

CHAPTER 2

Depressants

2.1. INTRODUCTION

The classical depressants include hypnotics (sleeping pills), most antianxiety medications (e.g., diazepam or Valium), and alcohol.^{1–5} This chapter focuses on the most commonly used drugs of this class (other than alcohol which is discussed in Chapters 3 and 4), including benzodiazepines, barbiturates, and barbiturate-like medications. Several related compounds, including kava and gamma-hydroxybutyric acid (GHB), are also briefly presented here, as their effects resemble those of the more classical depressants.^{6–8} All depressants have the potential for being misused, and many prescription drugs of this class find their way into the street marketplace. The prototypical depressant is the barbiturate, which has been available in many forms since the 1860s and has been prescribed for a wide variety of problems. The generic names of all barbiturate medications in the United States end in *-al* and in Britain, in *-one*. These drugs differ in some ways from benzodiazepines and where appropriate, these two subgroups are discussed separately.

2.1.1. Pharmacology

2.1.1.1. Predominant Effects, Including Sedative, Hypnotic, or Anxiolytic Intoxication (304.10 in DSM-IV)

The depressants result in reversible depression of the activity of excitable neuronal tissues—especially those of the CNS—with the greatest effects on specific receptors and the synapse (the space between two nerve cells).^{4,9,10} The resulting depression in activity can range from a slight lethargy or sleepiness, through levels of anesthesia, to death from breathing and heart depression.

2.1.1.2. Tolerance and Dependence

2.1.1.2.1. Tolerance

Tolerance to depressants occurs through both increased metabolism (*drug dispositional or metabolic tolerance*) and adaptation of the CNS to the presence of the drug (*pharmacodynamic tolerance*).^{1,4,11} The metabolic tolerance can also produce an enhanced metabolism if some other substances, including the anticoagulant medications, result in lowered blood levels of these additional agents. The degree of tolerance can be huge, as case histories of 1000 mg per day of benzodiazepines have been reported in individuals still awake and talking. As is true of all medications, tolerance is not an all-or none phenomenon, and users can reach a point where tolerance stops and the next increment in the dose is lethal.

An important aspect of tolerance occurs with the concomitant administration of additional depressant drugs. If a second drug is consumed when the body is free of the first, cross-tolerance can be seen, as a reflection of both metabolic and pharmacodynamic mechanisms. However, if the second depressant drug is administered at the same time as the first, the opposite can be seen as the two drugs compete for metabolism and can potentiate the effects of each other in the brain. For example, a patient regularly using high doses of alcohol who undergoes surgery while in an alcohol-free state is likely to show significant cross-tolerance to some preanesthetic and anesthetic medications. If, however, the same patient uses a barbiturate or a benzodiazepine while intoxicated with alcohol, he is likely to experience a potentiation of drug effects with a resulting toxic reaction or overdose. Therefore, even an individual tolerant to one drug can have a fatal overdose with a concomitantly administered second depressant drug.

2.1.1.2.2. Dependence and Abuse (304.10 and 305.40 in DSM-IV)

All depressants including benzodiazepines such as chlordiazepoxide (Librium), diazepam (Valium), and alprazolam (Xanax), produce a withdrawal state when stopped abruptly after a relatively continuous administration of high doses.^{12–15} The same may be true for benzodiazepine-like drugs such as zolpidem (Ambien), eszopiclone (Lunesta) and zaleplon (Sonata).^{16,17} The withdrawal picture resembles a rebound hyperexcitability characterized by body changes in a direction opposite to that seen with the first administration of the drug.

Signs of withdrawal can be seen with abstinence after several weeks of frequent intoxication. In general, the severity of the abstinence syndrome increases with the strength of the drug, with higher doses, and with longer periods of administration. For a substance like pentobarbital, for example, stopping the drug after the administration of 400 mg a day for 3 months results in EEG changes in at least 30% of the individuals; 600 mg for 1–2 months results in a mild to moderate level of withdrawal in 50% of the individuals, including 10% with severe withdrawal symptoms including seizures;

and 900 mg for 2 months results in seizures in 75%, often accompanied by states of confusion. As a general rule, use of 500 mg of a barbiturate or an equivalent dose of other drugs will result in a risk of withdrawal seizures.

With the benzodiazepines, moderate withdrawal symptoms can be seen in individuals taking two or three times the usual clinical dose for several weeks, although most people for whom these drugs are prescribed do not use them for intoxication. Symptoms of withdrawal are likely to include headaches and anxiety (in about 80%), insomnia (in about 70%), and tremor and fatigue (each seen in about 60%), as well as perceptual changes, tinnitus, sweating, and a decreased ability to concentrate.^{5,14,18} Similar to alcoholic withdrawal, abrupt abstinence after higher doses of benzodiazepines can precipitate delirium and seizures.^{5,18,19} There is also compelling evidence that mild symptoms are likely to occur with abstinence following months of daily benzodiazepines in therapeutic doses after long-term use.

Another indication of the dependence-producing properties of the benzodiazepines comes from observations of the use of these drugs “on the street,” where the value of diazepam and clonazepam (Klonopin) is estimated to be between \$2.00 and \$4.00 per pill.² Although many men and women who seek out these drugs for a “high” appear to move on to other agents relatively quickly, several groups of people have especially high risks for the continued misuse of benzodiazepines. First are heroin-dependent individuals and those on methadone maintenance, 75% or more of whom have admitted to taking benzodiazepines to enhance their intoxication or to deal with discomfort related to withdrawal symptoms from opioids.^{20,21} At least theoretically, individuals who are alcohol dependent are also at increased risk for benzodiazepine dependence, perhaps in an effort to diminish anxiety, insomnia, or other withdrawal symptoms that might be observed in a context of their alcoholism. However, it is difficult to marshal definitive data regarding an enhanced prevalence of benzodiazepine or other brain depressant dependence in men and women who misuse alcohol.

In summary, all of the DSM-IV items for abuse or dependence, can develop these in people taking high doses of depressants.²² Regarding dependence, these can include tolerance, withdrawal, use for longer periods than intended, interference with functioning, and so on. Regarding abuse, users can develop repetitive legal, occupational, and social problems, take these drugs in the context of hazardous activities, and continue their use despite these problems.

2.1.1.3. Specific Drugs

Tables 2.1 and 2.2 give examples of members of the different classes of hypnotic and antianxiety drugs. However, the actions of agents in the two major subclasses can overlap. For example, antianxiety drugs in high enough doses induce sleep, whereas some barbiturate hypnotics were labeled hypnotosedatives and administered to treat anxiety.^{4,5}

Table 2.1
Nonbenzodiazepine CNS Depressants

Drug type	Generic name	Trade name
Hypnotics/medical Uses		
Barbiturates		
Ultrashort-acting	Thiopental	Pentothal
	Methohexital	Brevital
Intermediate-acting	Pentobarbital	Nembutal
	Secobarbital	Seconal
	Amobarbital	Amytal
	Butobarbital	Butisol
Long-acting	Phenobarbital	Luminal
Others	Chloral hydrate	Noctec
	Paraldehyde	—
Antianxiety drugs		
Carbamates	Meprobamate	Miltown, Equanil

See Table 2.2 for the benzodiazepines.

2.1.1.3.1. Hypnotics

Although the most commonly used sleeping pills are the benzodiazepines or similar drugs, other hypnotics include the barbiturates and barbiturate-like drugs. These are presented in Tables 2.1 and 2.2.

The first subclass of *barbiturates* consists of the rarely misused *ultra-short*-acting drugs (used to induce anesthesia) with lengths of action of a few minutes (e.g., thiopental and methohexital). The *short* to *intermediate*-acting barbiturates exert their major effect for a period of approximately 4 h, so they help people get to sleep. These include the drugs prescribed and misused as hypnotics, such as pentobarbital (Nembutal) and secobarbital (Seconal). Finally, the *long-lasting* drugs, such as phenobarbital, are most often used to treat neurological conditions such as epilepsy. Abuse and dependence on phenobarbital-like drugs are relatively uncommon.

Another group of hypnotics discussed here is exemplified by chloral hydrate (Noctec) and paraldehyde. These drugs share most of the dangers outlined for the barbiturate and barbiturate-like hypnotics.

Four other hypnotic drugs are the benzodiazepines flurazepam (Dalmane), nitrazepam (Mogodan), temazepam (Restoril), and triazolam (Halcion). Overall, these drugs do not produce completely normal sleep, but disturb the sleep EEG less than most other hypnotics, benefiting the patient by decreasing the sleep latency and the number of awakenings while increasing total amount of sleep. At the same time, the amount of sleep in Stage 2 increases while the sleep in Stages 3 and 4 tends to decrease, and moderate changes in REM sleep are likely to occur.

Table 2.2
Benzodiazepines

Generic name	Trade name	Half-life (h)	Usual adult daily dose (mg) ^a
Alprazolam	Xanax	11–15	0.75–4
Chlordiazepoxide	Librium	5–30	5–25
Clonazepam ^b	Klonopin	20–50	0.5–10+
Clorazepate	Tranxene	30–60	15–60
Diazepam	Valium; Dizac	20–50	2–15
Eszopiclone	Lunesta	6–9	1–3
Flurazepam ^c	Dalmane	50–100	15–30 HS
Lorazepam	Ativan	10–20	2–6
Nitrazepam ^c	Mogodan	24	5–10 HS
Oxazepam	Serax	5–20	10–60
Temazepam ^c	Restoril	4–8	15–30 HS
Triazolam	Halcion	3–5	0.25–0.5
Zaleplon ^{c,d}	Sonata	1	5–10
Zolpidem ^{c,d}	Ambien	2–3	10–20

^aHS indicates use at bedtime (hour of sleep).
^bUsed mostly as an anticonvulsant.
^cUsed only as a hypnotic.
^dNot a true Bz, but similar in action.

There are also several relatively new hypnotics, including Zolpidem (Ambien), technically not a benzodiazepine but an agent that carries most of the dangers of that group of drugs. This medication, an imidazopyridine, induces sleep, but has no antianxiety or muscle-relaxant properties. Zolpidem has a 2–3-h half-life, and is less disruptive of Stages 3 and 4 of sleep than the benzodiazepines. Acting primarily through its effects on omega 1 (or Bz₁) benzodiazepine receptors, it shares some of the problems associated with classical benzodiazepines. Thus, zolpidem will be self-administered by animals, tolerance can be observed, and a mild withdrawal or rebound syndrome can be expected when the drug is stopped. Zaleplon (Sonata) has a short half-life, and little effect on respiratory depression or morning cognitive functioning, but is only helpful in falling asleep, not staying asleep.^{23,24}

Two other hypnotics are available outside the United States. Zopiclone (marketed in Europe as Zimovane and known on the street as “Zim Zims”) has been associated with a number of problems, including dependence.¹⁶ The second medication, flunitrazepam (Rohypnol), is marketed in Central and South America and has become a problem in the United States, especially in locales close to the Mexican border. Known on the street as roSHAY, roofies, and Roche, and used to induce sleep at levels of 1–2 mg, it is misused for intoxication, and has also gained a reputation as a “date rape drug.”^{25,26} Here, similar to the mixture of chloral hydrate and alcohol (known as a Mickey Finn), when dissolved in alcohol the mixture can produce somnolence, poor judgment, and amnesia for the episode. In recent years, the

United Nations Commission on Narcotic Drugs has moved this agent to the more restrictive Schedule III. Another new drug is eszopiclone (Lunesta).

In summary, most hypnotics have drawbacks. They disturb the natural sleep pattern, they can be dangerous if taken in an overdose, and all have a potential for misuse. It appears that *all* hypnotic medications lose some of their effectiveness if taken nightly for more than 2 weeks, or produce a rebound insomnia when stopped.^{4,27,28} Therefore, considering their potential as agents for suicide and their limited time of efficacy if used daily, it is not wise to prescribe these medications for anything more than a short-term, acute crisis.

Safer approaches to treating insomnia are available, and are discussed in detail in other texts.²⁸ For instance, after carefully ruling out problems to which insomnia might be secondary (e.g., sleep apnea), I prescribe a schedule of going to bed and getting up at the same time each day, no caffeinated beverages, and no naps. Milk at bedtime can be a useful adjunct, perhaps because of its tryptophan content.

2.1.1.3.2. Antianxiety Drugs

The class of drugs most frequently prescribed for acute anxiety is the benzodiazepines [e.g., diazepam (Valium, Table 2.2)]. These medications are effective in the short-term treatment of *acute* anxiety, but few well-controlled studies have proved that they work for more than 1 month when taken daily.^{2,4} Long-term use of these drugs is likely to produce rebound anxiety and insomnia when they are stopped; some patients find it very difficult to become drug free.²⁹

Dangers associated with benzodiazepines and with other antianxiety agents include disturbances in sleep pattern and a possible change in affect (increased irritability, hostility, and lethargy). The carbamates (Table 2.1) can be especially lethal when taken in overdose, and these drugs accumulate in the body over time because they have a length of action that exceeds the usual time between the administration of doses. I never prescribe the carbamates (meprobamate) because they also appear to have a higher potential for producing dependence and a greater possibility of fatality following overdose than the benzodiazepines.

Another drug has been marketed for the treatment of long-standing general feelings of anxiety, or Generalized Anxiety Disorder in DSM-IV. Buspirone (Buspar) is briefly discussed in Section 2.1.1.3.4, but it is not a true depressant drug and does not share most of their dangers.

2.1.1.3.3. Benzodiazepines

Although the drugs in this antianxiety subclass are depressants, they are discussed separately because of the richness of understanding of their mode of action, their widespread use, their lower intensity of physiological

changes, and the less intense toxic reactions on overdose. These drugs have peripheral body effects, but most actions discussed here occur in the brain. Benzodiazepines (Bzs) are used as muscle relaxants (e.g., after strains or in spinal disk disease), as anticonvulsants (usually for non-grand-mal seizures and/or for status epilepticus), and as antianxiety agents. Their usefulness in treating anxiety states is best limited to short-term help (2 or 3 weeks) for severe situational problems. The more long-term and chronic major anxiety disorders (e.g., agoraphobia or obsessive-compulsive disease) are not usual targets for their use, as these drugs are not effective over a long enough period of time, and there is a possible rebound increase in symptoms when the drugs are stopped.

Some specific drugs are listed in Table 2.2. Although there are variations among the medications (especially related to their half-lives), the drugs in this class have great clinical similarities. Compared with most other types of sedative/hypnotics such as the barbiturates and the carbamates, these drugs are relatively safe in overdose, induce less prominent metabolic tolerance, cause fewer changes in sleep stages, and appear to be less likely to produce physical dependence. All drugs of this class can be administered orally, and most are better absorbed by mouth than by intramuscular injection (diazepam can be given intravenously, and lorazepam is well absorbed intramuscularly). They usually reach peak blood levels in 2–4 h after oral administration, and most have active metabolites (except lorazepam and oxazepam). The recommended frequency of administration varies with the half-life, so lorazepam and oxazepam may need to be given four times a day to remain effective, whereas clorazepate and diazepam may be used once per day (usually at bedtime). With the exception of the Bzs that have shorter half-lives (which are the drugs without active metabolites), most of these substances accumulate in the body, reaching a steady state in 7–10 days. Therefore, clinicians must be certain that sedative side effects do not progressively interfere with life functioning, especially in the elderly.³⁰

The pharmacological mechanisms of the benzodiazepines have been extensively studied. All these drugs enhance the effects of the more sedating amino acid brain neurotransmitter, gamma-aminobutyric acid (GABA).^{31,32} Two types of GABA receptors are most relevant, including GABA_A which is most sensitive to the effects of depressants such as benzodiazepines, whereas GABA_B receptors have little relationship with the actions of brain depressants in the CNS. When a benzodiazepine or a related drug occupies a sub-component of a GABA receptor, it facilitates the flow of chloride ions into the cell, thus, potentiating the effects of GABA.

In addition to GABA receptors, there are also three benzodiazepine receptors in the brain⁴ that work in conjunction with GABA_A activity. The Bz₁ (or omega 1) receptors contribute to the sleep-inducing effects of these drugs and are the site of the most prominent actions of most sleeping pills, such as zolpidem. The Bz₂ and Bz₃ receptors (also called omega 2 and

omega 3) appear to be most active regarding the anticonvulsant, muscle-relaxant, and antianxiety actions.

The link between benzodiazepine receptors and the actions of other depressants has not been as well established. However, at relevant doses, at least one barbiturate, pentobarbital, increases binding at these receptors. As might be predicted from these data, recent studies have also identified benzodiazepines such as flumazenil (Romazicon) that act at the Bz/GABA sites to inhibit and *antagonize* the actions of other drugs of this class. These drugs are important in treating overdoses with medications that affect this receptor complex, but they produce symptoms of anxiety and can precipitate withdrawal in a Bz-dependent person.^{9,33}

2.1.1.3.4. Some Nonbenzodiazepine Anxiolytics and Hypnotics

A number of nonbenzodiazepine anxiety-affecting agents have been evaluated. This development reflects the recognition that benzodiazepines are not perfect, having associated problems of misuse, physical dependence, cognitive impairment, and interactions with other brain depressants as described elsewhere in this chapter. Even though these agents are technically not depressants, they are discussed here because they can be used in a manner similar to the benzodiazepines.

These substances have a variety of structures and potential activities. They include nabilone, a tetrahydrocannabinol homologue distinguished by its relationship to the active ingredient in marijuana, and fenobam, a potentially effective anxiolytic with few muscle-relaxant or sedative/hypnotic properties and minimal potential for interaction with other depressants.³⁴

The best known and most thoroughly studied of the nonbenzodiazepine anxiolytics is buspirone (Buspar), an unusual fat-soluble molecule of multiple rings with a structure unlike that of any other anxiolytic agent.^{35,36} This drug has either weak or no actions on benzodiazepine receptors, and it does not replace benzodiazepines from their binding sites, nor does it directly affect GABA binding. Buspirone is known to affect serotonin, norepinephrine, and acetylcholine systems, with the most clinically relevant effect probably being on serotonin.

In controlled trials for the treatment of generalized anxiety disorder, its key clinical target, buspirone shows no hypnotic effects but demonstrates some anxiolytic properties, usually after 2 weeks of administration. At the same time, this agent appears to offer fewer safety concerns, as there is little evidence of cognitive impairment with clinically relevant doses, and little evidence that it interacts with brain depressants such as alcohol. Additionally, animal or clinical studies do not demonstrate a high potential for misuse of this agent. Thus, buspirone may be the first effective anxiolytic without a clinically significant dependence risk. However, the clinical indications for this medication are rather narrow.

2.1.1.3.5. Some Additional Drugs

Gamma-hydroxybutyric acid is a depressant-like drug that boosts the brain activity of GABA and perhaps of dopamine.⁶ This substance, formerly available in health food stores, has for many years been used by athletes and bodybuilders, but a series of overdoses in the early 1990s resulted in its restriction from the legal markets. GHB still appears on the “streets” as a product of kitchen laboratories. Although not well studied, it appears that this drug is capable of producing the same pattern of problems seen with the other more typical brain depressants including dependence, withdrawal, and overdose.^{37–39}

A second drug with a much longer and more culturally syntonetic history has been used in Polynesia and Micronesia since at least the 1700s.⁴⁰ Kava is a complex mixture of substances extracted as a powder and consumed as a tea. It is made from the pepper plant (*Piper methysticum*) that grows in the South Pacific. The active ingredients, few of which have been isolated, produce a variety of effects including sedation and incoordination that can quickly progress to deep sleep. Intoxication is also associated with a decrease in cognitive functioning, and it is generally believed that Kava produces an alcohol-like effect. It has traditionally been used in a sundown ceremony for men on Fiji and on similar islands but is now also sold in different parts of the world as these populations have disbursed globally.

2.1.2. Epidemiology and Patterns of Use

The depressants are prescribed in great quantities. Supporting the high prevalence of use are studies demonstrating that more than one in three American adults had symptoms of insomnia during the preceding year, including 10% with chronic sleeping problems.⁴¹ As a result, 3–4% had used a prescribed hypnotic of some type, an additional 2% have taken other prescription drugs to help them sleep, and approximately 3% took over-the-counter sleeping pills.⁴¹ These figures include a total of 0.3% of the population (11% of users) who had taken the medication regularly over the last year. In addition, over 8% of the general population have used benzodiazepines to deal with anxiety.^{41,42}

Among the depressants, the Bzs receive the widest use.⁴³ In one year, over 2 billion tablets of diazepam were prescribed in the United States. Although use is widespread, these figures do not necessarily indicate abuse or dependence, as these drugs are generally used as prescribed for sleep and for anxiety. However, up to 10% of general medical/surgical patients and 30% of individuals with serious psychiatric histories have, at some time, felt psychologically dependent on these antianxiety or hypnotic drugs, with an outright substance use disorder in between 5 and 10%.

Many people in the United States have used depressant drugs for a high. In 2003, 10.2% of high school seniors reported having ever used a

“tranquilizer,” a figure similar to the 10.3% in 2001.⁴⁴ For this age group, 6.7% had used in the prior year (6.9% in 2001) and 2.8% in the prior 30 days. Among college students, the ones who had ever used depressants for intoxication were 10.7% overall, 6.7% in the prior year, and 3.0% in the last 30 days.

It is more difficult to establish the lifetime prevalence of abuse or dependence on these agents. According to a 2002 survey, during the prior year, almost 200,000 Americans had received treatment for a condition related to depressant drugs, often in the context of additional drugs of misuse.⁴⁵ However, to place this into perspective, during that same period, 2.2 million Americans had received treatment for alcohol-related disorders, thus, while the rate of treatment for alcoholism was as high as about 1% of the population, the proportion in treatment for depressants was one in almost 1500 people.

Some subgroups of the population are more likely than others to engage in depressant abuse or dependence. Probably the best studied of these are individuals who are opioid dependent, especially those taking part in methadone maintenance programs.²⁰ Here, a substantial proportion (perhaps almost a majority) report having used a Bz or a barbiturate to help them cope with the opioid withdrawal syndrome or to enhance their levels of intoxication while taking methadone. In some locales, 65% or more of stimulant or intravenous (IV) opioid drug users also reported a history of imbibing or injecting depressants.⁴⁶

Thus, misuse of depressant drugs should be considered in the evaluation of almost any patient seen in a usual medical setting, an emergency room, or in a crisis clinic. In light of the limited time that these medications stay effective when taken daily, there is rarely a valid clinical need to prescribe them for more than 2–4 weeks.

2.1.3. Establishing a Diagnosis

Identification of the individual misusing depressants requires a high index of suspicion, especially for patients with a delirium, a dementia, or with paranoid delusions, and for all men and women who insist on receiving prescriptions for any of these medications. It is imperative that special care be taken before these drugs are given to patients who are not known to the physician. Also, when they are prescribed, the script should be for only relatively small amounts, both to decrease the suicide overdose potential and to discourage misuse. No “repeats” should be allowed, bottles should be labeled as to the contents, and records should be evaluated to determine how long the patient has been on the medication.

2.2. EMERGENCY PROBLEMS

The following outline follows the general format presented in Table 1.5, reviewing the possible areas of difficulty seen in emergency rooms, in the

outpatient office, and in crisis clinics. The most common problems seen with the CNS depressants are toxic overdose, temporary psychosis, and withdrawal.

2.2.1. Toxic Reactions

See Sections 4.2.1, 6.2.1, and 13.2.1

As this is the first chapter to discuss overdose, it is important to remind the reader that this text only gives very general guidelines. It is essential to also consult a textbook of medicine or a text on emergency medicine.^{47,48}

2.2.1.1. Clinical Picture

2.2.1.1.1. History

The toxic reaction or overdose usually develops over a matter of minutes to hours, and the patient often presents in a confused or obtunded state with severe memory impairment.^{49–51} This reaction is more likely to be seen when an individual mixes two or more depressants (usually alcohol and hypnotics), develops a confused state that results in inadvertent repeated administration of the drug, unintentionally takes too high a dose of a street drug, or makes a deliberate suicide attempt.

2.2.1.1.2. Physical Signs and Symptoms

Toxic reactions are characterized by various levels of anesthesia and decreased CNS, cardiac, and respiratory functioning. Additional signs include a decreased temperature, diminished reflexes, and decreased gut motility.⁵² An overdose of a depressant drug can be very serious. The physical signs must be carefully evaluated in a manner similar to that suggested in Section 6.2.1 for opioids. Examination includes the following:

1. A careful evaluation of the vital signs and the reflexes, with the findings depending on the drug dose, the time elapsed since ingestion, and any complicating brain conditions, such as hypoxia.
2. A neurological exam to help establish the degree of coma. Important aspects include the following:
 - a. *Pupillary reflexes*: Usually midpoint and slowly reactive, with which pupils tend to be enlarged.
 - b. *Corneal reflexes*: Diminished or absent, except in mild coma.
 - c. *Tendon reflexes and pain reflexes*: Tend to be depressed.
3. An evaluation of possible cardiac arrhythmias, especially with the short-acting barbiturates.
4. Oscultation of lungs for congestion from heart failure or from positional or infective pneumonia.

2.2.1.1.3. Psychological State

Because the patient often presents in a stupor or in a coma, there are usually few other distinctive psychological attributes.

2.2.1.1.4. Relevant Laboratory Tests

See Section 6.2.1.1.4.

As with any shock-like state or comparable medical emergency, it is important to carefully monitor the vital signs and the blood gases (arterial oxygen and CO₂) to evaluate the need for a respirator. A toxicological screen on either urine (50 ml) or on blood (10 cc) should also be carried out to determine the specific drug involved and the amount of the substance in the blood, and baseline blood chemistries and blood counts should be taken as outlined in Table 1.6. If the cause of the stupor or the coma is not obvious, a thorough neurological evaluation for additional medical problems (including an EEG, skull x-rays, a spinal tap, and so on) must be done. Routine tests should include an EKG, chest film, glucose, and electrolytes. Arterial blood gases should be evaluated if necessary.

2.2.1.2. Treatment

See Section 6.2.1.2.

Treatment begins with emergency procedures to guarantee an adequate airway, to make sure that the heart is functioning, and to deal with any concomitant bleeding; i.e., the ABCs of care.⁵³ The general goal is to support the vital signs until enough of the drug has been metabolized so the patient is stable, following the general approach presented in Table 2.3. The specific emergency maneuvers will depend on the patient's clinical status. These steps may range from simple observation for mild overdoses to starting an IV infusion, placing the patient on a respirator, and admitting him to an intensive care unit.

Although toxic reactions involving the Bzs should not be taken lightly, the clinical picture tends to be more mild, and fewer than 5% of patients require intensive-unit care for 48 h or more.⁵⁴ If treatment is initiated quickly, deaths are relatively rare (fewer than 1%), and especially rapid recovery is to be expected with the short-acting drugs such as lorazepam and oxazepam, even if the blood levels are initially high.^{54,55}

A possible step for benzodiazepine overdose is to administer flumazenil (Romazicon). The usual dose is 0.2 mg IV every minute, up to 3 mg. If a Bz was involved, sedation should be quickly reversed, but there is a danger of precipitating seizures or increasing intracranial pressure.⁵² Because of the short half-life of flumazenil, it may need to be repeated in 20–30 min.^{9,33}

The additional steps for approaching the patient with a toxic reaction to depressants, not necessarily to be taken in the numbered order, include the following:

Table 2.3
Treatment of the Depressant Toxic Reaction

Diagnose	History, clinical signs
First steps	Airway, assist respiration
	Cardiac
	Check electrolytes
	Treat shock
Consider	Lavage (use cuff if obtunded; activated charcoal; castor oil?)
	Forced diuresis (limited value)
	Hemodialysis
Avoid	Stimulants

1. Establish a *clear airway*, *intubate* if needed (using an inflatable cuff in case you want to do a gastric lavage), and place on a *respirator* if necessary. The respirator should use compressed air (oxygen can decrease the respiratory drive) at a rate of 10–12 breaths per minute.
2. Evaluate the *cardiovascular status* and control *bleeding*; treat shock with plasma expanders, saline, dextran, or other relevant drugs.
3. Begin an IV (large-gauge needle), replacing all fluid loss (e.g., urine) plus 20 ml for insensible loss (from respiration and perspiration) each hour.
4. Establish a means of measuring *urinary output* (bladder catheter, if needed). Send 50 ml of urine for a toxicological screen.
5. Carry out *gastric lavage* with saline if oral medication was taken in the last 1–4 h. Continue lavage until you get a clear return. Consider giving 60 ml of *castor oil* via the stomach tube.
6. Repeated administration of activated charcoal or a similar agent (e.g., 1 g/kg or more of activated charcoal suspended in water and administered every 4 h or so, over the first 2 days) appears to help decrease absorption.
7. Because opioid overdoses can cause a similar clinical picture, and the patient may have ingested more than one type of medication, consider the possibility of a narcotic overdose. This is tested for through the administration of an opioid antagonist such as *naloxone* (Narcan) at a dose of 0.4–2 mg, given either intramuscularly (IM) or IV. If the patient has ingested opioids to the point of obtundation, a rapid reversal of the picture should be demonstrated. Doses of this short-acting opioid antagonist will need to be repeated as often as every 30 min, if initially effective.
8. Carry out a more thorough *physical* and *neurological exam*—which must include *pupils*, *corneal reflexes*, *tendon reflexes*, presence of *pathological reflexes* (e.g., snout reflex), *pain perception* (use Achilles tendon), and *awake/alert status* (see Sections 6.2.1.2 and 13.4.1).

9. Draw *bloods* for arterial blood gases if needed, general blood tests to evaluate liver and kidney functioning, blood counts, and a toxicological screen.
10. Gather a thorough *history* of
 - a. Recent drugs (type, amount, time)
 - b. Recent alcohol
 - c. Chronic diseases
 - d. Allergies
 - e. Current treatmentsObtain this information from the patient and/or from an available additional informant.
11. For the comatose patient, protect against *decubitus ulcers* (bedsores) by frequent turning, and *protect the eyes* by taping the lids closed if necessary.
12. Establish a *flow sheet* for
 - a. Vital signs
 - b. Level of reflexes
 - c. Urinary output
 - d. IV fluidsThese should be recorded up to every 30 min.
13. Consider *forced diuresis* especially for barbiturate overdose. This is not needed for patients with stable vital signs or for those where deep tendon reflexes are present (e.g., grade I or II coma), and rarely helps for chlorthalidone (Librium) or for diazepam (Valium). If either diuresis or dialysis is used, special care must be taken to maintain proper electrolyte levels and to avoid precipitating congestive failure. If diuresis is needed, you may use
 - a. Furosemide (Lasix), 40–120 mg, as often as needed to maintain 250 ml or more per hour;
 - b. IV fluids, with the general approach of giving enough saline and water with glucose to maintain urinary output in excess of 250 ml/h.
14. Alkalinization of the urine can be helpful with long-acting barbiturate overdose.⁵² This can be accomplished with an IV bolus of 1–2 mEq/kg of sodium bicarbonate, followed by 50–100 mEq added to 500 ml of a 5% dextrose solution
15. Hemodialysis or peritoneal dialysis can be considered for the patient in a deep coma but is rarely needed. Hemoperfusion may be helpful for patients who have grade IV coma with associated apnea and hypotension, for patients who show deterioration despite supportive treatment, for those in prolonged coma with cardiorespiratory complications, or for individuals with very high plasma drug levels.
16. Evaluate the need for *antibiotics*. Do *not* use them prophylactically.
17. Do *not* use stimulants such as amphetamines.

18. For the unresponsive patient who requires admission to an intensive care unit, the prognosis is likely to relate to the levels and the degree of change in systolic pressure, the central venous pressure, and the acid–base balance (pH). A special word of warning is required regarding the ability of the depressant drugs to produce a temporary flat EEG, which can reverse within a matter of days.

2.2.2. The Depressant Withdrawal Syndrome (292.0 and 292.81 in DSM-IV)

See Sections 4.2.2 and 6.2.2.

The depressant withdrawal syndrome consists of a constellation of symptoms that might develop (during abstinence) in an individual taking any of these drugs daily in excessive doses. The clinical picture is usually a mixture of any or all of the possible symptoms, running a time course that tends to last 3–7 days for the acute syndrome related to short-acting drugs such as oxazepam or lorazepam that have half-lives similar to alcohol, but is longer for longer acting drugs like diazepam (Valium). Following the acute withdrawal period, less intense symptoms are likely to be observed for 3–6 months as part of a protracted withdrawal syndrome.

Although less likely to cause physical dependence than other depressants, all Bzs can do so.^{4,15,56,57} As new Bz agents were introduced to the market, it was hoped that they might be less likely to be misused or associated with more mild abstinence syndromes, but this has usually not proven to be the case.

The Bzs are less popular as “street” drugs than other depressants, but they do have rewarding properties and are self-administered by animals. As is true of all depressants, the development of physical dependence relates to the drug dose and the period of time over which it was administered. Thus, physical withdrawal has been reported with diazepam in clinical dose ranges (e.g., 10–20 mg/day), as well as with alprazolam or with lorazepam (4 mg/day or less) when taken over a period of weeks to months.²⁷ When two to three times the normal maximal doses are ingested, physical dependence can probably be induced in a matter of days to weeks.

2.2.2.1. Clinical Picture

2.2.2.1.1. History

A depressant withdrawal syndrome must be considered in any individual who presents with signs of autonomic nervous system overactivity (e.g., a rapid pulse and elevated blood pressure) along with agitation, and who asks the physician for a depressant drug.^{2,4} This syndrome can be seen in the person who fits DSM-IV dependence, as well as the middle class recent user who obtains the drug on prescription but takes more than recommended. The

symptoms begin slowly over a period of hours and, similar to alcohol, may not peak until Day 2 or 3 for the short- to intermediate-half-life drugs.

The time course for the withdrawal from barbiturates, such as pentobarbital, or a drug like meprobamate (Miltown or Equanil) is outlined in Table 2.4. This table indicates the probable onset of symptoms within a half-day of stopping or decreasing the medications, a peak intensity at 24–72 hours, and diminished acute symptoms some time before Day 7. The time frame is a good deal longer for the longer acting barbiturates and the antianxiety drugs such as chlordiazepoxide (Librium), for which withdrawal seizures and delirium can begin as late as day 7 or 8. The acute stage of withdrawal is followed by the lingering symptoms of a protracted withdrawal condition that is likely to disappear by Months 3–6 following abstinence.⁵⁸

2.2.2.1.2. Physical Signs and Symptoms

The withdrawal symptoms consist of a mixture of both psychological and physical problems. The patient usually develops a fine tremor, gastrointestinal (GI) upset, muscle aches, increased pulse and respiration rates, a fever, and a labile blood pressure.^{2,43} Some atypical withdrawal syndromes can also be seen, especially with the Bzs, and may include headache, malaise, and abrupt weight loss. With any depressant, but especially the barbiturates, between 5 and 20% of individuals develop grand-mal convulsions—usually one or at the most two fits that only rarely progress to a state of repeated and continuous seizures known as status epilepticus.

2.2.2.1.3. Psychological State

The withdrawal symptoms include moderate to high levels of anxiety and a strong drive to obtain the drug.¹² In addition, between 5 and 20% of individuals develop a delirium, sometimes accompanied by hallucinations.

Table 2.4
Time Course of Acute Withdrawal from Short/Intermediate-Acting Barbiturates and Meprobamate

Time (after last dose)	Symptom	Severity
12–16 h	Intoxicated state Onset: Anxiety, tremors, anorexia, weakness, nausea/vomiting, cramps, hypotension, increased reflexes	Mild
24 h	Weakness, tremors, increased reflexes, increased pleading for drug High risk for grand-mal seizures; delirium	Mild Severe
24–72 h	Peak intensity	Greatest
3–7 days	Symptoms gradually disappear	Diminishing
1 week–6 months	Some anxiety, sleep disturbance, ANS irregularities	Mild

The state of confusion can include hallucinations or delusions similar to delirium tremens (DTs) described for alcohol in Chapter 4.

2.2.2.1.4. Relevant Laboratory Tests

Because the withdrawal syndrome is potentially more severe than most other drug withdrawals, it is essential that an adequate physical examination be carried out and that all baseline laboratory tests (including most of the chemistries and blood counts listed in Table 1.6) be evaluated. A toxicological screen (10 cc blood or 50 ml urine) may (or may not) reveal evidence of the drug, depending on the length of time since the last drug dose and the specific substance involved. It is imperative that the physical condition be carefully monitored throughout the acute withdrawal syndrome.

2.2.2.2. Treatment

See Sections 4.2.2.2 and 6.2.2.1.2.

An important aspect of treatment is prevention. Thus, patients should never be placed on a daily depressant for more than 2–3 weeks. Even with short-term use, the drug should be tapered off slowly rather than stopped abruptly.²⁷

The treatment of depressant withdrawal follows a relatively simple paradigm. This includes a good physical evaluation, general supportive care, education and reassurance, and, if needed, medication.^{2,13,59,60} The comments that follow apply to syndromes caused by withdrawal from depressants other than alcohol. Alcoholic withdrawal is discussed in Section 4.2.2.

1. To avoid delirium or convulsions, it is important to consider treatment of withdrawal in a *hospital setting*, although slow weaning off the drug as an outpatient is possible.
2. Each patient should receive an adequate *physical examination* and *general screening laboratory procedures*.
3. Assuming that the physical condition is stable and that the patient is being provided with good nutrition, rest, and multivitamins, treatment of the withdrawal itself can begin.
4. My preferred approach is to use the drug of abuse itself as a withdrawal agent, gradually tapering the doses over an approximate 4–8-week period (although this regimen does not result in a disappearance of all symptoms). There are few data to support the use of alpha adrenergic agonists (e.g., clonidine or Catapres) or beta blockers such as propranolol (Inderal) in the treatment of these syndromes. These agents run the risk of masking internal autonomic overactivity that can indicate impending seizures or delirium.
5. An alternate approach is to switch the patient to a long-acting depressant. This is listed for the sake of completeness, although I prefer

tapering the specific drug the patient is dependent upon. If a long-acting drug is chosen, you might consider phenobarbital (Luminal), which has a half-life of 12–24 h. This approach is based on the ease with which stable blood levels of this longer acting drug can be maintained, but suffers the drawback of some difficulty in determining the effective starting dose.

- a. One begins by estimating the dose of the drug of dependence and giving approximately 32 mg of phenobarbital for each 100 mg of estimated barbiturate, for each 400 mg of meprobamate (Equanil), for each 5 mg of diazepam (Valium), or for each 25 mg of chlordiazepoxide (Librium). The total dose of phenobarbital is divided into portions to be given four times per day (QID), with extra medication given if the patient begins to demonstrate signs of withdrawal. Doses up to 500 mg of phenobarbital are sometimes needed.
- b. One or two consecutive doses (or more) are withheld if the patient appears too sleepy or demonstrates some signs of intoxication, such as nystagmus or ataxia.
- c. The required dose is then utilized for 2 days, given in divided doses at 6 A.M., noon, or 6 P.M., and midnight, with the largest dose (approximately 1.5 times the other dose) being given at midnight.
- d. After this, the dose is decreased by approximately 30 mg per day—a 200 mg IM dose can be used if needed to control the emergence of serious withdrawal symptoms. If the patient looks sleepy or confused, the next dose should be withheld until he clears. It has not been shown that it is necessary to include phenytoin (Dilantin).
- e. This is a rough outline and the individual dose must be titrated for the specific patient. The goal is to reach a drug level at 24 h that decreases withdrawal symptomatology without intoxicating the patient or making him too sleepy. As with any drug that has a half-life of more than a few hours, it is important to recognize that the drug could accumulate in the body over time. This danger is especially relevant in elderly patients, and those with chronic dementia or serious liver impairment—situations some might consider to be inappropriate for the phenobarbital approach.

2.2.3. Delirium, Dementia, and Other Cognitive Disorders (292.81, 292.82, and 292.83 in DSM-IV)

See Section 1.7.3.

States of confusion can be seen with low doses of drugs in patients with an increased sensitivity to brain depressants (e.g., the elderly or people with brain damage) during severe intoxication, during an *overdose*, or in the context of depressant withdrawal.^{9,30,61,62}

2.2.3.1. General Comments

Several special cases of a delirium or dementia need further discussion. Individuals with decreased brain functioning (e.g., older people and those who have had previous brain damage as a result of trauma, infections, or other causes) are probably more sensitive to the effects of all depressants, including the Bzs.^{30,63} Thus, such individuals might be expected to show a clinically significant and relatively persistent, although rarely permanent, state of confusion when they take even moderate doses of hypnotics, alcohol, or most antianxiety drugs. Use or misuse of depressants should be considered as part of the differential diagnosis for all confused states of recent onset or for anyone demonstrating a rapid deterioration in his usual state of cognition.

A second important case involves the propensity of all of the brain depressants to interfere with the acquisition of new memories.^{49,50} This condition of anterograde amnesia is similar to an alcoholic blackout (see Section 3.2.4), and is most likely to be observed when the drugs are taken in high doses or IV. In fact, minor medical procedures such as cardioversion and dental operations take advantage of this property. Although seen with all brain-depressant drugs, several agents, including triazolam, are especially likely to produce anterograde amnesia at clinically relevant doses.

Another important topic involves the possible development of more persistent neuropsychological deficits in heavy users of depressant drugs.^{42,64} Significant memory problems have been reported in people who are depressant-dependent. These observations are corroborated by the demonstration of at least temporary psychological test deficits (e.g., on the Halstead–Reitan Battery) in a third or more of people with depressant dependence—deficits that can then remain during 3 weeks to 3 months of abstinence, or even longer.⁶⁴

The treatment of a state of confusion induced by a depressant involves a series of common-sense steps. First, the patient should be evaluated for any life-threatening causes of the diminished level of cognition including trauma (e.g., a subdural hematoma), serious infections in the CNS or elsewhere, blood loss, electrolyte imbalances, hypoglycemia, and so on. Next, all depressants should be stopped, and the patient should be observed over the next several weeks to monitor improvement. As with alcohol, it is possible that some patients may demonstrate more permanent neuropsychological deficits.

The discussion now highlights two specific categories of delirium and dementia in greater detail.

2.2.3.2. Diminished Cognition Caused by Mild Overdose

2.2.3.2.1. Clinical Picture

A toxic syndrome short of a coma is characterized by abnormal vital signs and confusion, disorientation, decreased mentation, and impaired memory. This picture resembles the one seen during severe alcohol intoxication.

It may develop even at low doses in individuals at high risk for confusion, such as older people.

2.2.3.2.2. Treatment

This state is best treated with observation and general support, usually in an inpatient setting where the patient is protected from wandering or from harming himself. For younger individuals, the confusion usually clears within a matter of hours to days, but for older people, it might require an extended treatment period of 2 weeks or longer. In either instance, it is best to avoid the concomitant administration of any other drug.

2.2.3.3. States of Confusion Observed During Withdrawal

2.2.3.3.1. Clinical Picture

A rapidly evolving delirium can be seen during withdrawal from these drugs.¹⁸ It is usually temporary, rarely lasting more than a few days even without treatment. When it develops, signs of withdrawal are usually prominent, but one must take care to rule out other potentially lethal causes of dementia, including trauma, occult bleeding, and brain damage.

2.2.3.3.2. Treatment

Treatment of a delirium during withdrawal is discussed in Section 2.2.2.2.

2.2.4. Psychosis (292.11 and 292.12 in DSM-IV)

See Sections 1.7.4, 4.2.4, and 5.2.4.

2.2.4.1. Clinical Picture

High repetitive doses of depressant drugs can produce a temporary psychosis, or a depressant-induced psychotic disorder, characterized by a relatively acute onset in a clear sensorium (the patient is alert and oriented), of auditory hallucinations, and/or paranoid delusions (e.g., thinking that someone is plotting against or trying to harm him). This picture has been more clearly established as it relates to alcohol, and thus is discussed in greater depth in Section 4.2.4. However, similar pictures can be expected with the misuse of any depressant.⁶⁵ It is probable that the generalizations presented for alcohol hold for the other depressants as well.

2.2.4.2. Treatment

With supportive care, the psychosis is likely to clear within 2 days to 4 weeks of abstinence. Antipsychotic medications do not have to be given unless the paranoia and/or hallucinations create a danger to the patient or to

those around him. Then, such drugs—that is, haloperidol (Haldol), or risperidone (Risperdal), 1–3 mg twice a day can be used until the clinical picture clears.

2.2.5. Flashbacks

There are no recognized flashbacks with depressants.

2.2.6. Anxiety and Depression (292.89 and 292.84 in DSM-IV)

See Sections 1.7.6, 5.2.6, 7.2.6, and 8.2.6.

Withdrawal from depressant drugs can produce temporary symptoms similar to major anxiety disorders, which is discussed as sedative-, hypnotic, or anxiolytic-induced anxiety disorders in DSM-IV.^{12,66} These can include symptoms of panic disorder, social phobia, agoraphobia, or generalized anxiety disorder. Intense *intoxication* with any brain depressant can mimic major depressive disorders, at least temporarily, although the syndrome is highly likely to disappear with continued abstinence.^{67,68}

2.2.6.1. Clinical Picture

During intoxication, people can demonstrate pervasive sadness, hopelessness, the inability to concentrate, problems in sleeping, loss of appetite, and so on.⁶⁸ Withdrawal states are likely to include panic attacks that resemble panic disorder, high levels of anxiety regarding social situations that can be misdiagnosed as social phobia, along with high levels of feelings of anxiety that could be mislabeled as generalized anxiety disorder. Whereas independent major depressive and anxiety syndromes tend to be long-term, and for the latter, lifelong, the substance-induced pictures are time limited, with symptoms likely to improve markedly within a month or so of abstinence, and then to totally disappear over the next several months.

2.2.6.2. Treatment

When observed in any clinical condition, intense depressions, especially those with associated suicidal thoughts, must be taken seriously.⁶⁹ Thus, depressant-induced temporary mood disorders might require short-term hospitalizations with suicide precautions until the intensity of the depressive symptoms decreases over the subsequent days to weeks. In addition, in the context of these mood disturbances, it is important that patients be reassured that, although the symptoms are troubling, they are only temporary and will improve with continued abstinence. Of course, if the severe depressions interfering with life functioning remain at intense levels beyond the first month or so of abstinence, there may be a careful psychiatric evaluation for the possibility that an independent long-term major depressive disorder is present.

Anxiety conditions, whether representing independent lifelong anxiety disorders or as part of depressant withdrawal, usually do not require emergency intervention. Patients are likely to respond to education and to reassurance regarding the temporary nature of their symptoms. Active efforts to help individuals learn relaxation approaches, and more formal cognitive therapies to help them adjust to the acute and more protracted (but temporary) brain depressant-related syndromes can also be beneficial. However, because of the temporary nature of these substance-induced anxiety syndromes, medications are rarely, if ever, justified.

2.2.7. Medical Problems

Whereas few medical disorders are known to be unique to people who are depressant-dependent, daily use of hypnotics is associated with a slight, but significant, overall increased mortality rate (1.22–1.35 fold in women and in men), even after controlling for all other factors.⁷⁰ The conditions that develop depend on the specific drug taken and the route of administration. A few “special” problems are discussed in this section.

1. Anecdotal information indicates an ability of extended use of these drugs to *impair memory* over an extended period of time—perhaps even permanently. However, this phenomenon has not been definitely established.
2. IV users are vulnerable to all the complications that can result from contaminated needles.⁷¹ These include hepatitis, tetanus, abscesses, acquired immunodeficiency syndrome (AIDS), and so on, as described for opioids in Section 6.2.7.
3. A special problem can result from the injection of these drugs into an artery. The resulting painful muscle and nervous tissue necrosis can necessitate amputation of a limb. Injection into veins can cause venous thrombosis.
4. A major difficulty with any depressant, including the Bzs, is the product of excessive *sedation*. This may cause impaired judgment and deterioration in work and motor performance, especially with longer acting drugs, which may accumulate in the body over time.⁷² Although the actual number of cases is unknown, it is likely that depressants contribute to many motor vehicle accidents each year. Cognitive problems are exaggerated in the presence of liver disease or decreased albumin in the blood, but all patients should be warned to avoid activities demanding high levels of alertness and/or motor performance if they are experiencing sedation side effects. An additional problem, especially in the elderly who are more sensitive to the effects of brain depressants, is the possibility of falls with a subsequent heightened risk for hip fractures.^{42,63}

5. At the usual doses, these drugs are not likely to induce serious *cardiac* symptoms in the average healthy individual. However, all depressants can suppress respirations, and thus, might precipitate respiratory failure in individuals with chronic obstructive lung disease.
6. All of these drugs can decrease inhibitions and have been reported to increase angry outbursts. Some patients with depression can react to depressants with an intensification of their sadness and irritability.
7. *Drug interactions* are a potential problem with all medications. The depressants are likely to potentiate the side effects of tricyclic-type antidepressants and anticonvulsants, and (through possible interference with liver metabolism) may increase blood levels of digoxin.⁷³ The actions of L-dopa may be inhibited by this class of drugs, and cimetidine may interfere with benzodiazepine metabolism and excretion. Of course, the interaction between two or more depressants can be severe, and an enhancement of Bz actions are likely to be noted after an individual drinks ethanol. Long-term oral contraceptive use can interfere with benzodiazepine metabolism, and antacids can interfere with their absorption.
8. No drug can be considered safe during *pregnancy*. Although there is some controversy, and other depressants such as thalidomide are highly toxic to the fetus, there is no strong evidence of specific teratogenicity for most of the currently used depressants.⁷⁴ Because this class of drugs is rarely necessary for sustaining life functioning, pregnant women should be told to avoid these medications, especially during the first trimester. This caveat probably extends to the neonatal period for women who are breast-feeding, as there is evidence that Bzs pass through the mother's milk to the baby and may be responsible for an accumulation of bilirubin.^{75,76}

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