A.7 BARBITURATES

INTRODUCTION

The term 'barbiturate' refers to drugs which are derivatives of barbituric acid (malonylurea). Barbituric acid itself has no significant psychotropic properties, but its derivatives may have a variety of effects on the central nervous system. Certain of those compounds with significant depressant or sedative-hypnotic properties are of primary importance in medical and nonmedical use. Many of the short-term subjective effects of the barbiturates are remarkably similar to those of alcohol.

The first drug of this class to be synthesized, barbital (also called barbitone or Veronal®) was introduced to medicine in Germany in 1903. Barbiturates rapidly gained a common usage as tranquilizers, sedatives, hypnotics (sleep inducers) and anesthetics, and today are considered indispensable to medical practice. In the past decade, however, the preference for barbiturates in some medical applications has declined, primarily due to the availability of other drugs with certain similar effects, including the minor tranquilizers (such as Valium®, Librium® or Equanil®). The minor tranquilizers and other non-barbiturate sedative-hypnotics are discussed in Appendix A.8 which follows. Although significant differences exist in some instances, the general pharmacological similarities between the barbiturates and many of these other drugs are such that these substances are often considered together as a group under the heading of "anxiolytic sedatives". In 1971, barbiturates were estimated to account for more than one-fifth of all prescriptions for mood-modifying drugs in Canada, and are second only to the minor tranquilizers in total prescriptions in both Canada and the United States.

Although some problems with non-medical barbiturate use were noted soon after these drugs were introduced, in the 1930s there was considerable controversy regarding the nature and extent of chronic barbiturate intoxication and the consequences of their non-medical consumption. The significance of barbiturate dependence and its similarity to alcoholism and, to a lesser degree, opiate narcotic dependence has become apparent only in the past few decades. For many years, barbiturates have been the leading toxic agents involved in fatal poisonings and suicides in North America.

In the past three-quarters of a century, an estimated 2,500 different pharmacologically active derivatives of barbituric acid have been developed, of which perhaps 25 to 50 have been marketed for medical use. Less than a dozen make up the bulk of current use in Canada. The barbiturates vary in the potency, latency and duration of their effects, but there is considerable overlap among them and differences are generally only a matter of degree. They
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are often classified by the duration of their sedative or hypnotic action at a standard dose.

Among the most widely used barbiturates in Canada are the short-to intermediate-acting compounds, including amobarbital (Amytal®), secobarbital (Seconal® or 'reds'), pentobarbital (Nembutal® or 'yellows') and butabarbital (Butisol®). Tuinal®, a mixture of amobarbital and secobarbital, is very popular in both medical and non-medical use. Similar barbiturates which have been singled out as likely candidates for non-medical use in the United States include cyclobarbital, heptabarbital, probarbital, talbutal and vinbarbita1.1" Long-acting barbiturates, such as phenobarbital (Luminal®) and the ultra-short-acting variety, such as hexobarbital (Evipal®) or thiopental (Pentothal®) are commonly employed for medical purposes, but are less often used non-medically than are the intermediate compounds.

In North America it has been traditional to use names ending in "al" for the barbiturates; in Great Britain the letters "one" are commonly suffixed instead (e.g., barbital or barbitone). In addition to descriptive slang terms based on the usual colour of the pharmaceutical capsule (e.g., 'reds', 'yellows', 'blues', 'rainbows', etc.), barbiturates are often referred to as 'sleeping pills', 'barbs', 'downers', or 'goof balls'.

It is frequently said that in North America the supply of barbiturates lawfully manufactured or imported greatly exceeds the requirements of legitimate medical use or exportation.'8, 156, 157 Many current non-medical users were initiated into barbiturate use under medical auspices; such persons may develop dependence and maintain use long after the original medical rationale for the prescription is absent. Apparently most of these barbiturate users continue to obtain the drugs through legitimate channels.63 Since many physicians do not adequately maintain or monitor prescription records, a patient may be able to arrange an increase in the frequency and/or quantity of drug prescribed. In addition, many chronic users of barbiturates and other prescription drugs obtain 'legitimate' prescriptions from a number of different doctors simultaneously, without the physicians' awareness." (See also Appendix B.7 Sources and Distribution of Minor Tranquilizers, Barbiturates and Other Sedative-Hypnotics.)

The occasional medical and non-medical use of barbiturates appears to be widespread across age groups and social classes, but the chronic use of these drugs has seemed to be most common among persons over 30 years of age. Prescription controls are only partially effective; possession of these drugs for personal use without medical authorization is not a criminal offence; and users do not appear to form a homogeneous, cohesive or easily recognized minority. Hence, the usual medical and legal data sources and other traditional research techniques have been of relatively little assistance in assessing the extent and consequences of non-medical barbiturate use in Canada. While a considerable body of research exists into the
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many medical applications of these drugs, there has been relatively little systematic investigation of non-medical use. As with other drugs which are widely available on a prescription basis, the distinction between the medical and non-medical use of barbiturates is often particularly difficult to make. An increase in the extent of barbiturate use among young people in the United States has recently become the focus of much attention. In Canada, there are some indications that the use of these drugs by teenagers and young adults may be growing as well. (See also Appendix C Extent and Patterns of Drug Use.)

MEDICAL USE

The medical uses of barbiturates are based on their sedative, hypnotic, or anti-convulsant effects. In low doses (e.g., 25-50 mg), the short- or intermediate-acting compounds are widely used as sedatives or tranquilizers in the treatment of tension and anxiety. The hypnotic effect of these drugs is familiar to thousands of Canadians who use barbiturates in higher doses (e.g., 100-200 mg) in the form of the common sleeping pill. Barbiturates are regularly administered as anesthetics or pre-anesthetics (often in conjunction with other drugs) in surgical or dental situations; but they have little effect on pain if used alone. The ultra-short-acting compounds are most commonly used as intravenous anesthetics. The anti-convulsant effects of certain barbiturates have been very important in the treatment or prevention of acute convulsions associated with tetanus, various neurological disorders including epilepsy, poisoning due to the overdose of stimulants such as strichnine, nicotine or cocaine, and withdrawal symptoms associated with alcoholism and other sedative drug dependence. The intermediate- to long-acting barbiturates are those most commonly employed in anti-convulsant applications. The convulsion-blocking properties of these drugs are not necessarily correlated with their general sedative potential. Barbiturates have also been employed in the treatment of asthma, pre-menstrual tension, motion sickness, nausea and vomiting, peptic ulcer and other gastrointestinal disturbances, hyperthyroidism, and high blood pressure and other cardiovascular disorders. Barbiturates may be used to treat adverse reactions or 'bad trips' associated with LSD and other hallucinogenic drugs.

Occasionally barbiturates may assist in the diagnosis and psychotherapy of certain psychiatric disorders. In some applications the drug is administered in a slow intravenous infusion with the dose adjusted to keep the patient in a semi-conscious state, relaxed and uninhibited, thereby facilitating communication, diagnosis and perhaps therapy. This procedure is essentially the same as that used in the so-called 'truth serum' application in criminal investigations. This latter effect is just a carefully monitored response to common barbiturates. While this procedure frequently results in information which is less inhibited or otherwise different than that normally communicated, there is little evidence that it actually exposes the 'truth' as such. As noted earlier, the use of barbiturates as day-time sedatives, tranquilizers and sleep inducers has declined somewhat in the last decade due to the increasing popularity of certain minor
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tranquilizers and non-barbiturate sedatives, some of which are considerably less physically toxic than the barbiturates. Heavy sedation of psychotic patients with barbiturates was once common in certain psychiatric hospitals, but these drugs have been largely replaced in such applications by the major tranquilizers or neuroleptics (such as the phenothiazines) which can control many symptoms of psychosis without extensive depression of central nervous system functioning.

In summary, the barbiturates are considered indispensable in certain aspects of medical practice, but in many common prescription applications they could be replaced by other drugs which are less likely to produce significant adverse effects as a result of non-medical use.

CHEMICAL ANALYSIS OF ILLICIT SAMPLES IN CANADA

There has been surprisingly little systematic chemical analysis of illicit barbiturates in Canada. These drugs were not specifically mentioned by Marshman and Gibbins in their summary discussion of illicit drug samples analysed at the Addiction Research Foundation of Ontario in 1969-70.105 The Health Protection Branch quantitative analysis study of police seizures does not include barbiturates as primary drugs for special analysis, nor were any found mixed with the opiate narcotic, amphetamine or hallucinogen samples reported by HPB to the Commission for 1971-72.62[b] The HPB has identified 339 barbiturate samples among the total police seizures for the 12-month period ending in March 1973.

In the Commission's study of illicit drug samples (1971-72) no barbiturates had been presented to the researchers as such.114 However, barbiturates were detected in 28 (2.9% ) of the 980 drug samples analysed. Eight samples were reported to contain only barbiturates; these had been represented as LSD, 'speed' or were of unspecified identity. Ten samples contained barbiturates in combination with methamphetamine and nine with LSD. These samples had generally been presented as methamphetamine or LSD respectively.[c]

These data suggest that barbiturates were not a major item in that part of the illicit drug distribution system assessed by these studies (i.e., primarily the youth-oriented market). It appears that the samples that were found came originally from legal sources; there were no indications of illicitly manufactured barbiturates. (See also Appendix B.7 Sources and Distribution of Minor Tranquilizers, Barbiturates, and Other Sedative-Hypnotics.)

ADMINISTRATION, ABSORPTION, DISTRIBUTION AND PHYSIOLOGICAL FATE
In crystalline form, barbiturates are odourless white or yellow powders with a slightly bitter taste. They are available as powders, elixirs, injectable solutions, suppositories, capsules or tablets (in both sustained and delayed release forms). Barbiturates are frequently marketed for medical use in mixtures with other drugs such as other sedatives, tranquilizers, analgesics, belladonna alkaloids (atropine or scopolamine), various stimulants (amphetamine or caffeine), vitamins and certain gastrointestinal therapeutic agents. Barbiturates are usually administered orally for both medical and nonmedical purposes, and are readily and efficiently absorbed by the stomach, small intestine, and rectum. After ingestion, absorption is most rapid on an empty stomach, and effects of some barbiturates may occur within 20 minutes. A full stomach may double the time required for effective absorption. Both intramuscular and intravenous injections are efficient, but they are prone to physical complications and are generally avoided except for special purposes. Barbiturates are almost never given subcutaneously since they can cause considerable local pain under the skin and may seriously damage the tissue. Persons who inject barbiturates non-medically usually prepare a solution of tap water and crushed tablets or capsules originally intended for oral use.

After absorption into the blood stream, barbiturates are distributed rather uniformly throughout the body, but the various barbiturates show some individual differences in the facility with which they enter the brain. These drugs readily cross the placental barrier into the fetus in pregnant women. Barbiturates are eliminated by the kidney in the urine, partly in their original form, but largely as breakdown products resulting from enzymatic metabolism in the liver. Metabolism is more extensive and subsequent excretion is faster with the shorter-acting barbiturates. Binding of the drug in the blood plasma or by tissue protein, and its affinity for tissue fat may also affect the rate at which the barbiturate is eliminated from the body and its net effect on the nervous system. The short-acting barbiturates are highly lipid soluble and may accumulate in body fats with repeated use. Variations in distribution, metabolism and excretion are largely responsible for the differences in potency, latency and duration of action of the different barbiturates.

Barbiturates stimulate the production of the enzymes responsible for their metabolism in the liver, thus resulting in more rapid and efficient deactivation and a shorter duration of action with repeated use. Since many drugs are metabolized by the same non-specific enzyme systems, barbiturate use may alter the body's response to other substances as well. Liver diseases or damage, such as those associated with chronic heavy alcohol use, reduce the rate of barbiturate metabolism and subsequent excretion, and may result in an exaggerated or extended response.

Barbiturates and their metabolites are readily detectable in body fluids using standard analytic methods. However, the quantity of fluid and the time required for extensive analysis using traditional techniques reduces the usefulness of the methods in certain situations.
applications. Recently, radio and spin immunoassay techniques have been described which allow a rapid, specific and extremely sensitive analysis of minute samples.$^{1,143}$

**PSYCHOLOGICAL EFFECTS**

The short-term psychological and behavioural effects of barbiturates are highly similar to those of alcohol. Depending on the conditions of use, at low doses barbiturates typically result in relaxation, a heightened sense of well-being, and often drowsiness and a moderate decrease in alertness and attention. Alternatively, the same dose may produce a period of excitement during which the individual is more sociable, jovial, impulsive, or energetic. There may be decreased inhibition of certain drives and, depending on the individual, one might feel more amorous, aggressive, creative, playful or hungry.

At higher doses, the effects of the drug on the motor system become apparent, and include a diminished ability to react quickly and to perform skilled precise tasks. Sedation is common. The emotions are often labile, and the individual may alternate between feelings and displays of unusual affection, euphoria, or hilarity, on the one hand, and rudeness, hostility, aggressiveness and violence, on the other. Emotional depression, self-pity and social withdrawal are not uncommon. (The involvement of barbiturates in suicide is discussed below.) At still higher doses slurred speech, blurred vision and an unsteady gait occur along with other signs of drunkenness. The individual may have difficulty walking or maneuvering around simple obstacles without collisions or falls, and there is characteristic confusion and difficulty communicating effectively. With such doses, behavioural sedation often becomes predominant and the individual may fall into a stupor or sleep. Intravenous barbiturate use may produce a 'warm rush', but not the 'flash' or 'splash' associated with cocaine or methamphetamine injection.

The variability in the short-term response under medically supervised conditions is described by Wilder:

After intravenous injection of 0.25 to 1.0 gm of amobarbital, a subject may fall asleep if he lies in bed undisturbed, yet he may be awake and voluble if interviewed by a psychiatrist, or he may exhibit ataxia on attempting to walk back to his bed, but he may 'sober up' promptly when instructed to pose for a motion picture demonstration of ataxia.'

Driving
Several reviews of the drugs and driving literature in Canada and the United States have concluded that there is little evidence that barbiturates have contributed significantly to highway crashes. In Canada, arrests for impaired driving involving barbiturates are rare, perhaps in part because the use of these drugs is not detectable with a Breathalyzer or other convenient test, nor do they produce any characteristic odour on the breath. Recently, an increase in driver and pedestrian arrests involving barbiturate use has been reported in some areas of the United States.

Definitive studies on barbiturates and driving have not yet been carried out and the data that do exist are incomplete and difficult to interpret. Road research has been hampered by numerous difficulties including practical problems in determining drug levels in the body at the time of accidents, and the possible confounding effects of other drugs. The role of alcohol in traffic accidents, for example, became more apparent after studies showed that drivers in accidents had higher blood alcohol levels than non-crash drivers who had been using the roads under similar circumstances.

Laboratory studies of psychomotor performance and other psychological functions presumed to be important in automobile driving indicate that barbiturates may produce a dose-related impairment, and that some effects may last up to a day after a large sleep-inducing dose. Under some conditions, low doses of barbiturates may improve performance. As noted earlier, the behavioural effects of barbiturates are very similar to those of alcohol. With high doses of either drug, the user may demonstrate a diminished ability to react quickly and to perform skilled precise tasks (particularly those requiring selective attention). Aggressiveness and risk-taking may increase. Low therapeutic doses may not cause driving problems, but further research is needed. It has been suggested that persons who are very tense may become safer drivers after low doses of barbiturates. Overall, it appears that in high doses barbiturates have the potential for contributing to automobile accidents and that barbiturates in combination with alcohol would be an added hazard.

Psychiatric Complications

Although heavy users of barbiturates may be hospitalized for the treatment of dependence, there is little indication of major psychiatric disorders directly attributable to the effects of these drugs. Acute toxic psychoses are uncommon, although delirium, paranoid symptoms and aggressiveness may be present during heavy intoxication. Short-term psychoses often occur during withdrawal in heavy dependent users. Secondary barbiturate involvement in, or
complication of, various psychological problems has been reported in many dependent users. In one study multiple drug users noted more adverse psychological effects with barbiturates than with heroin.28

The heavy use of barbiturates and other sedatives may contribute to what has been described as an "amotivational syndrome", characterized by apathy and reduced drive and ambition. It has been noted that the work output of certain barbiturate dependents is minimal, and may generally be lower than that of persons dependent on heroin, for example.28, 88 Considerable concern has been expressed over the possible adverse effects of chronic sedative use on the maturation process in adolescents.158,157 A recent United States Senate committee report on barbiturate use in juveniles summarized the testimony of Sidney Cohen as follows:

Those involved in the "downer" scene, even if they avoid the associated illnesses, injuries and fatalities, will sustain a significant defect in their personality development. They will have spent long periods during their maturation evading with chemicals the very elements of existence which promote human growth: the frustrations, problems and stress of daily life. It is this aspect of bedrugged adolescence which is particularly tragic—the loss of opportunity to grow up psychologically.[P.4]16

In the Commission's 1971 national survey of psychiatric hospitals barbiturates were mentioned in the primary diagnoses of 19 (0.08%) and in the secondary diagnoses of 9 (0.04%) of the 22,885 patients in the hospitals at that time.67.03 In British Columbia, general hospitals with psychiatric wards were surveyed as well; barbiturates were noted in the diagnosis of 6 of the 293 psychiatric patients in the reporting hospitals. The national mental health data collected by Statistics Canada for 1971, indicated that barbiturate dependence accounted for 66 (0.11% ) of the first admissions and 60 (0.11% ) of the readmissions to psychiatric hospitals and wards.18, 129, Le] More than half of these admissions involved females and the majority were over 25 years of age. These two sources of data suggest that in 1971 barbiturates were not a significant factor in psychiatric admissions in Canada. (See also Tables A.5, A.6 and A.7 in the Annex to this appendix.)

Crime

At present, barbiturate use does not appear to be a significant contributor to, or correlate of, crime in Canada. In the United States there are indications that barbiturate use is growing, particularly among youth, and an increase in barbiturate-related crime in that country has been
There are several ways in which barbiturate use might be associated with crime. As with alcohol, barbiturates may increase the likelihood of certain individuals becoming aggressive or violent. Persons dependent on barbiturates may commit crimes in an effort to obtain the drug, either by stealing it or by stealing money or property with cash value for the purpose of purchasing the drug. However, because of the ready availability of barbiturates from many legal sources and, consequently, the low price of illicit barbiturates (compared to heroin, for example) this type of barbiturate-related crime is relatively infrequent in Canada. Heavy barbiturate use by some delinquent groups in the United States has been noted, but the role of the drug in their illegal behaviour is not easily interpreted. Barbiturates may be used to gain confidence or to reduce nervousness in preparation for previously planned crimes. Most barbiturate users in Canada (including the majority of dependent users) are apparently adults who live an otherwise socially acceptable existence without significant involvement in criminal activities.

**PHYSIOLOGICAL EFFECTS**

The primary short-term physiological effect of barbiturates is a general depression of central nervous system and muscular activity, although the response to low doses may be quite variable. Initially, the electroencephalogram (EEG) may suggest some activation or arousal, but with sufficient dose (e.g., 100-200 mg), this brain wave pattern is usually replaced by signs of drowsiness or sleep. The somnolence induced by barbiturates generally resembles normal sleep with the exception of an initially marked reduction in dreaming and in the rapid eye movement (REM) sleep stage. (REM sleep is thought to be related to dreaming, but its overall significance is only beginning to be appreciated.) With repeated use some tolerance develops to REM suppression. As with alcohol, barbiturates are thought to produce their principal effects by inhibiting activity in the brain stem reticular formation, which among other things, controls sleep and wakefulness. Direct effects on other areas of the brain are likely involved as well.2 Drowsiness or 'hangover' symptoms may follow acute barbiturate intoxication or drug-induced sleep. Such 'hangovers' generally lack the nausea and other gastrointestinal disruption associated with alcohol since barbiturates have little irritant effect on the stomach and intestines.

A variety of transient or temporary physiological changes occur with moderate doses; the majority of these reflect a general slowing down of physiological activity which normally occurs with behavioural sedation, and are of little clinical significance. A minor decrease in gastrointestinal and autonomic nervous system activity may occur. The brain centres responsible for the control of breathing are especially sensitive to higher doses, and fatal depression of these mechanisms is the primary danger in barbiturate overdose.
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A toxic or poisoned state may be produced by five to ten times the normal sleep inducing dose, and is characterized by coma and a general shock syndrome (e.g., weak rapid pulse, shallow breathing, low blood pressure and cold sweaty skin). Larger quantities may be fatal as a result of respiratory arrest, cardiovascular collapse and/or kidney failure. Quantities of 15 to 20 times the usual hypnotic dose may produce death in a matter of minutes; however, if proper treatment is administered before breathing has stopped the chances of recovery are generally good. If the overdose is not fatal, a temporary jaundice (due to impaired liver function), respiratory complications, kidney dysfunction and skin reactions may result. Other damage may occur indirectly as a result of respiratory depression. Some of these toxic reactions may also appear with normal doses in individuals allergic or abnormally sensitive to the barbiturates. Because of the well-documented additive or potentiating effects among many sedatives, users of related drugs, such as alcohol, must be especially attentive to barbiturate dose levels.

Following chronic use of barbiturates there is generally fairly complete recovery from direct drug effects. Other than possible secondary complications of injections in some users, instances of severe physiological disorder, or of irreversible brain, liver, kidney, heart, gastrointestinal or other tissue damage are rarely noted. Barbiturates do not greatly affect eating habits and diet, and consequently nutrition is usually adequate, in contrast to the typical situation of heavy chronic alcohol consumption. Unlike barbiturates, alcohol provides calories and disrupts normal gastrointestinal function.

Chronic barbiturate intoxication may lead to an increased incidence of accidental injuries, including, among others, possible head injury and brain damage. In addition, neglect of personal hygiene and other factors important to health may render some heavy users more susceptible to certain forms of disease and infection. Heavy barbiturate users may also run a greater risk of becoming dependent on alcohol, a condition associated with a variety of health problems, as discussed earlier. Since barbiturates are highly effective orally and are typically taken by this route even by chronic heavy users, complications caused by injections are less commonly seen than with dependence on heroin or methamphetamine. The popular sodium salts of barbiturates are strongly alkaline and can cause considerable pain and tissue damage if injected under the skin. Abcesses and infections have been reported to result from unsuccessful attempts at intravenous injection. Cases have been reported where barbiturates were mistakenly injected into an artery instead of a vein. Rather than following the normal venous route through the general vascular system in the body, such arterial injections result in immediate high drug concentrations in the small peripheral blood vessels in the extremities. This produces excruciating pain, tissue damage and, in some instances, gangrene which may necessitate the amputation of parts of the hands or feet.

In addition to these possible direct effects of barbiturate injection, further complications including hepatitis, tetanus, malaria, abcesses and ulcers of the skin, and a variety of other infections may be caused by shared or unsterile needles or drugs. Repeated intravenous injections result
in scarred veins (`track marks') and other vascular damage. Furthermore, the injection of insoluble or colloidal particles (which are typically present in drug preparations intended for oral use) often damages lung tissue and can be fatal.4, 136

SELF-POISONING, SUICIDE AND ACCIDENTAL DEATH

The role of barbiturates in poisoning and death is quite different from that of most of the drugs discussed in this report. For decades barbiturates have been cited as a major source of poisoning and the leading cause of drug overdose deaths in North America. In Canada more acute overdose fatalities are attributed to barbiturates than to all other psychotropic drugs combined.15 Similarly in California, for example, barbiturates were involved in more than half of all drug-related deaths in 1970-71.1" The vast majority of the barbiturate-related fatalities in Canada involve deliberate self-poisoning by adults, with or without lethal intent.

In 1971, there were 2,134 non-fatal and fatal barbiturate poisonings reported to the Federal Poison Control Program." Among all pharmaceutical preparations, only acetylsalicylic acid compounds (e.g., Aspiring) and certain minor tranquilizers (e.g., Valium()) were responsible for more toxic reactions than barbiturates. Relatively few poisonings with these non-barbiturates were fatal, however. Barbiturate cases made up approximately 4% of the total of almost 53,000 poisonings reported for all substances (including drugs, household chemicals, weed killers, insecticides, etc.), but barbiturates were involved in one-quarter of the fatal poisonings reported to the Program. Of those substances noted in the report to "frequently lead to drug abuse" (excluding alcohol), barbiturates accounted for less than one-seventh of the toxic reaction cases, but more than half of the reported fatalities.

The rate of reported barbiturate poisonings in the population was highest for children under five years of age, but overdose fatalities in this group are rare. Adults over the age of 25 had the second highest per capita poisoning rate and accounted for the majority of both non-fatal and fatal poisonings. The proportion of total barbiturate poisonings which was accounted for by persons over 25 has risen slightly during 1965-71. Almost two-thirds of the cases were females. In 1971, of 1,478 instances of barbiturate poisoning where the disposition of the case was specified, 755 (51%) resulted in hospitalization; these patients received a median of four to five days hospital care. There were reports of 89 barbiturate-related deaths, of which 63% included mention of other drugs as well, with alcohol noted in the majority of these latter cases. Only six of the fatal poisonings involved persons between 10 and 24 years of age. Drug interactions in the non-fatal poisonings are not reported, and all cases appear under only one drug category in the official Poison Control Program Statistics.
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The proprietary barbiturate preparations most frequently mentioned in the 1971 poisoning reports were: Tuinal® (secobarbital and amobarbital, 458 cases); Seconal® (secobarbital, 425 cases); Carbital® (pentobarbital and carbromal, 148 cases); Fiorinal® (butalbital, caffeine, phenacetin and A.S.A., 102 cases); Amytal® (amobarbital, 95 cases); and Nembutal® (pentobarbital, 69 cases). Of 58 fatal reactions where the specific barbiturates were noted, secobarbital or amobarbital, either alone or together as Tuinal®, appeared in 49 (85%) of the reports.

According to the Causes of death statistics published by the Federal Government, in 1971 there were 482 drug overdose deaths in Canada which were attributed at least in part to the effects of barbiturates. In 309 cases (64%), barbiturates were the only drugs mentioned, but in 173 cases other drugs were indicated as well, with alcohol noted in 144 instances. These figures undoubtedly underestimate the total involvement of barbiturates in fatal poisonings. In most areas of Canada, autopsies are not carried out in a large proportion of self-poisoning or suicide cases, and screening for barbiturates in the body is even less common. Furthermore, some barbiturate-interaction deaths involving a variety of drugs are put in a general unspecified category in government statistics and, consequently, cannot be easily identified. In 1971 barbiturates were involved in 8.5% of 2,559 deaths attributed to suicide or intentional self-inflicted injury in the official statistics. Of 591 fatal self-poisoning cases involving a group of compounds designated as "solid or liquid substances" (which includes licit and illicit drugs, household chemicals, insecticides, etc.), 217 (37%) of the deaths were attributed to barbiturates, the most frequent toxic agents noted. Of all barbiturate fatalities, there were 283 cases where the circumstances of death had been specified; 77% of these were classified as suicide. This is likely an underestimate of the actual proportion of the total deaths which involved intentional self-poisoning (but not necessarily including fatal intent). In many instances adequate information is not readily available to ascertain the intentions of the deceased and such ambiguous cases are typically left unspecified or are classified as accidents. In addition, there is often considerable reluctance on the part of physicians to designate fatalities as suicides on death reports. Follow-up research indicates that a large proportion of fatal poisonings originally classified as accidents actually involved intentional self-injury or suicide.

Women constituted 78% of the cases reported as suicides and 59% of those designated as accidents in the official 1971 statistics. Quite consistently during 1965-71, approximately two-thirds of the barbiturate deaths have involved persons over 40 years of age. After rising somewhat in the late sixties, the number of barbiturate deaths in Canada has levelled off and declined slightly in the early seventies—reflecting, in part, the shift in medical prescribing away
from barbiturates to the minor tranquilizers and non-barbiturate sedatives.

It would appear that relatively few barbiturate deaths in Canada were purely accidental in the sense that they did not involve suicide attempts or intentional self-injury. Fatalities due to overdose in young persons taking barbiturates for the 'trip' or euphoriant effects are quite infrequent and make up a very small proportion of the total number of barbiturate-related deaths. As well, few deaths result from intended therapeutic use of these drugs. Consequently a more detailed examination of the concept and conditions of suicide is appropriate in this discussion.

Many researchers have concluded that the majority of "suicide attempts" might better be called "suicide gestures", and do not actually involve a serious intention of death. Most such acts are considered to be primarily sympathy- or attention-getting devices and are often a plea for help or an attempt to force the subsequent resolution of some personal conflict. Although cases of intentional self-poisoning and suicide frequently involve 'repeaters' with previous intentional self-injuries, the act is usually impulsive and not carefully planned in advance. Instances where individuals had actually acquired drugs for the purpose of self-injury are apparently infrequent. Typically, the drugs employed had been in the person's possession for some time prior to the poisoning, and were originally acquired through legitimate prescription for medical use. Many self-injuring individuals have a prior history of psychiatric disorder.

The use of alcohol in combination with barbiturates is common in self-poisonings, and a disproportionately large number of persons engaging in suicidal behaviour are problem drinkers. (The significant role of alcoholism in suicide is discussed in more detail in Appendix A.6.) It is thought that a significant number of self-poisoning suicide gestures result in unintended fatalities due to the accidental administration of a lethal dose, especially when the individual has been drinking heavily. Because of these frequently reported patterns, the careless or excessive prescribing of barbiturates for depressed patients, heavy drinkers or persons with a history of self-injury has been severely criticized.31, 81, 100, 134, 137

A phenomenon called "drug automatism" is sometimes mentioned in association with toxic barbiturate overdose, although many observers have expressed doubts as to its significance. In this situation, individuals in a drug-induced state of confusion or stupor are said to administer additional quantities of the drug without being fully aware of the extent of previous doses. In Canada, few, if any, such deaths have been documented.
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As noted earlier, in the past few years the minor tranquilizers have become more frequently prescribed than the barbiturates.18, 27 There has been a concomitant increase in self-poisoning with the minor tranquilizers as a result. However, since some of these latter compounds (particularly the benzodiazepines) have very low lethal toxic potential there has been a decline in the proportion of fatal outcomes in the total number of poisoning cases involving sedatives and tranquilizers. Apparently, a reduction in the availability of barbiturates does not necessarily reduce the total number of self-poisonings or suicide attempts, but it may result in fewer overdose fatalities if available alternative drugs are less toxic. The relative toxicity of these various sedatives and tranquilizers, the incidence of related poisonings, and the associated prescribing trends are discussed in more detail below in A.B. Minor Tranquilizers and Non-Barbiturate Sedative-Hypnotics.

TOLERANCE AND DEPENDENCE

Tolerance to some of the effects of barbiturates readily develops; the degree and rate of its development vary considerably with the particular drug, the dose, the mode and frequency of administration and the individual involved. A phenomenon called acute tolerance (lasting several hours) may occur after a single dose, thus reducing the response to further doses given at short intervals. Depending on the barbiturate taken and the pattern of use, more prolonged tolerance may begin to appear within days or weeks of daily administration.1°, 77' 94 The extent of maximum tolerance to sedative-hypnotics is quite limited compared to that which can result with opiate narcotics.85 Barbiturate tolerance occurs to the greatest extent to the mood, sedative and behavioural effects. Tolerance to the lethal toxicity (i.e., respiratory depression) develops more slowly and to a lesser degree. As with alcohol, when general barbiturate tolerance develops the safety margin between the psychologically effective and the lethal dose is narrowed.

Several mechanisms seem to operate in producing barbiturate tolerance.25, 70, 85 As noted above, barbiturates stimulate the production of metabolic enzymes in the liver which inactivate these and many other drugs. The resulting increase in the rate of metabolism and excretion is primarily responsible for general tolerance. As well, some overall reduction occurs in the sensitivity of the tissues to the drug. Certain learning processes are also likely to be involved in changing the character of the response with repeated use. Tolerance develops more quickly to the shorter-acting barbiturates than to the long-acting varieties, perhaps because of the greater importance of liver metabolism in the inactivation and excretion of the former compounds. Most aspects of tolerance disappear after a few weeks of abstinence from the drug. Some persons may become more sensitive to barbiturates after withdrawal than they were prior to chronic use.42, 70
The capacity of barbiturates to produce physical dependence was not generally recognized for decades after their wide medical acceptance, although considerable attention had been directed to problems associated with psychological dependence. A series of experiments by Isbell and associates, published in the early 1950s, clearly demonstrated that chronic use of large doses of barbiturates (i.e., several hundred milligrams per day) can produce profound physical dependence similar to that of alcohol. The abstinence syndrome following withdrawal from large doses of barbiturates may begin with a reduction in intoxication and an apparent improvement in condition. Within a few hours, however, general physical weakness, dizziness, anxiety, tremors (the `shakes'), hyperactivity, sleeplessness, nausea, abdominal cramps and vomiting may occur. These may be followed after several days by muscle spasms and grand-mal (epileptic) seizures. Between the third and seventh day, delirium, delusions and hallucinations may appear; these and other symptoms may last for days or even months, although general recovery usually occurs within a week or two. As with alcohol, death during the convulsive phase occasionally occurs. In extreme cases the barbiturate-or alcohol-type withdrawal syndrome is considerably more painful and dangerous than that associated with dependence on the opiate narcotics. Withdrawal effects following dependence on more moderate barbiturate doses are considerably less severe than the full syndrome described above. Most regular users of therapeutic doses do not develop significant tolerance or dependence. Babies born of mothers who are physically dependent on barbiturates are also typically physically dependent, and may suffer severe withdrawal symptoms if the condition is not recognized and treated soon after births.

Anxious or tense individuals may become psychologically dependent on even small doses in order to function in a manner which they consider satisfactory; many persons become dependent on barbiturate sleeping pills and feel that they cannot sleep without the drug; others become dependent on a variety of subjective effects which they feel are satisfying or perhaps essential to their well-being.

BARBITURATES AND OTHER DRUGS

The effects produced by combinations of barbiturates and other drugs may often resemble the interactions described earlier for alcohol. Because of the similarities among the barbiturates and other general sedatives, these drugs are often used interchangeably. Barbiturates combined with alcohol, minor tranquilizers, non-barbiturate sedatives or volatile solvents often result in a more intense and longer-lasting effect than is produced by either drug alone. In addition to direct additive effects, the presence of alcohol in the body may slow the metabolism of barbiturates.
A certain amount of cross-tolerance exists among these drugs and chronic users of barbiturates are generally quite resistant to many of the effects of the other sedatives.*** 84 This cross-tolerance, however, may not appreciably affect the lethal dose, and large quantities of alcohol and barbiturates taken simultaneously (acting in an additive or potentiating fashion) may produce a toxic or fatal reaction in persons tolerant to other effects. In addition, these drugs generally show some degree of cross-dependence and have the capacity to block or diminish the withdrawal symptoms associated with physical dependence on the other sedatives.32. 54 Barbiturates are frequently used therapeutically to reduce the severity of withdrawal in alcoholics. Since most sedatives show this cross-dependence, individuals dependent on one may turn to other sedatives if the preferred drug is unobtainable. Consequently, chronic barbiturate dependents are usually heavy alcohol users as well. Most sedatives can also reduce some of the acute 'hangover' symptoms associated with other drugs of this class. Multiple drug users often refer to the barbiturate intoxication as a 'dry drunk'. See A.6 Alcohol for further discussion of barbiturate-alcohol interaction.

Little research has been done regarding the interaction of barbiturates and opiate narcotics in humans. It is clear, however, that the dose of either of these drugs which produces sedation, toxicity and death is lower when they are used together. Although barbiturates and opiate narcotics do not show significant cross-tolerance or cross-dependence, barbiturates are sometimes used to reduce the unpleasantness of opiate narcotic withdrawal. Some subjective effects of the drugs apparently interact in a complementary way when used together and barbiturates reportedly modify and prolong the effects of heroin. Barbiturates are often employed by opiate narcotic users to strengthen or reinforce a weak heroin dose or as a substitute when opiate narcotics are unavailable.20, 28, 64, 116, 140, 147 Persons on methadone maintenance are frequently reported to use barbiturates and alcohol to get `high'.55 The use of barbiturates is not socially acceptable in some opiate narcotic-using groups, however.28

Barbiturates are often used in conjunction with amphetamines. The two drugs together may result in some enhanced psychological response, although certain of their central nervous system effects are antagonistic. Amphetamines are sometimes used in the treatment of barbiturate overdose, although the value of such applications is questionable.37 Likewise, barbiturates are sometimes employed to reduce the toxic effects of stimulant overdose. Dexamyl® is a popular prescription combination of dextroamphetamine and amobarbital which supposedly produces stimulation without the irritability or tension produced by amphetamines. An alternating cycle of sedation and stimulation has been frequently noted among certain medical and non-medical drug users. A stimulant may be used to overcome the drowsy hangover the day after a hypnotic dose of barbiturate. By evening, another sedative dose may be necessary to overcome the insomnia potentiated by the day's amphetamine. A somewhat related pattern has been demonstrated by some amphetamine-injecting 'speed freaks' who use
barbiturates to terminate the stimulant effect, `mellow the crash', or produce sleep after a 'speed run' of several days duration.

Apparently barbiturates are not often used in combination with cannabis, LSD or other hallucinogenic drugs in Canada. In rodent studies cannabis has been found to prolong barbiturate sedative-hypnotic effects, probably in part through metabolic interaction.56, 58, 96, 124, 154 Commission research showing marijuana enhancement of certain alcohol effects suggests that some interaction might be expected with cannabis and barbiturates.112, 127 Some concern has been expressed that even though cannabis is not very toxic physically, high doses taken in combination with barbiturates or other sedatives might enhance the toxicity of the latter drugs.122 In one animal study cannabis was shown to increase sensitivity to barbiturate overdose.47

The Commission study of illicit drug samples indicated that LSD-barbiturate mixtures do occur, although they are uncommon 114 Such combinations would be expected to reduce some of the psychedelic and stimulant effects of LSD.69 Barbiturates are often used to treat or terminate an LSD 'bad trip'. On some occasions barbiturates have reportedly been mixed with STP or MDA to reduce the amphetamine-like toxic side effects seen with large doses of these latter drugs.139 It seems likely that barbiturates would enhance the sedative effects of PCP at doses typically taken, but such combined use has not been documented.

Although a number of drugs can block or reduce certain barbiturate effects, there are no known general barbiturate antagonists. The development of radio-immunoassay techniques for the chemical analysis of barbiturates,1°1. 143 raises the possibility of a general immunization against barbiturate effects. However, no research in this latter area has been reported. Patterns of multiple-drug use are discussed in more detail in Appendix C Extent and Patterns of Drug Use.