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Barbiturate Self-Administration by Human Sedative Abusers

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Assessment of abuse or addiction liability of psychoactive drugs has been attempted with a variety of techniques. Early in the study of opiate drugs, substitution tests involving physically dependent subjects were employed (Himmelsbach and Andrews, 1943). The relative efficiency of a drug in suppressing the abstinence syndrome in morphine withdrawal was taken to indicate that the test drug produced addictive properties similar to morphine. Later, Fraser et al. (1957) used a similar substitution procedure to show that secobarbital and pentobarbital were interchangeable in subjects physically dependent on the compounds.

Tests of direct addiction have also been utilized, in which non-dependent subjects, usually former addicts, have been chronically exposed to test compounds in order to determine the presence of abstinence syndromes when medication is suddenly discontinued. While this has been done with opiates (Fraser et al., 1961) and meprobamate (Haizlip and Ewing, 1958), direct addiction studies with sedatives are presently considered too hazardous for human subjects (Jasinski, 1973).

Attempts to assay effects of single doses of possible addictive drugs have resulted in the development of subject and observer drug rating forms (Fraser et al., 1961; Martin et al., 1962). Questionnaires such as the Addiction Research Center Inventory (ARCI) (Hill et al., 1963) and various related scales intended to assess the subjective effects of doses of different drugs, for example, have been constructed (Haertzen, 1966; Martin et al., 1971). Responses to certain physiological measures such as pupillary dilation and post-rotatory nystagmus have been used to assess the abuse liability of stimulants and hallucinogens (Martin, 1973) as well as opiate and sedative drugs (Jasinski, 1973).

Behavioral measures of abuse liability of psychoactive compounds are not common with human subjects. An early study by Isbell et al., (1948) permitted opiate addicts to choose between morphine and methadone after exposure to methadone. Recently, Schuster et al., (1971) studied the rate of return to a clinic by groups of heroin addicts for pentazocine, methadone, codeine or placebo to assess preference for these drugs.

The present study is another attempt to use a behavioral procedure to determine the abuse liability of drugs in human subjects. It employs an option or choice procedure. Although variations of this procedure have been used to determine preference for drug doses of cocaine (Johanson, 1966; Iglauer and Woods, 1974) and preference between chlordiazepoxide and secobarbital (Findley et al., 1972) in rhesus monkeys, it has not previously been systematically employed with human subjects.

METHOD

Subjects:

The first subject (BD) was a 56-year old female of mixed caucasian and Indian ancestry. She had a recurrent problem with depression and drugs, including barbiturates, diazepam, chlordiazepoxide, various sleeping medications, antidepressants, phenothiazines, and alcohol. In addition, her history included two suicide attempts and periods of confusion consistent with mild sedative drug overdose.

The second subject (GW) was a 39-year old white female with a lengthy history of sedative drug use since the age of 15. Drugs used included phenobarbital, meprobamate, and various barbiturate sleeping medications. For three years prior to hospitalization she had been taking only meprobamate and had gradually increased her intake of 400 mg tablets from four to between thirty and fifty tablets each day. On admission she complained of

nausea and vomiting and extreme nervousness, and reported the drug was no longer effective in alleviating these complaints.

Procedure:

Initial screening. Shortly after the arrival on the hospital station, both subjects were given a 200 mg oral challenge dose of pentobarbital in a blanked, unmarked capsule. The same type capsule was subsequently used for all drug administrations. The subjects were then observed for evidence of sedative drug effects.

Drug stabilization. On the basis of the subjects' past history, BD was stabilized on 600 mg pentobarbital daily in the form of 100 mg capsules available a minimum of 2.5 hr apart, and GW was stabilized on 1000 mg pentobarbital daily in the form of 100 mg capsules available a minimum of 45 min apart. Capsules were obtained upon request from the nursing staff.

Drug preference. Following stabilization of drug intake, dispensing of drug capsules was shifted to an automatic vending machine. The vending machine was a standard 10-channel candy vendor (Automatic Products Co., St. Paul, Minnesota, Model 164-172) that had been modified by removing the coin slot and installing a keyed switch-lock and a small green stimulus light above the push-button for each vending channel. The subjects were issued keys to unlock assigned channels for drug dispensing. Drug availability was signaled by illumination of the appropriate stimulus light. When the light was illuminated, unlocking of the keyed switch and pressing of the push-button resulted in the delivery of a drug capsule in a small paper envelope. Following the vending operation, the stimulus light was extinguished for a pre-set period of time by a clock-timer located in an adjoining metal cabinet. When the stimulus light was extinguished, no drug could be obtained from that channel. The amount of drug (in mg) dispensed from each

channel was also counted by a predetermining counter which de-activated that channel (signaled by extinguishing of the stimulus light) when the maximum daily limit was reached. A chime sounded upon each operation of the vending machine, and a registered nurse verified the capsule was swallowed by the subject and did the medical recording. In addition, the operation of the channels was recorded on an Esterline Angus event recorder.

In determining drug preference, as described in this report, the locks of two adjoining channels were keyed the same, and the subject was allowed to receive drug from either channel. The subjects were instructed to select capsules alternately from the two channels until a preference was determined and then continue taking the drug from the preferred channel for the remainder of the day (until midnight). If no preference was found, the subject was to alternate selections for the remainder of the day. Selecting a drug from one channel was automatically programmed to extinguish both channels' stimulus lights and prohibit the subject from receiving drug from either channel for a pre-set period of time (2.5 hr for BD, 45 min for GW). In addition, the mg value of each drug dose was counted automatically on predetermining counters which were programmed to shut off both channels after a specified combined amount of total drug had been taken from the two channels.

While the subjects were told of the nature of the research and consented to participate and follow the research plan, they were not told of the specific medication or dosage being tested on a given day. On each option day the subject could select between a standard drug (same on all option days) and a test drug (a different drug or dosage on each option day). Options for BD were between 50 mg pentobarbital (standard) and 30, 50, and 100 mg pentobarbital or secobarbital (test compounds). Time between suc-

cessive drug administrations was minimally set at .5 hr for 30 mg doses, 1.0 hr for 50 mg doses, and 2.5 hr for 100 mg doses. Total daily amount of pentobarbital or secobarbital was limited to 600 mg. Options for GW were between 100 mg pentobarbital (standard) and 50, 100, and 200 mg pentobarbital or secobarbital (test compounds). In one case preference between 100 mg pentobarbital and 400 mg meprobamate (the subject's abused drug prior to hospitalization) was tested. Time between successive drug administrations was minimally limited to 45 min for all drugs and dosages to prevent discrimination of drug dose on the basis of channel time-out duration. Total amount of pentobarbital or secobarbital was limited to 1000 mg daily (or pentobarbital equivalents for meprobamate, where 400 mg meprobamate equals 50 mg pentobarbital).

For both subjects, each second option day was a control day in which the standard compound only was available in both channels, to assess channel biases and subjects' tendency to alternate channels in accordance with instructions. Control days were between 50 mg and 50 mg pentobarbital for BD, and between 100 mg and 100 mg pentobarbital for GW. All drugs were contained in identical unmarked capsules.

At the end of the study the subjects were detoxified and received appropriate psychiatric treatment for sedative abuse.

RESULTS

Both subjects were found to prefer higher dosages to lower dosages of both drugs (pentobarbital and secobarbital). At equal dosages, no preference between pentobarbital and secobarbital was seen.

Figure 1 shows event records of responding for standard compound (50 mg pentobarbital) and various dosages of test compounds (30, 50, and 100

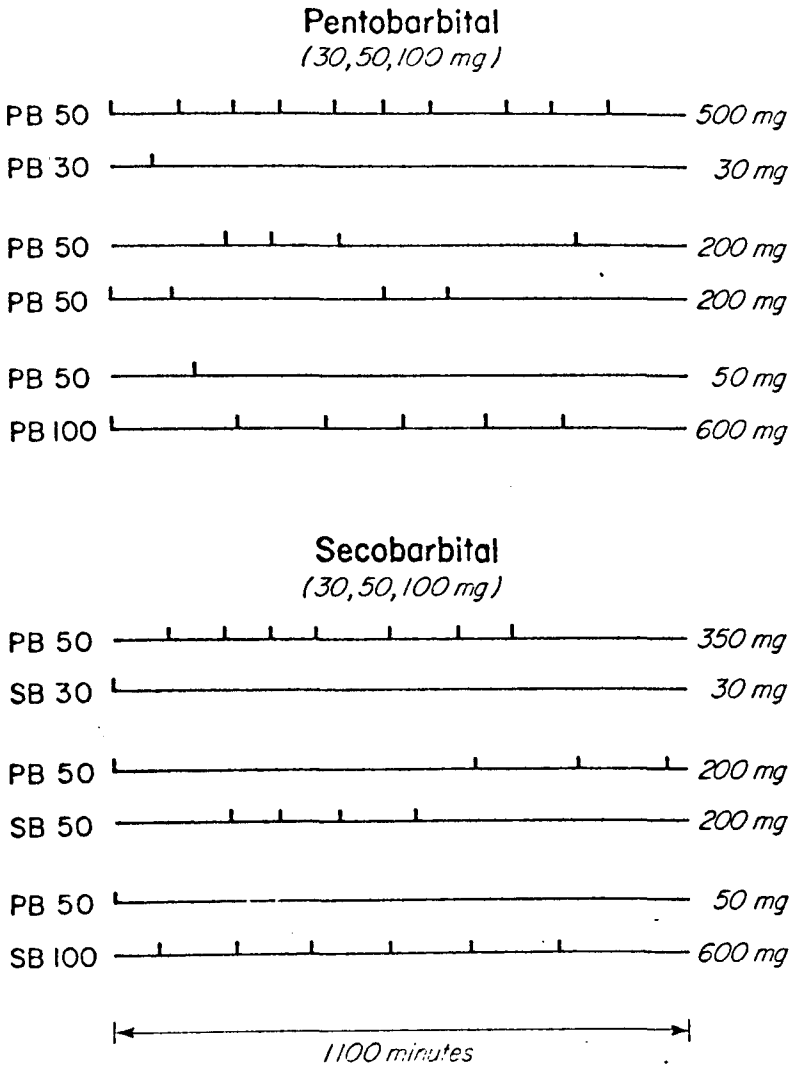

Figure 1. Event records of drug responding for subject BD. Records begin with the first drug response each day. Capsule dosage shown at left and total drug intake shown at right of each line pair. PB = pentobarbital; SB = secobarbital.

mg pentobarbital or secobarbital) for BD. On each option pair, the upper line shows responding for standard drug and the lower line shows responding for test drug. The total drug intake in pentobarbital or pentobarbital equivalents is shown to the right of each line pair. As can be seen, the subject preferred the high (100 mg) dose of pentobarbital or secobarbital to the intermediate (50 mg) dose of the standard (pentobarbital) compound. A preference was also apparent for the intermediate dose of the standard compound (50 mg pentobarbital) over the 30 mg dosages of pentobarbital. No clear-cut preference was evident on control days (50 mg vs. 50 mg pentobarbital), or with 50 mg dosages of pentobarbital and secobarbital. The drug intake of BD varied between 400-650* mg pentobarbital or its equivalents daily. The total amount of drug taken increased significantly ($p < .01$) as higher test dosages of drug were made available. While the subject did not always take as many drug capsules as was possible at the 30 mg and 50 mg dosages, she almost always did so at the higher (100 mg) dosages.

Figure 2 shows event records of responding for standard compound (100 mg pentobarbital) and various dosages of test compounds (50, 100, and 200 mg pentobarbital or secobarbital) for GW. The format is similar to that described previously for Figure 1. A clear preference is seen for 100 mg pentobarbital (standard) over 50 mg pentobarbital or secobarbital (test compounds). However, when options were provided between 100 mg pentobarbital (standard) and 200 mg pentobarbital or secobarbital, no clear-cut preference was readily apparent. There was also a lack of preference between 100 mg

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* Because of programming complications, it was possible to slightly exceed to upper daily drug limit with certain combinations of standard and test drug dosages and response patterns. This rarely happened, however.

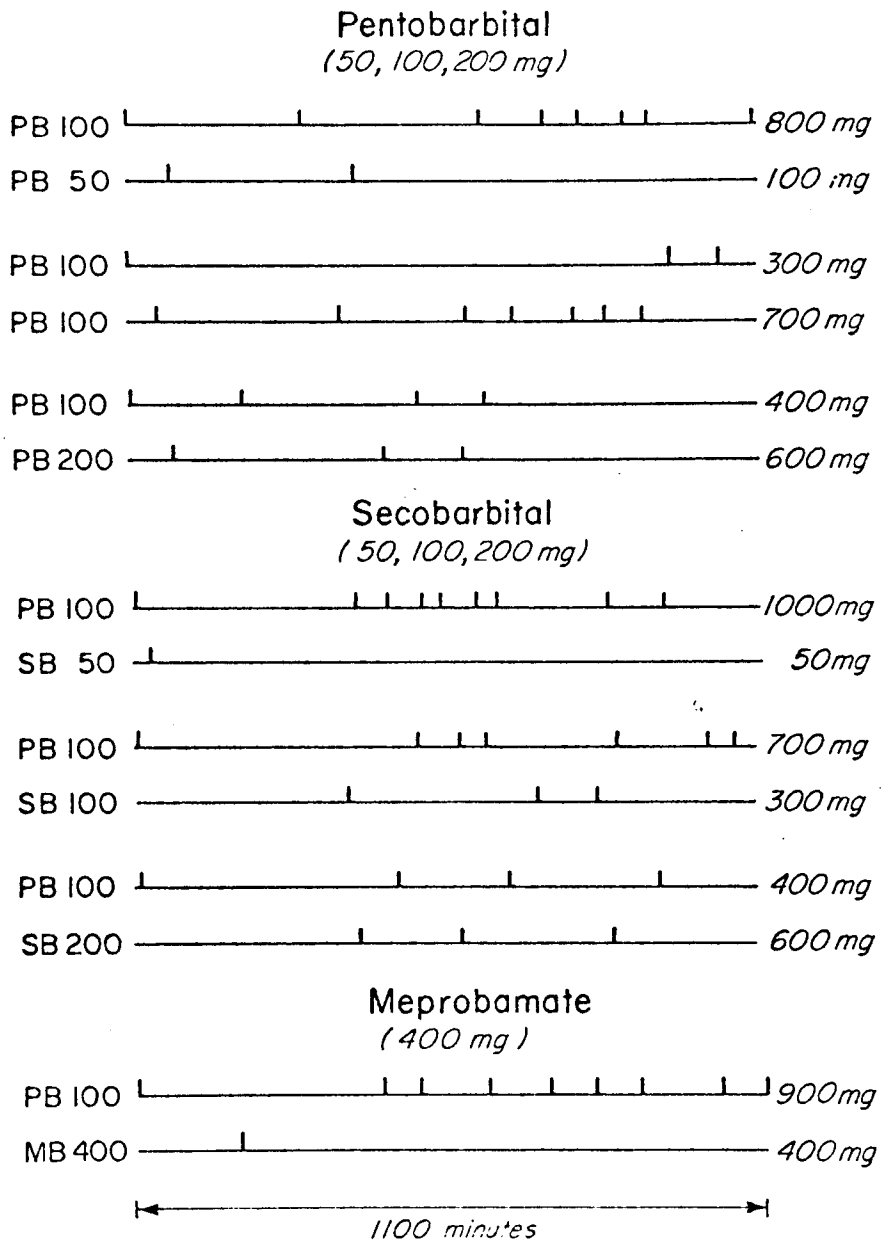

Figure 2. Event records of drug responding for subject GW. Records begin with first drug response each day. Capsule dosage shown at left and total drug intake shown at right of each line pair. PB = pentobarbital; SB = secobarbital; MB = meprobamate.

vs. 100 mg pentobarbital (control days) and 100 mg pentobarbital and 100 mg secobarbital. Dosages of 100 mg pentobarbital were preferred to 400 mg meprobamate. The total amount of drug taken daily by this subject was relatively constant, ranging from 900-1050* mg pentobarbital or pentobarbital equivalents.

To quantify the above preferences, the data were expressed as a preference ratio, the ratio of number of selections of the test drug to the number of total drug selections (test + standard) on a given day. Ratio value of .5 indicates equal preference between test and standard compound (e.g., 10/10 + 10 = .5), whereas ratio values less than .5 indicate preference for the standard compound over the test compound, and ratio values greater than .5 indicate preference for the test compound over the standard. Since on control days (when both channels contain the same compound) it is not possible to specify which channels contain the test and standard drugs, drug preference is expressed as a range of ratios representing the most extreme conditions of channel selection. In one case, all of the most frequently selected component of each option pair are treated as the test drug; in the other case, all of the least frequently selected component of each option pair are treated as the test drug. While the midpoint of this range (always conveniently .5) is used for graphing purposes, test drug preferences on non-control option days must exceed to range of control values to be considered significant.

Figure 3 shows preference ratios for BD between 50 mg pentobarbital (standard) and 30, 50, and 100 mg pentobarbital or secobarbital (test compounds). The dashed line indicates no preference (.5) between the standard

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* See eariler footnote of explanation.

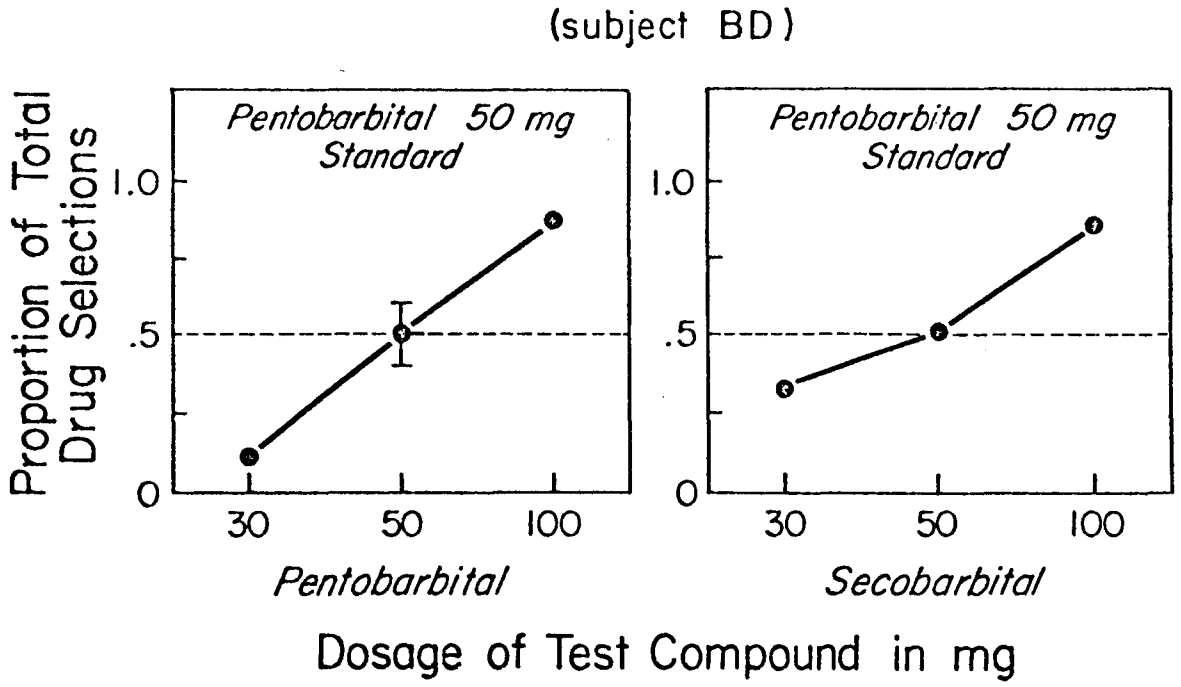

Figure 3. Preference ratios for standard (50 mg pentobarbital) and test (30, 50, 100 mg pentobarbital and secobarbital) drugs for subject BD. See text for further explanation.

and test compounds; deviations away from this line indicate preference for the test compound (ratio values > .5) or preference for the standard compound (ratio values < .5). The range of possible ratio values on control days when both channels contain the same compound is also shown. As can be seen, preferences for the test compound over the standard compound increases with increases in dosage of the test compound, for both pentobarbital and secobarbital. Figure 4 shows similar results for GW, except at the higher doses (200 mg) of the test compounds, where the preference ratio values failed to exceed the range for control days.

Except for slurred speech and some disorientation on the days when 200 mg dosages of pentobarbital or secobarbital were available to GW, neither subject showed obvious signs of drug intoxication despite the substantial amount of drug taken. Despite the evidence of greater pharmacological effect of the 200 mg dosage, however, the subject showed no clear-cut preference for the dosage in the option testing and expressed dissatisfaction with the intoxication symptoms.

DISCUSSION

Comparisons of addictive properties of pentobarbital and secobarbital in human subjects have shown them to be generally similar. It was demonstrated by Fraser et al. (1957) that pentobarbital in equivalent doses could be substituted in secobarbital-dependent patients and prevent abstinence symptoms. More recently a comparison of varying intramuscular doses of secobarbital and pentobarbital in human subjects has been made. In this investigation, single doses of the drugs were determined on the Pentobarbital, Chlorpromazine, Alcohol Group (PCAG) scale of the Addiction Research Center Inventory (ARCI), on facilitation of post-rotatory nystagmus, and on sub-

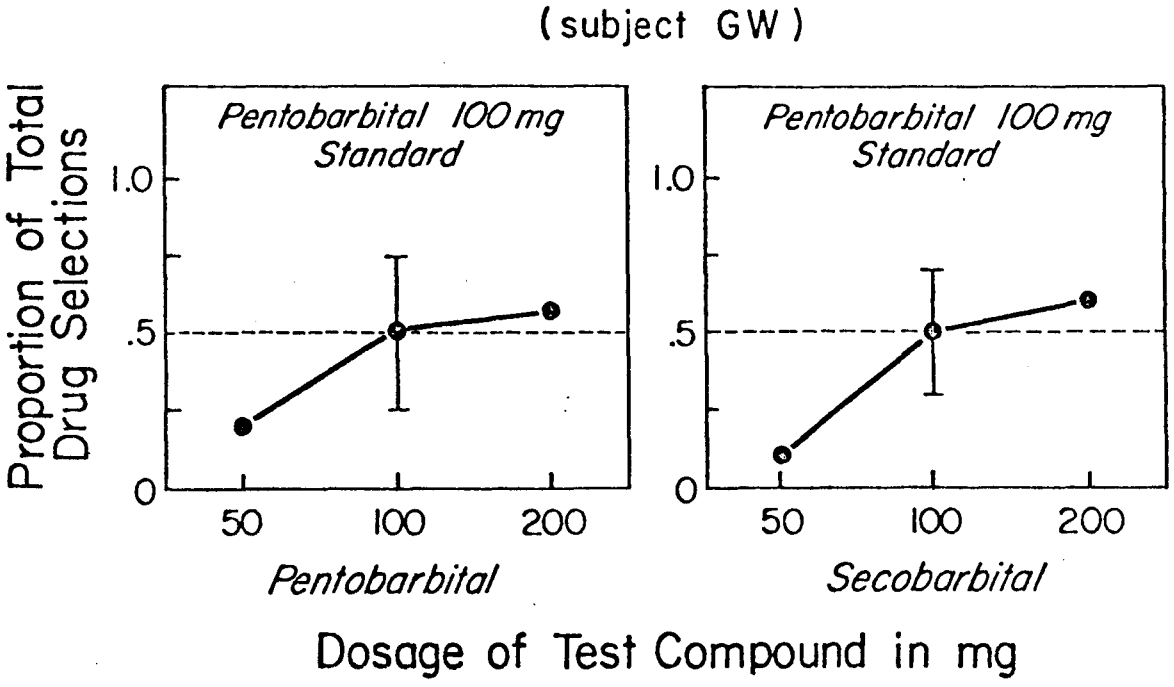

Figure 4. Preference ratios for standard (100 mg pentobarbital) and test (50, 100, 200 mg pentobarbital and secobarbital) drugs for subject GW. See text for further explanation.

ject observer estimates of liking. By regression lines drawn from these measures, potency ratios of secobarbital to pentobarbital were made which varied from 0.8 to 1.2 (Jasinski, 1973). The inference from these data is that secobarbital and pentobarbital are approximately equivalent in addictive liability. Similar results were obtained in the present study in which no preference was observed between equivalent doses of secobarbital and pentobarbital in either subject.

The result of varying dosage of pentobarbital and secobarbital on preference is more difficult to interpret. Doses of secobarbital (75, 180, and 432 mg/70 kg) and pentobarbital (50, 120, and 288 mg/70 kg) showed dose--dependent increases in scores on the PCAG scale of the ARCI as well as dose-related increases in frequency and duration of post-rotatory nystagmus (Jasinski, 1973). An earlier study by Martin et al. (1962) showed dose--dependent increases in post-rotatory nystagmus for pentobarbital in 150, 200, and 250 mg doses, although the subjects' liking varied inversely with dosage. Therefore, it appears that the subjects' liking does not necessarily follow the same shape dose-response curve as does the PCAG scale of the ARCI or the effect of pentobarbital and secobarbital on post-rotatory nystagmus. This is in partial agreement with the present findings in which it appears that higher doses of pentobarbital or secobarbital are preferred to lower doses only up to the 100 mg dose. Doses of 200 mg secobarbital or pentobarbital taken by GW were not preferred to 100 mg according to the criterion used in the study. Signs of intoxication were, however, apparent when this subject took 200 mg doses which were not apparent when she took 100 mg doses.

The preference of 100 mg pentobarbital to 400 mg meprobamate by GW was of interest largely because meprobamate had been her primary drug of abuse

prior to hospitalization. It has been documented that meprobamate can produce physical dependence and a barbiturate-like abstinence syndrome (Haizlip and Ewing, 1958). Unfortunately, higher doses of meprobamate could not be tested against 100 mg dose of pentobarbital as meprobamate tablets are large and no more than one could be put into the blanked capsules employed in the study. Therefore, it is unknown whether this preference for pentobarbital would have been maintained if higher doses of meprobamate had been offered.

A major difference between the present study and others which have studied sedative drug abuse-liability is its use of a behavioral measure or indicator of the subjects' preference. Subjects were to indicate the preferred drug and dose by consuming it over another compound. This technique may provide another means for assaying abuse liability of different sedative compounds in human subjects. As has been discussed, the findings with this method are in general agreement with previous studies in which other measures have found that the relative abuse liability of secobarbital and pentobarbital are approximately equal. They do, however, appear to suggest some different conclusions regarding dosage influence on abuse liability or preference, as it appears that at least on the upper end of the dosage range, the higher pentobarbital and secobarbital doses are not necessarily preferred to somewhat lower ones.

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