A.8 MINOR TRANQUILIZERS AND NON-BARBITURATE SEDATIVE-HYPNOTICS

INTRODUCTION
There are many common drugs which have significant sedative-hypnotic properties. Alcohol and barbiturates have been discussed separately in this appendix, and their many pharmacological similarities were indicated. Barbiturates are often considered the prototype of sedative-hypnotic drugs; pharmacologically related compounds are frequently identified or discussed in terms of their similarities to and differences from them. We shall consider a rather heterogeneous aggregate of sedative compounds in this section under the general rubric of minor tranquilizers and non-barbiturate sedative-hypnotics. Because of significant similarities in effects, many of these drugs, and alcohol and barbiturates as well, are often considered together in broad categories given such titles as sedative-hypnotics, psychosedatives, anxiolytic sedatives (or just sedatives), non-selective depressants (or just depressants), ataractics, or psycholeptics.3. 32' 79' 125

TABLE A.4
MINOR TRANQUILIZERS AND NON-BARBITURATE SEDATIVE-HYPNOTICS
(1) Acetaldehyde derivatives
(e.g., chloral hydrate [Noctec®], paraldehyde)
(2) Propranediol derivatives
(e.g., meprobamate [Equanil®, Miltown()], tybamate [Solacen®])
(3) Benzodiazepine derivatives
(e.g., chlordiazepoxide [Librium®], diazepam [Valium®, Vivol®], oxazepam [Serax®, nitrazepam [Mogadon®])
(4) Piperidinedione derivatives
(e.g., glutethimide [Doriden®], methyprylon [Noludar®])
(5) Pentynol derivatives
(e.g., ethchlorvynol [Placidyl®], ethinamate [Valmid®])
(6) Quinazolone derivatives
(e.g., methaqualone [Mandrax®, Mequelon®, Quaalude®, Sopor®, Parest®])
(7) Miscellaneous:
(a) Monoureides (e.g., carbromal)
(b) Bromides (e.g., Nytol®
(c) Anticholinergics (e.g., scopolamine, benactyzine)
(d) Antihistamines (e.g., dimenhydrinate [Gravol®, Dramamine®], diphenhydramine [Benadryl®], doxylamine [Decapryn®], hydroxyzine [Atarax®], methapyrilene [M-P®], phenyltoloxamine [Bristamin®], promethazine [Histantil®], pyrilamine [Neo-Antergan®], triprolidine [Actifed®])

The minor tranquilizers and non-barbiturate sedative-hypnotics can be divided into several groups as indicated in Table A.4.3, 79 With few exceptions, the drugs in the first six groups share significant common pharmacological properties and are similar to alcohol and barbiturates in many important respects: these drugs reduce anxiety and tension, and produce drowsiness and sleep at progressively higher doses; they elicit similar psychological and
physiological signs of intoxication and overdose; they have relatively little effect on autonomic nervous system functions; they generally elevate the convulsion threshold; limited but significant tolerance develops with chronic heavy use; physical dependence can also occur with high-dose use; psychological dependence is sometimes reported; and significant but often incomplete cross-tolerance and cross-dependence may occur among them. The various drugs may differ to some extent in their potential for producing these effects. The major exceptions to some of these generalizations about sedative drugs are certain anticholinergic (acetylcholine blocking), antihistaminic (histamine blocking) and bromide compounds, although even these are similar to the other sedatives in many respects. In addition, most of the volatile solvents and gases have somewhat comparable sedative properties. Under certain conditions, cannabis has significant sedative or tranquilizing effects and has been used medically in Canada and many other countries for these purposes. Some further distinctions among the various sedative drugs are made in the following discussion.

The term "minor tranquilizer" was introduced in the scientific literature in the 1950s to distinguish some of the newer non-barbiturate drugs prescribed to reduce anxiety and tension from the "major tranquilizers" or neuroleptics, such as the phenothiazines (e.g., chlorpromazine) and rauwolfa alkaloids (e.g., reserpine), which are employed more as antipsychotic drugs in the treatment of such disorders as schizophrenia. The minor tranquilizers are intended to reduce anxiety, tension and agitation at doses which have relatively few other significant effects on emotional, cognitive or perceptual processes. The degree to which they approximate this goal and the extent to which they actually differ in this regard from the various barbiturate and non-barbiturate sedatives is still a matter of some controversy. In this report, and in much of the scientific literature, the label "minor tranquilizer" is restricted to the benzodiazepine and propranediol derivatives (e.g., Valium®, Librium®, Equanil®, Miltown®), but the term is often used in a broader sense to refer to other of the newer non-barbiturate sedatives as well. Although the benzodiazepines are perhaps most unique, few clear pharmacological distinctions can be drawn between most of these sedatives.

Much confusion is caused by the non-specific usage of the general label "tranquilizer". Both major and minor tranquilizers are often indiscriminately grouped together under the broad heading of "tranquilizer" in spite of the fact that these two classes of drugs are quite dissimilar chemically and pharmacologically, and have generally different medical applications and patterns of non-medical use. The major tranquilizers do not produce euphoria or other pleasant psychological side effects and are consequently rarely used non-medically. The minor tranquilizers, on the other hand, typically produce effects subjectively similar to those of alcohol and barbiturates, and may be used non-medically because of these properties. Dependence on the minor tranquilizers has often been reported in the literature. In spite of significant differences (especially as regards non-medical use), many official and lay sources continue to use the general category "tranquilizer", with no further differentiation, thereby confusing and confounding many important issues.

The sedative effect of bromide was first used in medicine in the 1850s in the treatment of epilepsy. Bromides were soon employed on a large scale for a variety of psychological and neurological disorders. Unlike most other drugs which depress the functioning of the central nervous system, the bromides do not effectively induce sleep in large single doses. They are usually administered chronically for their general cumulative sedative effects. Although
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bromides are still employed in a variety of nerve tonics, headache remedies (e.g., Bromoseltzer®) and non-prescription 'sleeping pills' (e.g., Nytol®), they have generally been replaced in medical use by a variety of more effective and less toxic drugs.\(^\text{109}\)

Chloral hydrate and paraldehyde are very effective sedative-hypnotics which were introduced into medicine in the latter part of the 19th century and are still employed in clinical therapeutics today. Chloral hydrate was the first widely used synthetic sleep-inducing (hypnotic) drug, and as 'knockout drops' added to alcohol produces the so-called 'Mickey Finn'. Both chloral hydrate and paraldehyde have been used in the treatment of alcohol withdrawal. Dependence on these drugs has become rare but is still sometimes seen.\(^\text{85, 90, 109}\)

Barbiturates were first used medically in 1903 and dominated the area of sedative-hypnotic therapeutics for the following half-century.\(^\text{109}\) Most of the drugs in groups 2 to 6 of Table A.4 were developed in the 1950s or later, and have tended to replace barbiturates in many areas of medical and non-medical use. Many of these sedatives were introduced specifically as "non-barbiturates", suggesting major distinctions in dependence liability, toxicity and certain other effects. In some instances significant differences between barbiturates and the newer sedatives and minor tranquilizers are clearly documented, but many of these drugs have been shown to be more like barbiturates than was originally realized. Compared to the barbiturates, much less is known about the effects of both the medical and non-medical use of these newer drugs. It is interesting to note that thalidomide was introduced into medicine as a non-barbiturate sedative-hypnotic and is a very effective sleep-inducer.

The minor tranquilizers and non-barbiturate sedatives are among the most widely used drugs in medicine. In 1971, a Canadian Medical Association survey suggested that these drugs accounted for half of all mood-modifying drug prescriptions in Canada. In comparison, barbiturates made up one-fifth of such prescriptions.\(^\text{"}\) Valium® (a benzodiazepine minor tranquilizer) is the widest selling prescription drug in Canada.\(^\text{59}\)

Until recently, the non-medical use of these sedatives was considered largely the domain of the 'average middle-class adult', but recent reports indicate that some of these compounds are gaining in popularity among youth as well.\(^\text{51}\) The non-medical use of Mandrax® (methaqualone and diphenhydramine) and other methaqualone preparations has frequently been noted in Canada in recent months. (See also Appendix C Extent and Patterns of Drug Use.)

Atropine and scopolamine (l-hyoscine) are belladonna alkaloids which block certain effects of acetylcholine in the body. Atropine generally produces central nervous system excitation, but scopolamine has mild sedative properties in moderate doses. In higher doses, however, both belladonna alkaloids have similar effects and may produce delirium and hallucinogenic responses.\(^\text{27, 5°, 58, 62}\) Scopolamine is found chiefly in Hyoscyamus niger (henbane), Datura stramonium (Jimson or Jamestown weed, also known as thorn-apple or stink weed) and other Datura varieties. These drugs have been used in many societies since ancient times for a variety of medical and non-medical purposes. They were frequent ingredients in sorcerers' potions and poisons, and have served important religious functions in certain cultures.\(^\text{22, 62, 83}\)

In the United States, scopolamine was commonly employed in non-prescription sedative and motion-sickness preparations, but in recent years it has been removed from many such over-the-counter products. It has not been commonly used for such purposes in Canada. Because of unpleasant side effects at high doses, these drugs are not frequently used non-medically, although a few reports exist, for example, of young people using such
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stramonium preparations as Asmador® cigarettes for hallucinogenic purposes. There is a wide variety of drugs which are used medically for their antihistaminic and anticholinergic properties; many have significant central nervous system effects which are of interest here. Since antihistamines were first discovered in France in the 1930s, hundreds of pharmacologically related substances have been identified and synthesized.12, 34, 106 Many antihistamine-containing preparations are sold in Canada without prescription for use in the symptomatic treatment of a variety of ailments, including the common cold (e.g., Contact®), allergies (e.g., Actifed® [triprodine and pseudo-ephedrine]) and motion sickness (e.g., Gravol® [dimenhydrinate]). Labels on many such antihistamine-containing products warn the user that drowsiness may be an expected side effect. The sedative properties of certain antihistamines are made direct use of, alone and with other drugs, in a variety of non-prescription and prescription sedative preparations (e.g., Sominex®, Mandrax®). The antihistamine drugs vary considerably in their sedative properties; some do not exert significant effects on CNS activity or may have mixed stimulant and depressant effects, while a few may rival the barbiturates in their tranquilizing or sleep-inducing capacity.32, 88, 113 Some antihistamines produce significant psychological excitation at high doses and hallucinogenic effects have been noted under such conditions.13, 84 There is apparently relatively little non-medical use of antihistamines alone, although, for example, the use of large doses of Gravol® to get 'high' (often in combination with alcohol) has occasionally been reported among juveniles. Antihistamines with sedative capacity generally have significant anticholinergic properties as well, which may account for some of their central nervous system effects.109 Consequently, clear distinctions cannot be made between anticholinergic and antihistaminic classifications in many instances. There are many over-the-counter preparations which are sold as tranquilizers or sedatives. Most contain some combination of bromides, salicylates, anticholinergics, antihistamines or other drugs (e.g., Sominex®, Sleep-eze®, Nytof®, Devarex®, Compoz0). The pharmacological rationale and effectiveness of some of these concoctions has been questioned on numerous occasions, and it would appear that many such preparations are of little or no therapeutic value and may have significant adverse side effects.76,78,82,83,101

MEDICAL USE

As with barbiturates, the minor tranquilizers and non-barbiturate sedatives are mainly prescribed for patients suffering from anxiety, tension, behavioural excitement, and insomnia. Some are also used in the treatment of lower back pain, convulsive disorders, withdrawal symptoms of barbiturate-alcohol type dependence, and acute anxiety and panic reactions which sometimes occur with certain hallucinogenic drugs. Some minor tranquilizers are effective muscle relaxants.4, 79, 88, 199 Some clinicians feel that chemotherapy of anxiety should be a secondary approach in psychiatry (although frequently the most expedient) and that drugs should be used primarily to relieve immediate distress, and to aid the patient only until other treatment procedures become effective.79

In addition to their use as sedatives, certain antihistamines (e.g., dimenhydrinate) and anticholinergic drugs (e.g., scopolamine) are employed in the prevention and treatment of nausea and vomiting associated with early pregnancy, motion sickness and other conditions. Antihistamines are commonly used for the symptomatic treatment of hay fever and numerous other allergic reactions. They also relieve nasal congestion and discharge associated with the common cold, lessen rigidity and tremor of parkinsonism, and some are moderately effective local anesthetics.4, 1. Scopolamine and other belladonna alkaloids are used medically, for
example, in the symptomatic treatment of parkinsonism, congestion due to allergies and the
common cold, peptic ulcer, and bed-wetting, and are employed in conjunction with other drugs
in certain anesthetic applications.27, 62,

CHEMICAL ANALYSIS OF ILLICIT SAMPLES IN CANADA
There has been relatively little chemical analysis of illicit minor tranquilizers and non-barbiturate
sedatives in Canada. None was mentioned in Marshman and Gibbings' 1970 report from
Ontario." The Health Protection Branch special study of police seizures does not focus on these
substances, but methaqualone was identified in 20 samples combined with other drugs.54, [b]
There were 18 samples involving methaqualone and an antihistamine; LSD was also present in
14 of these cases and heroin was detected in four. There were also two samples of LSD and
methaqualone together. These samples contained a median of 20 mg (range: 11-77 mg) of
methaqualone per unit dose and approximately 2 mg per capsule of the antihistamine was
typically found.
In the Commission's collection of illicit drug samples and our national survey of authorized
analytic facilities (1971-72), 15 samples of high purity methaqualone were found along with two
LSD-methaqualone combinations."; [e] Of the unmixed methaqualone samples, two had been
represented as mescaline, five as Mandrax® and eight were of unspecified identity. In addition,
four samples of chlordiazepoxide, and one each of diazepam, oxazepam, ethchlorvynol and
methyprylon were reported. No antihistamines were noted in this study. Two samples of plant
materials containing belladonna alkaloids were found.

ADMINISTRATION, ABSORPTION, DISTRIBUTION AND PHYSIOLOGICAL FATE
The minor tranquilizers and non-barbiturate sedatives are usually administered orally as tablets,
capsules or elixirs, but some are occasionally injected for both medical and non-medical
purposes. These drugs are generally rapidly absorbed by the stomach, intestine and rectum,
and absorption after oral administration is typically most rapid with an empty stomach. Once
absorbed, the drugs are generally distributed quite uniformly throughout the body. Some are
metabolized, or otherwise chemically altered (usually in the liver), and excreted into the urine,
while others are eliminated unchanged. As with barbiturates, some of these drugs increase the
body's production of the enzymes responsible for their metabolism. Certain of these substances
may be detected in the urine for several weeks after use is discontinued. The factors of
distribution, metabolism, and excretion are responsible for many of the differences in potency
and duration of action of these drugs.14, 32, 88, 109, 122
Methods of detection of some of these drugs and their metabolites in urine and blood are
sophisticated and expensive, while others are readily identified with standard analytic
techniques.23, 30, 39, 64, 115, 123 There are currently no immunoassay methods available for
any of these sedatives.

GENERAL EFFECTS
With most of these drugs, psychological and behavioural responses to low doses are quite
variable. There may be sedation in some instances and, in others, an increase in activity.
Studies reveal that complex interactions between the specific drug and the level of anxiety may
occur, even within the same pharmacological group; psychological and behavioural
performance may be impaired or improved, depending on the dose, personality of the user and the degree of anxiety present.32, 79
Normal doses usually provide relaxation, a feeling of well-being and perhaps some loss of inhibition—effects not unlike those associated with social alcohol drinking. The response to moderate and high doses of most of these sedatives is a general depression of nervous and muscular activity and certain other body functions. Compared with other sedatives, minor tranquilizers are thought to have less inhibitory effect on the parts of the brain which are responsible for arousal and motor control, and may have greater muscle relaxant effects.32, 38, 79, 88, 109 The taming effect of minor tranquilizers in animals has frequently been observed.9, 57, 118 As noted earlier, certain antihistaminic and anticholinergic drugs produce considerable excitation in high doses; hallucinogenic effects have been reported with some of these substances.°°, 58, 78, 84
Excessive use of most sedatives may produce drowsiness, ataxia, lethargy, disorientation, confusion, memory impairment, trance-like episodes, double vision, personality alterations, rage reactions, and other symptoms resembling those of drunkenness. Other side effects observed with certain of these sedatives include skin rashes, nausea, diminished sex interest, menstrual and ovulatory irregularities, blood abnormalities and increased sensitivity to alcohol.32, 79, 88, 109
The national mental health data collected by Statistics Canada for 1971 indicated that dependence on non-barbiturate sedative-hypnotics and minor tranquilizers (ICDA-304.3) accounted for 51 (0.09%) of the first admissions and 33 (0.06%) of the readmissions to psychiatric hospitals and wards. More than half of these admissions involved females and the majority were over 25 years of age. These data suggest that in 1971 these drugs were not a significant factor in psychiatric admissions in Canada.[e] (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

DRIVING
The current knowledge regarding the role of minor tranquilizers and non-barbiturate sedatives in automobile accidents is somewhat similar to that described for barbiturates. Existing data suggest that these drugs have not contributed greatly to highway crashes.71, 97, 114 121In Canada it is an offence to drive while intoxicated by any drugs, and the penalties are the same as those for drunken driving. Traffic convictions involving drugs other than alcohol rarely occur, in part because of the difficulties in proving intoxication.

A number of studies have attempted to estimate the incidence of drug use in the general population, in the driving population, and in the victims of automobile crashes; other reports have focussed on the driving records of individuals known to be users of one or another drug. In general these data have proven to be incomplete and frequently difficult to interpret. There is a clear need for further research in this area. Such research should include emphasis on the chemical detection of drugs in the body fluids or tissues of drivers involved in crashes as compared to persons not involved in such accidents but using the roads under similar circumstances.
Laboratory studies have shown that large quantities of some minor tranquilizers and non-barbiturate sedatives can disrupt performance on certain psychomotor, intellectual and
perceptual functions—suggesting that with sufficient dose such drugs may have the potential for increasing the likelihood of automobile crashes. Ordinary clinical doses may not have such effects.

Certain antihistamines and belladonna alkaloids might disrupt performance on tasks related to driving, but little relevant research exists. In one study the accident rate in a group of drivers using prescribed doses of Librium® was ten times the accident rate for the general population, but it is not clear whether the accident rate among these drivers, who "needed" a tranquilizer, was so high because of, or in spite of, the drug they were taking.

TOXICITY, POISONING AND DEATH
As with barbiturates, the majority of serious overdose cases with the minor tranquilizers and non-barbiturate sedatives involve adult intentional self-poisoning (although not necessarily with fatal intent). Much of this literature was reviewed previously in A.7 Barbiturates. The number of poisonings or toxic reactions involving these various drugs is generally related to their availability through medical prescription. However, the various sedatives differ considerably in their lethal toxicity, and certain compounds (e.g., the benzodiazepine derivatives) which are involved in many poisonings, may result in very few deaths. It should be noted that official mortality statistics must be interpreted with caution. In many cases autopsies are not performed and a thorough drug identification and chemical investigation of the cause of death is often not conducted.

In the 1971 Poison Control Program Statistics there were 4,966 poisonings attributed to "tranquilizers" (both the major and minor categories together) and 1,588 to non-barbiturate sedatives and hypnotics. En Diazepam (Valium® or Vivol®) accounted for 2,758 toxic reactions and was second only to acetylsalicylic acid compounds (e.g., Aspiring) as a source of poisoning in Canada. Chlordiazepoxide (e.g., Librium®) was noted in 922 cases, oxazepam (e.g., Serax®) in 62, a chlordiazepoxide and bromide combination (Librax®) in 60, and meprobamate (e.g., Equanil®) in 52. Females outnumbered males by almost two to one in these data. Approximately one-quarter of the minor tranquilizer poisonings occurred in children under five years of age, but none of these cases was reported to be fatal. There were 23 drug death reports which mentioned either diazepam or chlordiazepoxide; in 20 of these cases other drugs were specified as well. Three fatal poisoning reports mentioning only Valium® were generally incomplete. One meprobamate interaction death was reported. It should be noted that well-documented cases of simple overdose deaths involving chlordiazepoxide or diazepam are rare or non-existent in the scientific literature.

The Poison Control Program category of "other sedatives and hypnotics" contains a heterogeneous group of chemicals. Methaqualone-containing compounds were reported in 437 cases, with Mandrax® noted in 391 of these. One methaqualone death (Mandrax® and Librium®) was reported. The other most frequently named sedatives were: Noludar® (methyprylon), 264 cases; Placidyl® (ethchlorvynol), 147 cases; Doriden® (glutethimide), 85 cases; and chloral hydrate, 53 cases. There were 12 deaths involving these latter drugs, primarily as interactions with other compounds. There were also 80 toxic reaction cases involving Sominex® preparations (typically containing bromides, antihistamines and other substances) and 42 Nytol® (bromides) reports. Listed
separately were 160 Gravol® and 133 Actifed® toxic reactions. Poisonings with other antihistamines were noted as well. There were no deaths attributed to any of these latter drugs. Including drug interaction deaths, the number of fatalities reported per thousand poisonings were: 59 for barbiturates, 10.7 for non-barbiturate sedatives (and meprobamate) as a group, and 6.3 for the benzodiazepine minor tranquilizers. If only single drug fatalities are considered, the corresponding rates for these three drug groups are 25.8, 3.3 and 0.8 respectively. In other words, excluding drug interaction reports, barbiturate poisonings were 7.8 and 32 times as likely to be reported fatal as were the non-barbiturate sedative and the benzodiazepine minor tranquilizer cases respectively.[k]

Because of the variety of different compounds subsumed under the topic of minor tranquilizers and non-barbiturate sedative-hypnotics, it is not possible to derive a clear picture of the fatalities involving these drugs from the Causes of death statistics published by the Federal Government.18 These various drugs are often not differentiated or specified in official statistics and are frequently considered together with many other psychotherapeutic agents —particularly when drug interaction is involved.[m]

In the Causes of death report for 1971, 32 deaths were ascribed to "tranquilizers" in genera1.18 A detailed list of the specific drugs involved revealed that four deaths were attributed to diazepam, one to chlordiazepoxide and four to meprobamate." The remainder involved major tranquilizers. A similar situation existed for 1969 and 1970 as well, when 12 and 15 deaths respectively were ascribed to the former three drugs. Over the three-year period, two-thirds of these individuals were women and approximately two-thirds of the cases had been designated as suicides. No specific information is available from these government statistics regarding interactions involving these and other drugs.

In the same 1971 report, 61 deaths were attributed to non-barbiturate sedatives and hypnotics alone, with an additional 29 noted in combination with alcohol." Little other specific information is available regarding fatalities due to interactions of these and other drugs. Only three fatalities involving persons under 20 years of age were noted and these were in the 15-19 age category. The majority of the deaths occurred in persons over 40 years of age. Chloral hydrate, paraldehyde, or bromides were specified in four cases, but all other non-barbiturate sedatives were pooled in a single class in the official statistics. There is no methaqualone-specific category in these statistics, but our survey of provincial coroners indicated that a number of drug-related deaths in young people have involved methaqualone—usually in combination with other drugs.58. [g] We have no reliable information on the extent of such occurrences.

For 1971, there was a total of 99 deaths which involved minor tranquilizers or non-barbiturate sedatives, alone or in combination with other drugs, in the official national statistics.18 In contrast, there were 482 barbiturate-related deaths for the same period. After adjustment for the number of prescriptions issued (using the Canadian Medical Association's prescription estimates"), barbiturates were approximately 100 times as likely to be associated with drug overdose fatalities (per prescription) as were the minor tranquilizers (benzodiazepine and propranediol derivatives) and more than three times as likely as the other non-barbiturate sedatives as a group. In a United States report, the incidence of suicide with barbiturates was 32 times the incidence of suicide with "minor tranquilizers" (meprobamate or chlordiazepoxide), and 2.8 times as great as that involving "new non-barbiturate hypnotics", when related to prescriptions written."

The variation in fatalities among these drugs is possibly due to a combination of factors, including differences in: direct lethal toxicity, interaction with other drugs, drug-induced
confusional states, potentiation of emotional depression, unit dosage size, number of doses per prescription and certain personality characteristics and disorders of the persons involved. Further research in this area is clearly indicated.

TOLERANCE AND DEPENDENCE
Tolerance can develop to most of the effects of these sedatives with regular use, and the dose may be increased by some users in order to maintain the desired effects. Although originally introduced as 'non-habituating', most of these drugs have been shown to be capable of producing both psychological and physiological dependence resembling that seen with alcohol and the barbiturates. Physical dependence is infrequently seen, but can occur with sustained use of large doses of almost all of the drugs in groups 1 to 6 of Table A.4. Significant tolerance and dependence generally does not occur with therapeutic doses.32, 36, 40, 61, 65, 79, 110 Some tolerance to the sedative effects of the anticholinergic and antihistaminic drugs may develop with regular use, but dependence has not been reported. The clinical descriptions of the abstinence syndrome following abrupt withdrawal after excessive use of some of these drugs indicate a marked similarity to one another and to those of alcohol-barbiturate dependence. The syndrome may be characterized by anxiety, apprehension, tremulousness, muscle twitches, insomnia, headache, rapid pulse rate, fever, loss of appetite, nausea, vomiting, abdominal cramps, sweating, fainting, hyperactive reflexes, convulsions, and uncontrolled urination and defecation. In addition, delirious states can occur with motor agitation, hallucinations, delusions, disorientation and confusion. After very heavy daily use for long periods of time, the abstinence syndrome can be very serious, and a few deaths have been attributed to withdrawal from some of these drugs.38, 39

MINOR TRANQUILIZERS, NON-BARBITURATE SEDATIVES AND OTHER DRUGS
Although these various sedatives have many common features, as noted earlier, there may be significant differences in certain effects, and all of the sedatives cannot be expected to interact with other drugs in the same way. Since the number of different compounds under consideration is large, determining interaction effects for all possible drug combinations would be an enormous undertaking. So far such interactions have generally been investigated only superficially, and consequently only the most general statements are possible. Some of the following topics have been covered in more detail in the previous discussions of alcohol and barbiturates.
Recent detailed studies of alcohol-meprobamate interaction conducted by researchers at the Addiction Research Foundation of Ontario and Rutgers University are indicative of the complexities of this topic. The direction and intensity of the interactions of these two drugs were shown to depend on various dose, time and administration factors, as well as the particular response examined.20
Under many conditions, combinations of the various sedative drugs may result in more intense and longer lasting effects than are produced by a given dose of one of the drugs administered singly. Some antihistamine and anticholinergic drugs may also enhance the effects of other
sedatives at certain doses.6, 15, 26, 35, 45, 124
Cross-tolerance and cross-dependence occur among many sedative drugs.„, 65 Persons
dependent on one of these drugs may turn to the others for a desired effect. Minor tranquilizers
and other sedatives are often used to reduce the severity of the alcohol withdrawal syndrome.
The development of cross-tolerance among the sedatives does not appear to significantly affect
the lethal dose and large but sub-toxic doses of each drug, if taken together, may produce a
toxic or fatal reaction in persons tolerant to other effects.

Very little research has been done regarding the interaction of opiate narcotics and the various
minor tranquilizers and other sedative drugs. It is expected that certain effects of these drugs
would add in such a way that the doses which produce sedation, toxicity and death are lower
when they are combined.
The interaction between the various sedatives and the stimulants is complex, with some
responses being additive, and others dominated by one or the other drug. Certain sedative
effects may be antagonized by stimulants. Various sedatives are reportedly taken in alternation
with stimulants by a variety of users. As an extreme example of this phenomenon, intravenous
users of amphetamines may take sedatives to ease the discomfort of the 'crash' at the end of a
long 'speed run'.

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