DRUG ABUSE

Social and Psychopharmacological Aspects

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This text is representative of current research and thought about what now appears to be a significant area of social and medical concern. It provides a currently valid sample of the research and scientific concern invested in the problems of the abusive use of psychoactive substances, some of which are not ordinarily considered to be drugs of abuse.

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Chapter 6

FACTORS AFFECTING WITHDRAWAL RESPONSE TO CERTAIN MINOR TRANQUILIZERS

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THE increasing concern of our society with the rights of the individual is well mirrored in the field of public health by the increasing concern with the safety and effectiveness of drugs available to the public. In this context, drugs likely to be habit forming, such as the barbiturates, have attracted a good deal of attention and drugs with a pharmacological action similar to the barbiturates, such as meprobamate and chlordiazepoxide, recently have been involved in this controversy.

The pharmacological effects of meprobamate are usually described as "very similar to those of the barbiturates" (14), although there is not complete agreement on such a similarity (3). As with barbiturates, withdrawal symptoms have been described after sudden termination of meprobamate treatment. In addition to

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several clinical reports of withdrawal reactions after intake of meprobamate in doses higher than usual, research studies have been published reporting definite evidence of an abstinence syndrome after continuous administration of amounts exceeding the usual therapeutic doses (23, 15, 9). Controlled studies have failed to show definite indications of withdrawal reactions after treatment with the usual doses (4, 6).

Chlordiazepoxide so far has not been classified as clearly similar or clearly different from the barbiturates in pharmacological action (14). Furthermore, experimental evidence has been presented (5) that chlordiazepoxide differs in animal and human subjects from meprobamate and pentobarbital in its effects on conditioning. As far as withdrawal reactions are concerned, Hollister *et al.* (12) found an abstinence syndrome after sudden withdrawal of chlordiazepoxide, which had been given for one to six months in high doses ranging from 100 to 600 mg daily. The existing literature reveals no report of an abstinence syndrome after treatment with chlordiazepoxide with the most commonly employed therapeutic doses.

The problem of identifying drug dependence* is complicated by the interplay of psychic dependence with physical dependence and by the possibility of cross-tolerance among similar drugs. While psychic dependence can exist without physical dependence and therefore without an abstinence syndrome after withdrawal of the drug, Eddy *et al.* (7) point out that ". . . the withdrawal or abstinence syndromes are made up of specific arrays of symptoms and signs of psychic and physical nature that are characteristic for each drug type." Furthermore, it should be kept in mind that "These conditions are relieved by readministration of the same drug or of another drug of similar pharmacological action within the same generic type." The necessary consequence of these considerations is that medications taken prior to beginning meprobamate or chlordiazepoxide treatment should be closely scrutinized. Such information on prior medication is partic-

* "Drug dependence is a state of psychic or physical dependence or both on a drug, arising in a person following the administration of that drug on a periodic or continuous basis" (7).

ularly important because of the fact that ". . . physical dependence is an inevitable result of the pharmacological action of some drugs with sufficient amount and time of administration" (7).

The present pilot study was aimed at investigating the possible appearance of withdrawal effects in anxious outpatients who had been treated for four months with the prescribed daily dosage of 1600 mg of meprobamate, 40 mg of chlordiazepoxide, or placebo.

METHOD

At the end of a four-week methodologically oriented double-blind study of treatment with meprobamate, chlordiazepoxide, and placebo, (phase 1) most completed patients were referred for a further three months of treatment with the same medication, but with a different doctor and with a less frequent visit schedule (phase 2). Referred patients were seen for five more visits, and at the final week every patient was given placebo in a single-blind arrangement.* Figure 6-I shows a flow chart of the study.

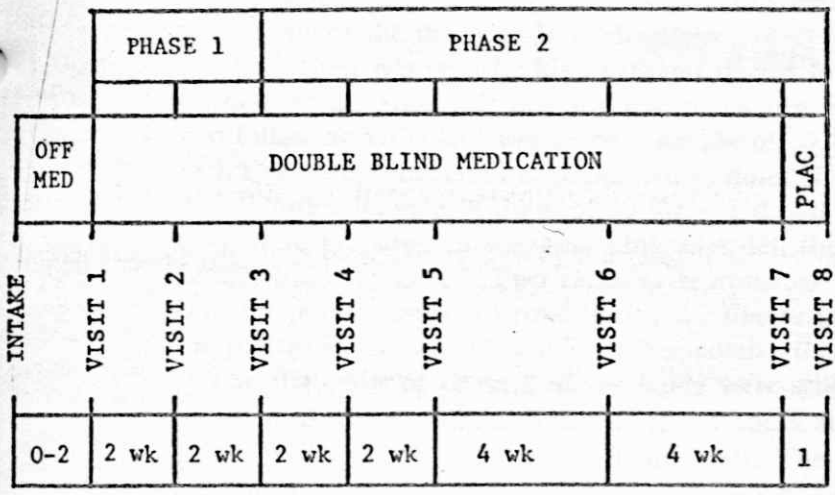

FIGURE 6-1. Flow chart for study.

* Withdrawal by means of placebo substitution is reported by Wiener *et al* (25) to be generally accepted as the best method of studying withdrawal effects.

The participating clinics were the Outpatient Department of The Henry Phipps Psychiatric Clinic at the Johns Hopkins Hospital (JHH), the Outpatient Psychiatric Clinic of the Philadelphia General Hospital (PGH) and the Outpatient Psychiatric Clinic of the Hospital of the University of Pennsylvania (HUP), coordinated by the Psychopharmacology Research Branch of the National Institute of Mental Health.

At each clinic all patients admitted to phase 1 of the study were screened by a psychiatrist at an intake interview. Psychotic, alcoholic, sociopathic, and organic patients, as well as depressive patients with no overt anxiety, were excluded. All other patients between eighteen and sixty years of age were accepted, provided that some overt anxiety was present and that they were literate enough to complete the study questionnaires.

During the intake interview, detailed information was obtained concerning the patient's present status and past history, including drugs taken during the past three years. If the patient was taking a drug at the time of intake, he was asked to stop the drug for at least four days prior to his next visit (which was the first study treatment visit).

The patient was then assigned at random to a senior psychiatrist and to one of the three study medications.

The patient was seen by his treatment doctor for about thirty minutes at the first visit and for five to twenty minutes at the two following visits and was given a supply of coded medication each time. Meprobamate was prescribed in doses of 400 mg q. i. d. and chlordiazepoxide in doses of 10 mg q. i. d. All three medications were prepared in identical pink capsules, the content uniformly bitter to taste.* Two capsules represented one dose. Except for protocol-imposed time limits, the doctor interacted wtih the patient in the way he would in "supportive therapy."

The five visits of phase 2 of the study were scheduled over a period of thirteen weeks as follows: visits 4 and 5 at two-week intervals, visits 6 and 7 at one-month intervals. The patients were continued on the coded medication until visit 7, when every pa-

* The capsules were kindly supplied by Wallace Laboratory and Hoffmann-La Roche Laboratories.

tient was given placebo in identical capsules and was asked to return a week later for visit 8. The forms and questionnaires employed at each visit during phase 1 of the study were continued throughout phase 2.

During phase 2 the patients were treated by different doctors from the ones during phase 1. These new doctors, usually psychiatric residents, held their interivews in a manner similar to the previous doctors.

After each visit, the doctor made notes about the patient's improvement, possible side effects, and deviations from the prescribed regimen. After the last visit, he also completed a physician's checklist of twenty-four items designed to reveal any withdrawal effects as shown in Figure 6-2.

Did patient manifest or describe the appearance or increase of any of the following since drug cessation (check and describe in detail on separate pages) :

I. *G.I.*
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Anorexia

II. *Motor*
- Fatigue
- Lethargy
- Loss of drive
- Poor coordination
- Tremors
- Restlessness

III. *Sleep*
- Insomnia
- Frequent waking

IV. *Mood and Interpersonal*
- Euphoria
- Depression
- Change in anxiety
- Change in rapport
- Increased irritability
- Increased psychomotor activity

V. Any increase in drug or alcohol intake (check) :
1. Coffee
2. Aspirin
3. Sleep Rx
4. Energizers
5. Other Rx

FIGURE 6-2. Physician's checklist.

At JHH the study doctors wrote a short note on all the patients who presented some symptoms falling within the physician's checklist. Besides expanding on the clinical picture and giving any pertinent details, the doctors attempted to judge whether habituation was present. At PGH and HUP a similar procedure was followed, but while judgment of habituation was attempted, the

general expectation was that symptom recurrence or worsening at the end of the placebo week does not represent habituation.

Along with other measures, the patients completed a symptom checklist (SCL), a sixty-two-item version of a discomfort list originally devised by Parloff *et al.* (20). The patient scored how much each symptom had bothered him during the previous one week, including the day of the visit, on a scale from 0 to 3.

This SCL had been used extensively in earlier studies carried out by our collaborative group (17, 18, 19, 24) to evaluate improvement in a wide range of neurotic symptoms. Within the SCL are included a group of symptoms which approximate those described by Eddy *et al.* (7)* as characteristic of drug dependence of the barbiturate type. These symptoms are 1) faintness or dizziness, 2) tired or fatigued during the day, 3) feeling low in energy or slowed down, 4) trembling, 5) poor appetite, 6) nausea or upset stomach, 7) sleepy during the day, 8) difficulty in falling asleep or staying asleep, and 9) weakness in parts of your body. Symptoms of overt anxiety, which were listed by Eddy *et al.* as the earliest manifestation of an abstinence syndrome were excluded from the nine symptoms quoted. Since overt anxiety was a leading symptom in this group of neurotic patients, increased anxiety would not distinguish an abstinence syndrome from an exacerbation of the original illness.

Most patients who completed phase 1 of the study were referred to phase 2. A small number of patients completing phase 1 required a different medication (antidepressants or phenothiazines in most cases) or declined to continue treatment. At one of the clinics (PGH) a few completers were assigned to psychotherapy for administrative reasons.

The 163 patients who actually began phase 2 of the study were distributed as follows: 64 at JHH, 65 at PGH, and 34 at HUP.

* "The complex of symptoms constituting the abstinence syndrome, in approximate order of appearance includes anxiety, twitching of muscles, tremor of hands and fingers, progressive weakness, dizziness, distortion in visual perception, nausea, vomiting, insomnia, weight loss and precipitous drop in blood pressure while standing, convulsions of the grand mal type, and a delirium resembling alcoholic delirium tremens, or a major psychotic episode" (7).

RESULTS

In the course of three months of further treatment, thirty-three patients completed the study at JHH; thirty-nine patients completed at PGH, and eleven patients completed at HUP.

To the best of our knowledge, no study patient took more than the prescribed dose of medication. Convulsions or delirium were not reported in any patient.

TABLE 6-I

DOCTORS' JUDGMENT OF PRESENCE OF SYMPTOMS OF "HABITUATION" OR "RECURRENCE"

	Meprobamate and Chlordiazepoxide		*Placebo*	
	Recurrence or habituation	*No Recurrence or habituation*	*Recurrence or habituation*	*No Recurrence or habituation*
PGH and HUP	17	22	4	7
JHH	9	12	1	11

On the basis of the physician's checklist and of the clinical notes, fifteen patients at PGH* and six patients at HUP were judged to be presenting symptom recurrence at the end of the placebo week. On the basis of similar data, ten patients at JHH were judged to be presenting symptoms of probable habituation.

The judgments of probable habituation (see Table 6-I) at JHH were tested by Fisher's Exact Probability Test for the significance of the difference between patients on the two drugs and patients on placebo. The trend (1-tailed $p=.06$) was found for more drug patients than placebo patients to be judged as habituated. There was no significant difference between the number of meprobamate patients judged habituated and the number of chlordiazepoxide patients judged habituated.

The judgments of symptoms recurrence at PGH and HUP were subjected to similar tests, and no significant differences were found.

* At PGH the judgment of symptom recurrence seems to be time related, with the majority (10 judgments) appearing in the first eleven patients, and with the remaining five judgments distributed among the remaining twenty-eight patients.

The data available from the intake visits, including clinical notes by the intake psychiatrists and transcripts of the recordings of the first treatment visit, were carefully reviewed in order to establish what medication, if any, the completed patients had been taking on a regular schedule prior to entering the study. Although insufficient information was available for three PGH patients and three HUP patients, all other patients could be classified with a certain degree of accuracy into two groups: 1) patients who had received meprobamate, chlordiazepoxide, diazepam,* or barbiturates** within a month of the start of the study*** and 2) patients who had not received the above medications within a month of starting the study. This second group included many patients who had received phenothiazines or other psychotropic medications but no "minor tranquilizers" or barbiturates. The first group was considered as medicated for more than four months; whereas the second group was considered as medicated for four months only.

TABLE 6-II

TOTAL LENGTH OF DRUG INTAKE AND DOCTORS' JUDGMENT OF PRESENCE OF SYMPTOMS OF HABITUATION AT JHH

	Meprobamate			*Chlordiazepoxide*			*Placebo*			
	Yes	*No*	*Total*	*Yes*	*No*	*Total*	*Yes*	*No*	*Total*	
> 4 mos	3	2	5	4	2	6	1	4	5	
4 mos	2	5	7	0	3	3	0	7	7	
Total	5	7	*12*	4	5	*9*	1	11	*12*	*33*

The judgments of probable habituation at JHH now were tested for the significance of the difference between patients taking the two drugs for more than four months and four months only. More patients on drugs longer than four months than patients on drugs for four months only had been judged habituated (1-tailed p=.085). Patients on drugs for more than four months

* Only one patient in this group had received diazepam.

** According to Bakewell and Wickler (1), barbiturates, sedatives, and "minor tranquilizers" are "equivalent, at least insofar as the development of tolerance and cross-tolerance is concerned."

*** In most cases such medications had been taken for periods of months to years prior to entering the study.

were then compared with all patients on placebo. Significantly (1-tailed $p=.025$) more patients on drugs for longer than four months than patients on placebo had been judged habituated.

Patients on meprobamate longer than four months did not show appreciably more instances of habituation than patients on placebo; whereas patients on chlordiazepoxide longer than four months showed reliably more instances of habituation than patients on placebo (1-tailed $p=.022$). The judgments of habituation at JHH, therefore, were attributable almost entirely to patients who had been taking chlordiazepoxide during the four months of the study and related medications prior to that time.

Comparable treatment of the data from PGH and HUP (see Table 6-III) produced no significant findings.

TABLE 6-III

TOTAL LENGTH OF DRUG INTAKE AND DOCTORS' JUDGMENT OF PRESENCE OF SYMPTOM RECURRENCE AT PGH AND HUP

	Meprobamate			*Chlordiazepoxide*			*Placebo*			
	Yes	*No*	*Total*	*Yes*	*No*	*Total*	*Yes*	*No*	*Total*	
> 4 mos	1	7	8	3	3	6	1	2	3	
4 mos	4	4*	8	4	6*	10	2*	2	4	*PGH*
Total	5	11	*16*	7	9	*16*	3	4	*7*	*39*
> 4 mos	1	0	1	2	0	2	1	0	1	
4 mos	0	2*	2	2*	0	2	0	3*	3	*HUP*
Total	1	2	*3*	4	0	*4*	1	3	*4*	*11*

* Information on prior medication insufficient for 1 patient in this group.

The nine-symptoms score derived from patients' self-ratings on the SCL offered the possibility of determining presence or absence of an abstinence syndrome uniformly at all three clinics. Since an analysis of the results after the placebo week (trial) could be compared to the results of the previous three visits (visit 5, 6, and 7) as control, a trend analysis of all the SCLs nine-symptoms scores of all the patients who completed the study was undertaken.

A trend-analysis computer program developed by Shaffer *et al.* (21) was applied to these data. The nine-symptoms score was obtained for each SCL on every patient with data on medications taken prior to the study. As mentioned above, six patients, three for each Philadelphia clinic, had prior medications data missing, so that the total N for these analyses was 77.

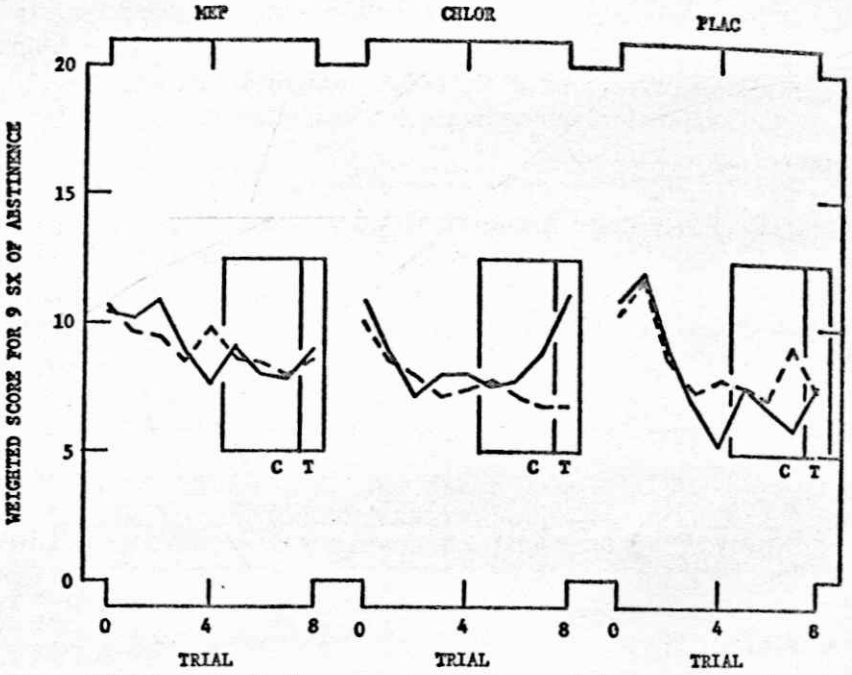

FIGURE 6-3. Mean weighted score or nine symptoms of abstinence at each study visit for patients grouped by study medication and history of prior medication.

Figure 6-3 shows that meprobamate and placebo patients followed an essentially similar course, whether they had been on medication longer than four months or not. The course followed by chlordiazepoxide patients, on the other hand, depended upon how long they took medication. Those who took medication longer than four months showed a gradual increase in the nine-symptoms score beginning after visit 6, and a further sharp increase after the placebo week. Those who took medication only for four months showed no increase in score towards the end of the period of medication. This difference in the course of the two groups of chlordiazepoxide patients is significant by several statistical tests, particularly when only the last four visits are considered.

A comparable analysis of total scores (62 items) of the SCLs at each visit also appeared indicated in order to examine the decrease or increase of all the neurotic symptoms included in the SCL.

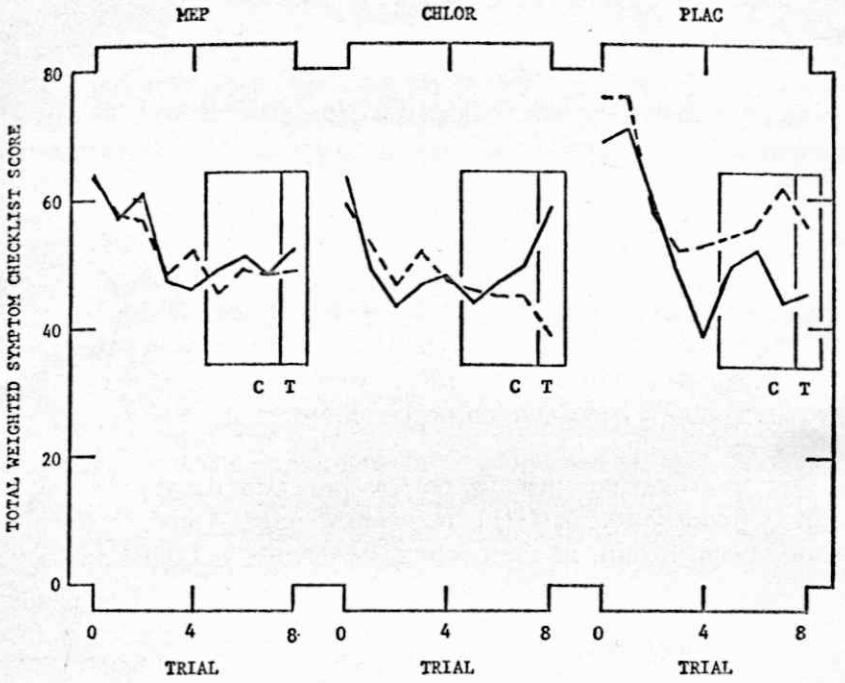

FIGURE 6-4. Mean total weighted symptom checklist score at each study visit for patients grouped by study medication and history of prior medication.

Figure 6-4 shows that the same types of curves were obtained again, with a significant difference in the effect of chlordiazepoxide for patients taking medication for more than four months and for patients taking medication for only four months. There was also a less reliable difference in the response of these two groups of patients to placebo. The significance of this difference is not yet clear, but it suggests a distinction between chronic and acute patients.

In both these analyses, the contrasting course of chlordiazepoxide patients taking medications longer than four months and four months only was evident at PGH and HUP as well as at JHH. Thus, while an analysis of clinic results within drugs showed the group of patients on chlordiazepoxide taken as a whole getting worse at JHH and HUP but getting better at PGH, an analysis of the PGH results alone revealed that patients on chlordiaze-

poxide for only four months tended to improve; whereas patients on medications longer than four months tended to get worse.*

DISCUSSION

The results here presented indicate that chlordiazepoxide patients who had received similar medications prior to entering the study showed both an abstinence snydrome after being withdrawn from chlordiazepoxide and a progressive increase of distress after seven to eight weeks of study treatment. While patients' self-ratings at all clinics indicated such results to be reliable, doctors judgments following chlordiazepoxide withdrawal were found to discriminate between chlordiazepoxide and placebo at one clinic only.

While a different orientation was noted in the doctors' judgments (habituation at JHH, recurrence at PGH and HUP), the lack of significance of the doctors' judgments at HUP was probably determined by the small number of patients. At PGH, on the other hand, not only lack of significance of the doctors' judgments was found, but also improvement in the chlordiazepoxide patients' subjective symptoms was apparent; this improvement, however, was clearly due to the larger proportion of patients who had not received similar medication prior to beginning chlordiazepoxide treatment.

On the other hand, the similarity of the results of the trend analysis when using the sixty-two-symptoms score and when using the nine symptoms-of-abstinence score may be indicating the lack of a sharp distinction between abstinence symptoms and recurrence of neurotic symptoms. This lack of distinction may be partially explained considering the fact that in this group of patients the leading symptom was anxiety and that anxiety is reported (7) to be one of the symptoms constituting the abstinence syndrome typical of drug dependence of the barbiturate type.

The meaning of the finding of an increased level of symptoms in the chlordiazepoxide patients who had received similar medications prior to entering the study is not completely clear; it could

* This last difference was, however, not statistically significant because of the small number of patients in each subgroup (6 and 9 respectively).

be related to the change of doctors and of schedule of visits, but this explanation may not explain the different course of the meprobamate patients. An interesting possible interpretation could be that of a tolerance phenomenon and one may wonder in this context whether increased dosage at that point could have modified the clinical course while perhaps accentuating the withdrawal effects of the placebo week.

The course of the meprobamate patients as compared to the chlordiazepoxide patients is also somewhat puzzling. The difference between the two drugs has been pointed out repeatedly in the literature. Essig (8) maintains that meprobamate closely resembles barbiturates in its withdrawal effects, while the chlordiazepoxide "abstinence syndrome is slower to develop and less acute than the meprobamate or barbiturate withdrawal syndrome." There has also been a statement that with continuous treatment with meprobamate "decreasing amounts are needed to produce the same reaction" (16).

Another possibility is that the design of the study made it more sensitive to abstinence symptoms from chlordiazepoxide than from meprobamate. Jaffe (13) points out that "with the short-acting barbiturates and meprobamate the sympoms usutally reach their peak during the second and third day of abstinence . . . with the onger-acting barbiturates and chlordiazepoxide, symptoms reach their peak more slowly and seizures may not occur at all or may occur as late as the seventh or eighth day." As a result of this difference in the course of the possible abstinence symptoms, the meprobamate patients could have been relieved of the symptoms at the time of the postplacebo visit, while the chlordiazepoxide patients could have been experiencing at that point their most acute distress from the abstinence. This difference could then be reflected in the symptom checklist self-ratings as well as in the doctors' clinical findings. The fact, however, that the meprobamate patients did not show the increasing level of distress in phase 2 of the study shown by the chlordiazepoxide patients seems to indicate a real difference between the two drugs.

In order to place the preliminary findings reported here in their proper context, it should be stressed that 1) we are dealing with a highly selected group of patients and we have not as yet

analyzed the influence of dropouts on study results, 2) further criterion information is available but not analyzed, and 3) the design of the four-month plus placebo week study was compromised by the fact that patients were primarily selected for a four-week methodologically focused study (phase 1) which had very different goals. For example, a large dropout occurred when patients were switched from their original phase 1 study doctor to their new phase 2 study doctor.

Had the major initial focus of the entire study been on long-term effectiveness and withdrawal, patients probably would have been selected somewhat differently, visits would have been scheduled differently, and doctors would not have been switched in "midstream."

We have learned a great deal from this study and are currently planning to design a more definitive study specifically focused on the issue of long-term efficacy and possible withdrawal effects associated with the so-called minor tranquilizers.

We would suggest, therefore, that the reader interpret the findings reported here as suggestive rather than conclusive. Within this same context we should like to report that we were unable to find a reliable difference in clinical efficacy among the three medications tested over the last three months of this trial, using data from patients who completed this trial period. Again, dropouts may have seriously biased these results.

Preliminary data analysis of the first study phase suggests that reliable differences did exist between active medications and placebo on the very much larger sample of patients over the initial two-week treatment period.

References

1. Bakewell, W. E., Jr., and Wickler, A.: The incidence of non-narcotic drug addiction in a university hospital psychiatric ward. Read in part at the Annual Meeting of the A.M.A. in Atlantic City, N. J., June 22, 1965.

2. Barsa, J. A., and Kline, N. S.: Use of meprobamate in the treatment of psychotic patients. *Amer J Psyohiat, 112*:1023, 1956.

3. BERGER, F. M.: The tranquilizer decade. *J Neuropsychiat, 5:*403-410, 1966.

4. BOYD, L. J.: CRAMMER, L.: MULINOS, M. G.; HUPPERT, V. F., AND HAMMER, H.: Meprobamate addiction. *JAMA, 168:*1839-1843, 1958.

5. COOK, L., AND KELLEHER, R. T.: Effects of drugs on behavior. *Ann Rev Pharmacol, 3:*205-222, 1963.

6. DICKEL, H. A.; DIXON, H. H.; SHANKLIN, J. G., AND DIXON, H. H., JR.: A clinical, double-blind comparison of Librium, meprobamate and phenobarbital. *Psychosomatics, 3:*129-133, 1962.

7. EDDY, N. B.; HALBACH, H.; ISBELL, H., AND SEEVERS, M. H.: Drug dependence: its significance and characteristics. *WHO Techn Rep Ser, No. 281,* 1964; reprinted in *Psychopharmacol Bull, 3:*1-12, 1966.

8. ESSIG, C. F.: Addiction to nonbarbiturate sedatives and tranquilizing drugs. *Clin Pharmacol Ther, 5:*334-343, 1964.

9. GEORGE, W. K., AND STUBBS, J. B.: Meprobamate withdrawal syndrome. *Texas Med, 61:*48, 1965.

10. HAIZLIP, T. M., AND EWING, J. A.: Meprobamate habituation: a controlled clinical study. *New Eng J Med, 258:*1181-1186, 1958.

11. HOLLISTER, L. E., AND GLAZENER, F. S.: Withdrawal reactions from meprobamate, alone and combined with promazine: a controlled study. *Psychopharmacologia (Berlin), 1:*336-341, 1960.

12. HOLLISTER, L. E.; MOTZENBECKER, F. P., AND DEGAN, R. O.: Withdrawal reactions from chlordiazepoxide (Librium). *Psychopharmacologia (Berlin), 2:*63-68, 1961.

13. JAFFE, J. H.: Addiction and drug abuse. In *The Pharmacological Basis of Therapeutics, Third Edition,* L. S. Goodman and A. Gilman (Eds.). New York, Macmillan, 285-311, 1965.

14. JARVIK, M. E.: Drugs used in the treatment of psychiatric disorders. In *The Pharmacological Basis of Therapeutics, Third* Edition, L. S. Goodman and A. Gilman (Eds.). New York, Macmillan, 159-214, 1965.

15. KANE, F. J., JR., AND WIDMANN, D. E.: Seizures after withdrawal of meprobamate. *JAMA, 187:*782, 1964.

16. LAMERE, F.: Drug habituation (correspondence). *JAMA, 160:* 1431, 1956.

17. LIPMAN, R. S.; PARK, L. C., AND RICKELS, K.: Paradoxical influence of a therapeutic side-effect interpretation. *Arch Gen Psychiat (Chicago), 15:*462-474, 1966.

18. LIPMAN, R. S.; COLE, J. O.; PARK, L. C., AND RICKELS, K.: Sensitivity of symptom and nonsymptom-focused criteria of outpatient drug efficacy. *Amer J Psychiat, 122:*24-27, 1965.

19. PARK, L. C., AND COVI, L.: Nonblind placebo trial. *Arch Gen Psychiat (Chicago), 12:*336-345, 1965.

20. PARLOFF, M. B.; KELMAN, H. C., AND FRANK, J. D.: Comfort, effectiveness and self-awareness as criteria of improvement in psychotherapy. *Amer J Psychiat, 111:*343-351, 1954.

21. SHAFFER, J. W.; FORBES, J. A., AND DEFELICE, E. A.: Some suggested approaches to the analysis of chronic toxicity and chronic drug administration data. *Toxic Appl Pharmacol, 10:* 514-522, 1967.

22. STOUGH, A. R.: Possible habituating properties of meprobamate: clinical study in an institutionalized, highly susceptible population. *JAMA, 166:*882-888, 1958.

23. SWANSON, L. A., AND OKADA, T.: Death after withdrawal of meprobamate. *JAMA, 184:*780-781, 1963.

24. UHLENHUTH, E. H.; RICKELS, K.; FISHER, S.; PARK, L. C.; LIPMAN, R. S., AND MOCK, J.: Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia (Berlin), 9:*392-418, 1966.

25. WIENER, D. N.; FEINBERG, P.; NAGOBADS, I. J.; WESTENDORF, F., AND WARREN, P. W.: Effects of withdrawal of tranquilizers. *Arch Gen Psychiat (Chicago), 9:*513-519, 1963.