good predictions about drugs of this type. Antipsychotic and tricylic antidepressants have novel clinical actions unlike any we had before. Both types of drugs were discovered fortuitously in the clinic so that their pharmacologic properties were correlated retrospectively with their therapeutic effects. To make matters worse, pharmacologic effects of these drugs in most animals and human beings have little apparent relevance to the clinical disorders they are supposed to treat. Knowing these correlations, we can devise screening batteries to detect many other drugs similar to those that we now have, but none that are truly different. Until we have better human or animal models for the disorders in question or a better hypothetic basis for constructing drugs to treat these disorders, we may be stymied. It does not seem likely that one can predict these effects in any useful or innovative way from the study of such drugs in normal, asymptomatic human subjects.

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One would not ordinarily think of testing psychotherapeutic drugs in normal subjects for therapeutic uses, as suitable patients are usually abundant. Still, it is of some interest to determine to what extent one might be able to predict uses of drugs from experiences in normal subjects. In toto, one can conclude that, in this particular area of clinical pharmacology, predictions can be made with at least as great accuracy as in any other, none being highly accurate.

Most of this paper is a summary of my observations of the effects of various types of psychotherapeutic drugs as revealed in double-blind controlled studies using normal volunteers over the past 17 years. The number of such studies is not great and, as they were not specifically devised to test predictability of therapeutic effects, only limited conclusions can be drawn. Still, on the basis of experience to date, I would risk the following statements:

1. Sedative and stimulant effects, at least in the classical models, can be detected in man. Predictions should be reasonably accurate for detecting drugs essentially like those that have been available for the past 30 to 60 years.

2. Antianxiety drugs can be predicted indirectly on the basis of sedation as long

as they are essentially similar to conventional sedative-hypnotic drugs. Any antianxiety drug with a novel action would very likely be missed.

3. Antipsychotic and antidepressant effects would not only be unpredictable, but such studies would very likely lead to erroneous conclusions about these drugs.

Prediction of sedative effects

Meprobamate was given in doses of 800 mg. to fasting subjects in the morning as part of an experiment measuring the physiologic availability of drugs in various dosage forms. Clyde Mood Scale (CMS) data were obtained during the course of the drug action, as the subjects carried out essentially normal activity between periods of testing. The score for sleepiness was significantly increased as compared with placebo. The score for clear thinking tended to be decreased. No changes were noted in the scores for "friendly," "aggressive," "unhappy" or "dizzy."[8]

In another study, in which meprobamate was compared with placebo and a cogener, tybamate, the McNair-Lorr Mood Scale (MLMS) was used to measure the effects of 800 and 1,200 mg. single doses given to volunteers in the morning. As compared with placebo, meprobamate significantly reduced the tension factor and increased factors for fatigue and bewilderment; a trend toward decrease on the excited factor was also noted; no changes were noted on "energetic," "angry," "dejected," "thoughtful," or "composed" factors.[7]

Plasma levels of the drug were obtained at various times during both studies and attempts were made to correlate these with various factor scores on the mood scales and questionnaire data obtained at similar times. Plasma levels of meprobamate correlated positively with sleepiness on the questionnaire, but not on the CMS. They correlated negatively with factors for "energy" and "thoughtful" and positively with factors for "fatigue" and "bewilderment."[9]

In short, using single doses somewhat greater than those used therapeutically, one can detect in normal subjects evidence of sedation (decreased tension) as well as a variety of unwanted effects (sleepiness, fuzzy thinking, fatigue, and confusion). To varying degrees, one would expect to detect similar changes from other drugs in this class. But what would happen if one were to test propranolol, a drug which is an effective antianxiety agent, but which has only minimal sedative properties of the classical sort?[2]

The recent trend has been away from using normal volunteers in the initial screening of agents of this type. It is quite reasonable to give single doses of sedatives to patients with anxiety and get more pertinent information than from normal subjects. Some investigators are beginning to use nonpatient anxious subjects, who might be preferable to anxious patients, as their prior exposure to antianxiety drugs may be less.[1] Not only can one give single doses, but one can arrange for dose-ranging subchronic studies, especially in hospitalized patients with anxiety. We have used a technique of dose ranging in individual patients over a 10 day period (2 periods of 5 days in each of 2 successive weeks), gradually increasing from single daily doses to repeated doses raised by small increments. Only one patient at a time is used, the succeeding patient starting at a dose somewhat higher or lower than that of his predecessor until the full range of dosage has been explored.

Another possible technique that we are just starting is to induce anxiety experimentally to provide a human pharmacologic model. A group of normal volunteer subjects is selected on the basis of having symptoms of anxiety evoked by a sympathomimetic agent (ephedrine is the first provoking drug to be tried). Then they will be tested with placebo, a standard drug, and a novel treatment (in the first instance, propranolol) to determine the sensitivity of this model to drug effects. Thus, it may be possible still to use normal volunteer subjects productively in screening antianxiety drugs.

Prediction of stimulant effects

Dextroamphetamine in doses of 5 and 10 mg. was compared with placebo as well as another potential stimulant (pimetine) with the use of the MLMS as well as a questionnaire. Factors for "excited" and "tense" were significantly increased over placebo; trends toward increased "cheerful" and "energy" scores and decreased "fatigue" and "composed" scores were also noted. No changes were observed in "angry," "dejected," or "bewildered" factors. Patients reported increased palpitation, insomnia, and decreased appetite.[7]

A second study compared the effects of 20 mg. of dextroamphetamine in 2 divided doses 90 minutes apart against 2 doses of a possible stimulant (prolintane), as well as placebo. Fatigued volunteers were used. Four of 6 CMS factors were significantly changed as compared with placebo over at least one time period: "increased friendly," "clear thinking," and "unhappy" scores and decreased "sleepy" scores were observed; scores for "aggression" and "dizzy" were unchanged. Symptoms reported with greater frequency following the drug were nervousness, tension, increased energy, anorexia, and insomnia. Performance was increased on a drawing test (Flexibility of Closure). The only physiologic changes of consequence were increased systolic and diastolic blood pressures and increased pulse rate.[12]

Recently, we have used dextroamphetamine as a comparison drug in studies of marihuana and ethanol. Dextroamphetamine was distinguished from the other 2 drugs and placebo in these nonfatigued normal subjects by several types of changes. On a self-reporting mood scale, factors for "drowsy" feelings were decreased and factors for "stimulated" or "active" feelings were increased as compared with placebo or the other drugs. Performance was increased on the Flexibility of Closure test and the Digit-Symbol Substitution test, even in these nonfatigued subjects.[11] Appetite and food intake were diminished by dextroamphetamine and plasma free fatty acids were increased as compared with the other treatments.[5]

In summary, stimulant effects (increased energy, decreased fatigue, increased clear thinking, and increased performance) as well as a number of unwanted effects (increased excitement and tension, nervousness, unhappiness, insomnia, anorexia, palpitations, and increased blood pressure and pulse rate) were evident with reasonable clinical doses of dextroamphetamine. It is of some interest that in each of these comparisons, dextroamphetamine, the standard drug, proved to be superior to the test drugs, pimetine and prolintane, despite the fact that the latter drugs passed the usual animal pharmacologic screens for stimulants. It may very well be that we can detect sympathomimetic stimulants quite precisely, because we know what to look for, but would miss a novel stimulant which did not fit this model.

Prediction of antipsychotic effects

Very early, we compared reserpine in doses of 0.5 mg. twice daily for 3 to 7 days with placebo in normal subjects.[14] With only one exception, all the subjects correctly identified their medication. Lack of initiative, irritability, and depression were noted in the subjects who received reserpine. None liked the effects of the drug, and some stopped taking it before the assigned goal of 7 days of treatment was completed. Later, the depression-provoking effects of reserpine, particularly in hypertensive patients, were elucidated much more completely. Had we been asked to define the action of this drug based on this experience with normal subjects, we would probably have classified it among the minor dysleptics.

Sometime later, during an investigation of the physiologic availability of chlorpromazine and thioridazine, we had occasion to administer both drugs in 200 mg. single oral doses and 50 mg. intramuscular doses.[13] Both drugs produced profound sedation and were uniformly found to be disagreeable by the subjects. Scores on the

Table I. *Plasma free fatty acids following centrally acting drugs*

Drug	*Dose*	*Route*	*% change from base line*
Desipramine	50 mg.	IM	+ 41
Chlorpromazine	50 mg.	IM	+ 51
Reserpine	2.5 mg.	IM	+ 78
Benzquinamide	300 mg.	IM	+136
LSD-25	1.5 μg/Kg.	oral	+ 73
Mescaline	5 mg./Kg.	oral	+115

IM = intramuscular.

CMS showed decrease in "friendly," "energetic," and "clear thinking" with a tendency toward decreased "aggression" as compared with pretreatment scores. Both systolic and diastolic blood pressure were markedly reduced, and the pulse rate rose.

Thiothixene given orally in single doses of 5 to 20 mg. produced effects in normal subjects ranging from sedation to uncomfortable, strange feelings characterized by inner restlessness and fuzziness. Molindone in doses of 5 to 50 mg. produced drowsiness, fatigue, depression, restlessness, and fuzziness. I can personally testify that a dose of 50 mg. of this drug educated me to the true meaning to 2 psychiatric terms, akathisia and anhedonia.[6]

Recently, we used a few normal volunteer subjects in testing the physiologic availability of chlorpromazine in various dosage forms. Only with difficulty were we able to persuade 6 subjects to complete 4 trials (3 oral doses of 150 mg. and one intramuscular dose of 50 mg.). The differences between the concentrations of drug in plasma following single doses of the various dosage forms were similar in these normal subjects and in schizophrenic patients in steady-state conditions,[10] although the latter condition tended to obliterate differences found after single doses. The excretion of urinary metabolites was not much different between the two groups (73 per cent conjugated metabolites in patients, 68 per cent in normal subjects) suggesting that the metabolic handling of this drug may not be much different. Still, one has little enthusiasm as an experimenter in trying to persuade normal volunteers to take drugs of this type. You have to be crazy, either literally or figuratively, to take them.

In summary, experience with antipsychotic drugs in normal human beings might lead one to the conclusion that they are strange beasts which can produce, simultaneously, sedation and restlessness, excitation and fuzziness in thinking, fatigue, and nervousness. These feelings in general are strange and uncomfortable. As mentioned, one would be hard pressed to have guessed in advance some 15 years ago that such a strange conglomeration of noxious effects would be therapeutic for some schizophrenic patients.

Prediction of antidepressant effects

We have not had much occasion to give tricyclic antidepressants to normal volunteer subjects. In one experiment, imipramine and desipramine given in 50 mg. intramuscular doses produced sedation similar to that from the phenothiazines but less profound (greater from imipramine than from desipramine).[4] This production of sedation, more by imipramine than by desipramine, has held true in the experience of other investigators with normal subjects which I have reviewed.[3] Chronic treatment with imipramine lowered critical flicker fusion thresholds, similar to what might be expected from sedative drugs. Tachycardia and orthostatic hypotension following tricyclics occur in subjects as well as patients; in this regard these drugs strongly resemble the phenothiazines.

Using the elevation of plasma free fatty acids in the rested, fasted state as an indication of the "excitant" effects of a drug, we find little difference between desipramine and chlorpromazine (Table I). The excitant effects of some antipsychotic drugs, especially when large short-term doses are used, are comparable to those of hallucinogens. Thus, it would appear that, like the phenothiazines, tricyclics have a strange mixture of sedative and excitant effects.

Antidepressants, which seem to retain the sedative qualities of the phenothiazines and some of the unpleasant excitant effects, might very likely have been considered as promising new sedatives. In this regard, it is of some interest that a recent study comparing amitriptyline and sodium secobarbital as a hypnotic for presurgical patients found 25 mg. of the former to be the equivalent of 100 mg. of the latter. In all candor, we would not have been able to predict that this class of drugs would be antidepressants.

Some extrapolations to other drugs

While I have no personal experience with the use of volunteer subjects for testing other drugs affecting the central nervous system, some common sense approaches to the problem indicate situations which are appropriate and those which are not. Normal volunteers are useful for sleep laboratory studies of potential hypnotic drugs, especially in regard to their effects on normal sleep patterns.[15] Patients with insomnia are increasingly used in sleep laboratory studies, as well as in clinical evaluations of hypnotics. Assessment of the respiratory depressant effects of various centrally acting drugs, using the ventilatory response to carbon dioxide, is much more easily accomplished in normal volunteer subjects than in patients. On the other hand, it is possible that the consequences of such depression will be underestimated in normal subjects as compared to patients with various degrees of lung failure. Antitussives can be tested in normal volunteer subjects, using the experimental production of cough by a variety of methods. One might question, however, whether such a disagreeable symptom should be deliberately induced for testing such drugs. As we have been able to show with dextroamphetamine and marihuana, it is possible to screen drugs for stimulating or inhibiting appetite in normal volunteers, but the task may be better accomplished in patients suffering from disorders of appetite.

One can think of a great number of instances in which the use of normal volunteers would be rather inappropriate and possibly misleading, much as the evaluation of antipsychotic and antidepressant drugs was. Normal subjects are little suited to the study of anticonvulsant, analgesic, or anti-Parkinson drugs. While they might be suitable for studying anesthetics or antiemetics (emesis being induced), one can hardly justify such employment of normal subjects on the basis of need or ethical considerations.

As one departs from the classes of central nervous system drugs, it becomes even more difficult to find a place for the use of normal subjects in screening drugs. Drugs for angina pectoris and antimicrobial agents, for example, have specific indications for conditions not found in normal individuals. Cardiac glycosides might now be detected in normal subjects (although until a few years ago their effects would have been missed) and one might be able to detect diuretics in hydrated and sodium-loaded subjects, but one would expect to gain much more useful information from patients. With these drugs, as with those that might be employed in shock, the distribution and binding of the drug might be quite different in patients and in normal subjects. Limited screening of antihypertensive drugs, as well as screening of anticoagulants, might be accomplished in normal subjects. Both types of drugs generally operate by altering normal physiologic control mechanisms. Still, it seems scarcely necessary to prove this information in man when animal models have been fairly good for predicting these clinical effects.

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