General approach to drug and substance abuse

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مخاطب: الو مشاوره دارو؟

کارشناس: بله بفرمایید

مخاطب: پسرم تینر (حلال رنگ نقاشی) خورده چه کار کنم؟

کارشناس: چند سالشونه؟

مادر بیمار: ۱۷ ساله شه

کارشناس: کی (چه موقع؟) این اتفاق افتاده؟

مادر بیمار: چند دقیقه، آره حدود پنج دقیقه پیش، تقصیره باباش شد داره نقاشی میکنه باقی مونده تینر رو ریخته تو قوطی نوشابه گذاشته رو میز، دخترم اومده خونه رو مرتب کرده فکر کرده ظرف آبه اونو گذاشته تو یخچال حالا این اومده خورده.

کارشناس: چه قدر خورده؟

مادر بیمار: یکی دوتا قلوپ (کلمه عامیانه جرعه)

کارشناس: الان مشکلی داره؟

مادر: زبون و حلقش می سوزه

کارشناس: بعد از اینکه تینر رو خورد چی شد؟

مادر: اولش نفهمید بعد که دهنش سوخت فهمید که بلافاصله رفت دهنش رو خالی کرد و با آب شست، انگشت کردم تو دهنش همه شو بالا آورد.

کارشناس: الان کجاست؟

مادر: تو دستشوییه

کارشناس: سرفه میکنه؟

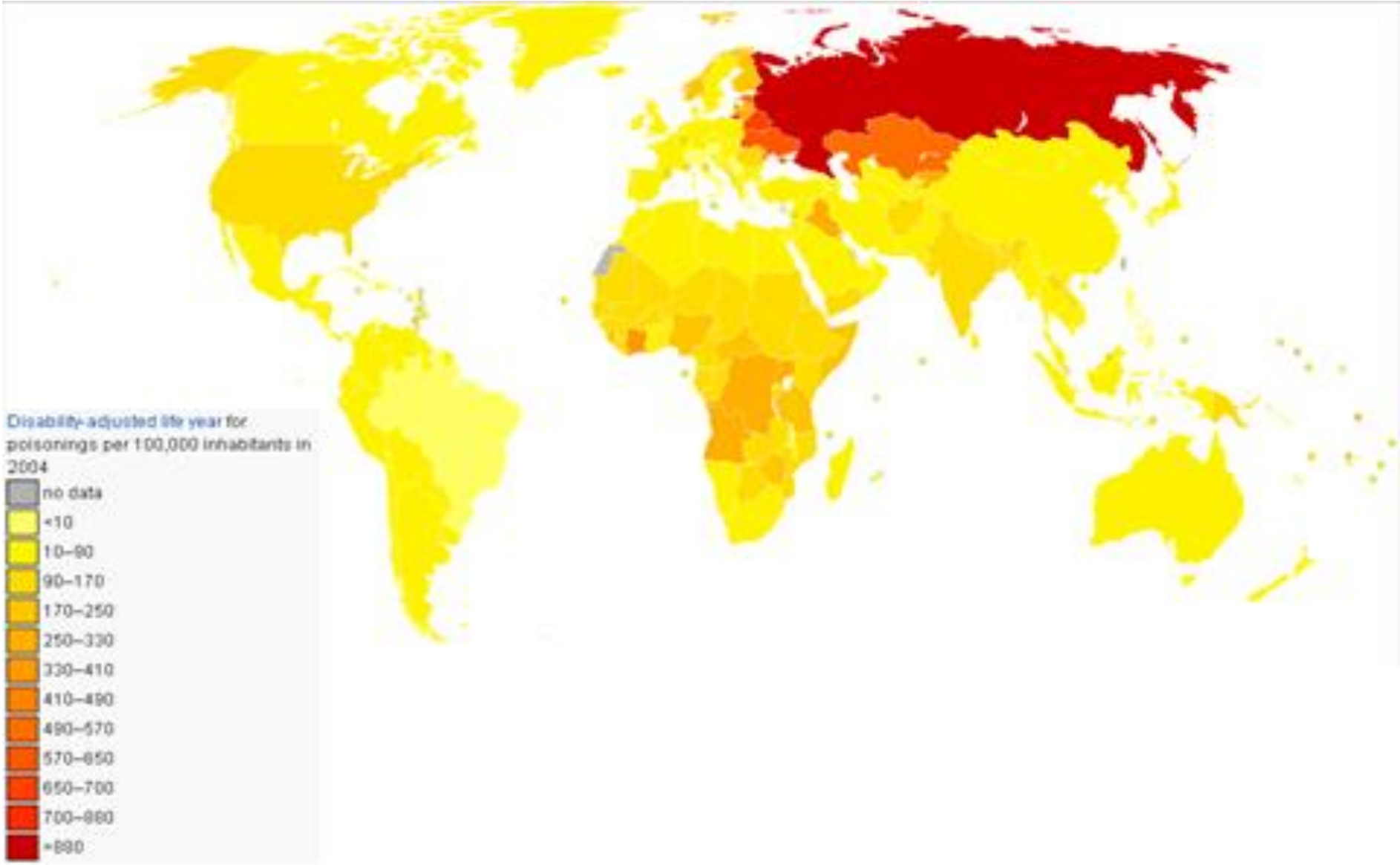
- **مادر:** آره سرفه هم میکنه
- **کارشناس:** چرا اول زنگ نزدی؟ کی گفت انگشت بکنید تو حلقش؟
- **مادر:** چرا؟ چی میشه؟ بخدا اول اومدم زنگ زدم خط اشغال بود آهنگ میزد وصل نشد. منم گفتم حتما سمی قبل از اینکه دیر بشه استفراغ کنه که راحت بشه.
- **کارشناس:** فعلا سریع منتقلش کنید به بیمارستان لقمان بخش مسمومین یا یه بیمارستان تخصصی ریه مثل مسیح دانشوری
- **مادر:** مگه چی میشه؟
- **کارشناس:** فامیل شما چیه؟ یک شماره تماس هم بهم بدید که بتونیم به شما تماس بگیریم. بعد از انتقال حدود نیم ساعت دیگه با شما تماس می‌گیرم و توضیح میدم.
- **مادر:** ۰۹۳۸۹۷۵... ن. ق ممنون
- **کارشناس:** فعلاً خدانگه دار.

Epidemiology

- ~ 250,000 case of poisoning happen in every year in Tehran
- Admitted cases: 51% ♂ & 49% ♀
- 38% of cases were 21-30 years (Ver. 35-54 years in US)
- 79% were intentional \ 21% were unintentional
- 69.13% of acute poisoning were drugs

Epidemiology

- 15.36% Sedative-hypnotics (Ver. 12.9% Analgesic in US)
- 12.34%Opioids (Ver. 11% sedatives & antipsychotics in US)
- 6.21%pesticides esp. organophosphates (Ver. 6.4% antidepressants in US)
- Mortality rate was 1.3%
- Death was mostly occurred by Opioids (41.54%), Drugs (28%) & Pesticides (12%)


Disability-adjusted life year for poisonings per 100,000 inhabitants in 2004
no data
<10
10–90
90–170
170–250
250–330
330–410
410–490
490–570
570–650
650–700
700–860
>880

Definition

- Poisoning (Intentional & Unintentional)
- Overdose or Intoxication (Intentional)
- Substance Abuse: using illicit drugs (e.g. Alcohol's, Narcotics)
- Poison: Are substances that cause disturbances to organisms
- Toxin: Poisons produced by some biological function in nature
- Venom: Toxins that are injected by a bite or sting to cause their effect

Clinical Evaluation

Information to be taken

- Who?
- How Much?
- When?
- Why?
- Medical/Psychiatric History?
- Drug History?
- Interventions Done?
- Present Manifestations?

Common symptom

Bradycardia (PACED)

- Propanolol (β-Blockers)
- Phenylpropanolamine (α-Agonists)
- Anticholinesterase Drugs
- Clonidine
- Ethanol / Alcohols
- Digoxin
- Opiates

Tachycardia (FAST)

- Free Bases (Cocaine/Stimulants)
- Anticholinergics, Antihistamines
- Sympathomimetics
- Theophylline (Methylxanthines)

Hypotension (CRASH)

- Clonidine
- Reserpine (Antihypertensives)
- Antidepressants
- Sedative hypnotics
- Heroin (opiates)

Hypertension (CT SCAN)

- Cocaine
- Theophylline, Thyroid Supplements
- Sympathomimetics
- Caffeine
- Anticholinergics, Amphetamines, Antihistamines
- Nicotine

Hyperthermia (NASA)

- Neuroleptic malignant syndrome
- Antihistamines
- Salicylates, Sympathomimetics, Serotonin syndrome
- Anticholinergics, Antidepressants, Antihistamines

Neuroleptic malignant syndrome (NMS)

Incidence rates for neuroleptic malignant syndrome (NMS) range from 0.02 to 3 percent among patients taking neuroleptic agents

NMS is defined by its association with a class of medications that block dopamine transmission

clinical features: fever, rigidity, mental status changes, and autonomic instabilit

Neuroleptic agents

- NMS is most often seen with the "typical" high potency neuroleptic agents (eg, haloperidol , fluphenazine)
- However, every class of neuroleptic drug has been implicated, including the low potency (eg, chlorpromazine) and the newer "atypical" antipsychotic drugs (eg, clozapine , risperidone , olanzapine)
- as well as antiemetic drugs (eg, metoclopramide , promethazine)

Antiparkinson medication withdrawal

Drugs asso with NMS

Drugs that can cause neuroleptic malignant syndrome

Neuroleptic agents	Antiemetic agents
Aripiprazole	Domperidone
Chlorpromazine	Droperidol
Clozapine	Metoclopromide
Fluphenazine	Prochlorperazine
Haloperidol	Promethazine
Olanzapine	
Paliperidone	
Perphenazine	
Quetiapine	
Risperidone	
Thioridazine	
Ziprasidone	

Laboratory abnormalities

- CK is typically more than 1000 IU/L and can be as high as 100,000 IU/L
- leukocytosis, with a white blood cell count typically 10,000 to 40,000/mm3
- Mild elevations of lactate dehydrogenase, alkaline phosphatase, and liver transaminases are common
- Electrolyte abnormalities - hypocalcemia, hypomagnesemia, hypo and hypernatremia, hyperkalemia, and metabolic acidosis are frequently observed
- A low serum iron concentration

Serotonin syndrome: Rapid overview

To obtain emergent consultation with a medical toxicologist, call the United States Poison Control Network at 1-800-222-1222, or access the World Health Organization's list of international poison centers (www.who.int/gho/phe/chemical_safety/poisons_centres/en/index.html).

Clinical and laboratory features

The Hunter Criteria for serotonin syndrome (SS) are fulfilled if the patient has taken a serotonergic agent and has one of the following:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature above 38°C and ocular clonus or inducible clonus

SS is a clinical diagnosis; no laboratory test can confirm the diagnosis. SS can manifest a wide range of clinical symptoms from mild tremor to life-threatening hyperthermia and shock.

Examination findings can include: hyperthermia, agitation, ocular clonus, tremor, akathisia, deep tendon hyperreflexia, inducible or spontaneous clonus, muscle rigidity, dilated pupils, dry mucus membranes, increased bowel sounds, flushed skin, and diaphoresis. Neuromuscular findings are typically more pronounced in the lower extremities.

The following tests may be helpful in severe cases of SS to narrow the differential and to monitor potential complications:

- Complete blood count, basic electrolytes, creatinine and BUN
- Creatine phosphokinase, hepatic transaminases, coagulation studies
- Blood culture, urinalysis, urine culture
- Chest radiograph
- Head computed tomography, lumbar puncture

Differential diagnosis
Neuroleptic malignant syndrome
Anticholinergic toxicity
Malignant hyperthermia
Sympathomimetic toxicity
Meningitis or encephalitis
Treatment
Discontinue serotonergic agents
Sedate using benzodiazepines (eg, lorazepam 1 to 2 mg IV per dose; 0.02 to 0.04 mg/kg/dose in children): goal is to eliminate agitation, neuromuscular abnormalities (eg, tremor, clonus), and elevations i heart rate and blood pressure; titrate dose to effect
Provide: oxygen (maintain SpO2 ≥94); IV fluids; continuous cardiac monitoring
Anticipate complications; in severe SS vital signs can fluctuate widely and rapidly
If benzodiazepines and supportive care fail to improve agitation and abnormal vital signs, give cyproheptadine (12 mg orally or by orogastric tube for initial adult dose; pediatric doses included in main text
Treat patients with temperature >41.1°C with immediate sedation, paralysis, and endotracheal intubation; treat hyperthermia with standard measures; avoid antipyretics such as acetaminophen

Hypothermia (COOLS)

- Carbon monoxide
- Opiates
- Oral hypoglycemics/Insulin
- Liquor (EtOH)
- Sedative hypnotics

Pupils

Miosis

- Clonidin/Cholinergicse
- Opiates/Organophosphates
- Sedative hypnotics

MydriASis

- Antihistamines
- Antidepressants
- Anticholinergics
- Sympathomimetics

Odors

- Bitter almonds – Cyanide
- Fruity – DKA, Isopropanol
- Rotten Eggs – Sulfur Dioxide, Hydrogen Sulfide
- Garlic – Organophosphates, Arsenic

Sedatives and hypnotics abuse and dependence

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sedative

- lowers excitement and calms the awake patient

hypnotic

- produces drowsiness and promotes sleep

they are categorized into a single class because of their common ability to induce sedation and sleep.
includes benzodiazepines, barbiturates, and various other hypnotics

Barbiturates are now largely limited to induction of anesthesia, while benzodiazepines are widely used for purposes other than sedation, including the treatment of anxiety, insomnia, and epilepsy

benzodiazepines are more specifically anxiolytic. They do not produce surgical anesthesia, coma, or death, even at high doses, except when co-administered with other agents that suppress respiration.

Despite their relative safety, issues related to potential abuse, withdrawal, and side effects of benzodiazepines remain

Clinicians must learn to distinguish between patients who use benzodiazepines safely, even over long periods of time, and patients who use benzodiazepines as part of a pattern of drug or alcohol abuse.

HISTORICAL CONTEXT

— Barbital was introduced into medical practice in 1903, and phenobarbital in 1912. Their rapid success led to the development of over 2,000 derivatives of barbituric acid, with dozens being used in medical practice

The only non-opiate sedatives to precede the barbiturates were the bromides and chloral hydrate, both in widespread use before the end of the nineteenth century.

Benzodiazepines were first recognized in the 1950s for their ability to produce "taming" without apparent sedation in animal experiments. Chlordiazepoxide (Librium), the first benzodiazepine used in clinical practice, was introduced in 1961.

The benzodiazepines were recognized as comparatively problem-free compared to the barbiturates, and rapidly replaced earlier sedatives

Benzodiazepines

- Benzodiazepines exert their principal pharmacodynamic effect via CNS GABA receptors, potentiating the effects of endogenous GABA, the main inhibitory neurotransmitter.

- GABA receptors are membrane-bound proteins divided into three subtypes, GABAA, GABAB, and GABAC receptors.
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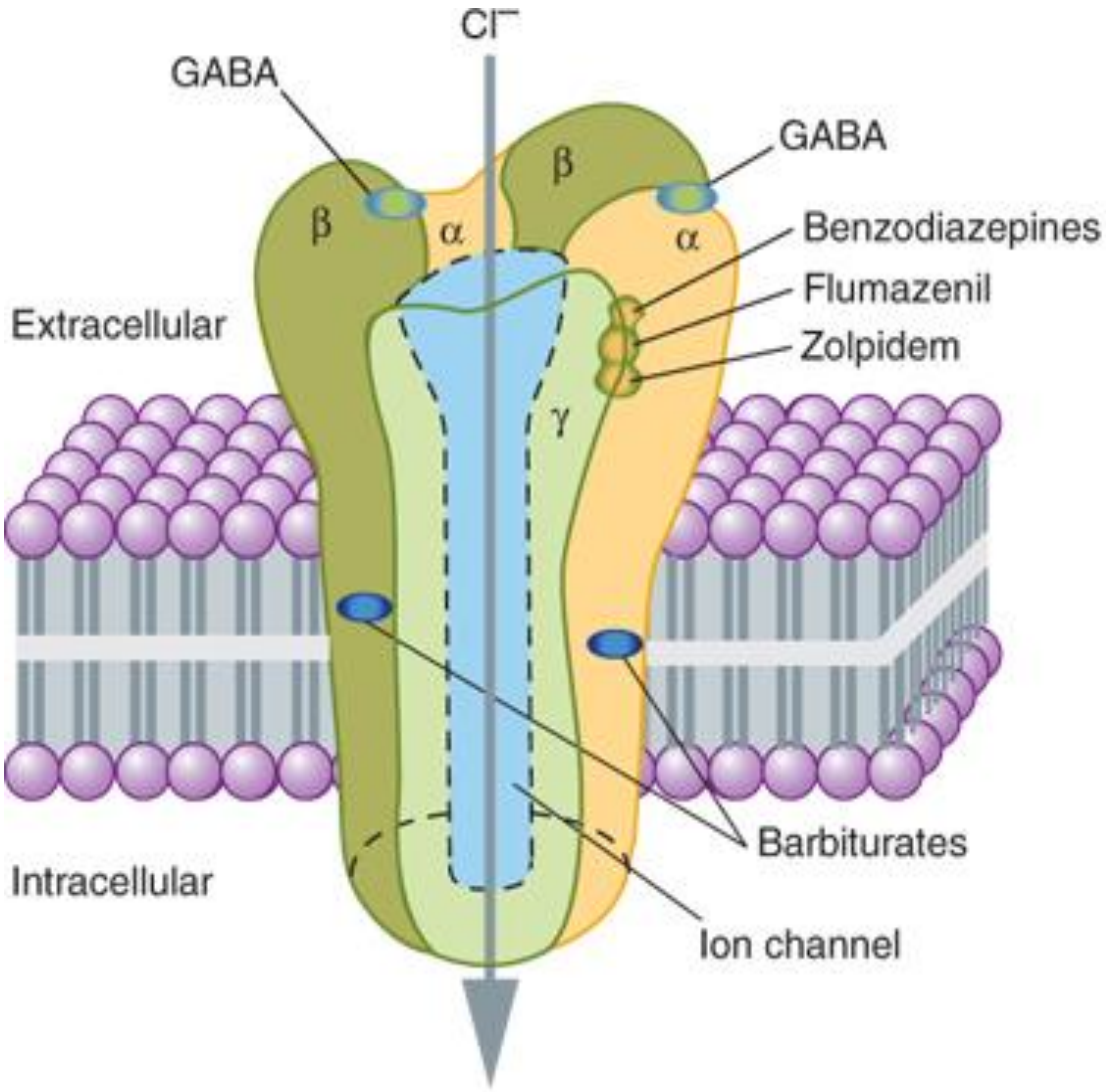
- The GABAA receptors are composed of five subunits that together form the chloride channel, which primarily mediates neuronal excitability (seizures), rapid mood changes, clinical anxiety, and sleep.
- GABAB receptors mediate memory, mood, and analgesia. The role of the GABAC receptors remains unclear
- Flumazenil, a benzodiazepine antagonist, interacts with GABAA receptors and is used clinically to rapidly reverse the effects of benzodiazepine overdoses



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

pharmacologic differences among the benzodiazepines

- rapidity of onset (distributional half-life),
- persistence of active drug and/or metabolite in the body (elimination half-life),
- major metabolic breakdown pathways (conjugation versus oxidation),
- specific molecular structure (eg, alprazolam has a unique triazolo ring that may account for some difference in its clinical effects

Speed of onset

The most important distinction among the benzodiazepines, in the context of abuse potential, is the speed of onset

Drugs that more rapidly reach peak brain levels after oral administration are relatively more likely to produce brain reward or euphoria, and are therefore more likely to be abused.

Benzodiazepines with a slow onset (because they are either slowly absorbed or must be metabolized to produce an active substance) have a relatively lower abuse potential.

Drug	Adult oral dose (mg)*	Comparative potency (mg) •	Onset after oral dose	Metabolism	Elimination half-life (hours) Δ
Used primarily to treat anxiety disorders					
Alprazolam	0.5-4	0.5	Intermediate	Hepatic by CYP3A4 oxidation. One metabolite possesses partial activity.	12-15
Alprazolam extended release ◊	0.5-6 once daily				
Clonazepam	0.5-4	0.25-0.5	Intermediate	Hepatic by CYP3A4 oxidation. No active metabolite.	18-50
Lorazepam	0.5-6 0.5-4 (hypnotic)	1	Intermediate	Hepatic by glucuronidation (rapid). No active metabolite.	10-14
Oxazepam	30-120 15-30 (hypnotic)	15-30	Intermediate	Hepatic by glucuronidation (rapid). No active metabolite.	5-15
Chlordiazepoxide	5-100	10	Intermediate	Hepatic by CYP3A4 oxidation to active metabolites.	30-100
Diazepam	4-40	5	Rapid	Hepatic by CYP2C19 and 3A4 oxidation. Multiple active metabolites.	50-100
Clorazepate	7.5-60	7.5	Rapid	Hepatic by CYP3A4 oxidation to active metabolite. Requires acidity for activation of parent compound.	36-200
Prazepam §	10-60	15	Slow	Hepatic by CYP3A4 oxidation. Multiple active metabolites. Extensive first-pass metabolism.	30-200
Used primarily to treat insomnia ¥					
Triazolam	0.125-0.25	0.1	Rapid	Hepatic by rapid CYP3A4 hydroxylation. No active metabolite.	2-5
Estazolam	1-2	0.3	Intermediate	Hepatic by CYP3A4 oxidation. No active metabolite.	10-24
Temazepam	15-30	5	Intermediate	Hepatic by UGT2B7, 2C19, 3A4 glucuronidation. No active metabolite.	10-40
Flurazepam	15-30	5	Intermediate	Hepatic by CYP3A4 oxidation to active metabolites.	

Diazepam has a relatively rapid onset of action and is therefore among the most effective producers of euphoria.

In contrast, clorazepate with inactive parent compounds, are less likely to be abused.

Oxazepam and the other slower onset benzodiazepines also appear to have relatively low abuse potentials.

Other researchers attribute the greater abuse potential for diazepam , lorazepam , and alprazolam both to their more rapid absorption and penetration of the blood-brain barrier due to greater lipid solubility

new delivery mechanisms

- Alprazolam is now available in an extended release formulation, Xanax XR.
- It has the advantage of slower onset of action, which reduces initial sedation in the hour or two after administration.
- Slower onset of action also lowers the abuse potential of Xanax XR, since it is the rapid onset of action that triggers the brain reward that addicts seek.
- This new formulation of alprazolam permits once-a-day, or at most BID, dosing and reduces the risk of "clock watching", which may be seen with frequent dosing throughout the day.
- Clonazepam has been reformulated into an orally disintegrating tablet for easy administration without swallowing a pill

Benzodiazepines metabolized primarily via conjugation (lorazepam , oxazepam , and temazepam) are cleared largely by the kidneys and are less dependent on liver functioning.

These medications have fewer P450 interactions and are better choices for patients taking multiple medications and for patients with compromised liver function, including alcohol abusers and the elderly

Oxazepam is both a slow-onset and a conjugated benzodiazepine, making it perhaps the best choice for methadone -maintained patients who are treated with a benzodiazepine. Oxazepam has a short elimination half-life, and must be taken three or four times a day for continuous therapeutic effects.

Generic name	Trade name	Usual dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions
Alprazolam	Xanax	0.25-0.5 mg	1-2	6-27	Inactive	Yes
Clonazepam	Klonopin	0.25-0.5mg	1-2	18-50	Inactive	Limited
Chlordiazepoxide	Librium	5-25 mg	0.5-4	5-30	Active	Yes
Clorazepate	Tranxene	7.5-15 mg	1-2	Prodrug	Active	No
Diazepam	Valium	2-10 mg	0.5-1	20-50	Active	Limited
Lorazepam	Ativan	0.5-3 mg	2-4	10-20	Inactive	No
Flurazepam	Dalmane	15-30 mg	0.5-1	2-4	Active	Limited
Flunitrazepam •	Rohypnol	0.5-2 mg	1-2	16-35	Active	Limited
Midazolam	Versed	0.025-0.1 mg	1-2	1.5-3	Active	Yes
Oxazepam	Serax	10-30 mg	2-4	5-20	Inactive	No
Temazepam	Restoril	7.5-30 mg	1-2	3-19	Inactive	No
Triazolam	Halcion	0.125-0.25 mg	0.7-2	2-3	Inactive	Yes
Nonbenzodiazepine hypnotics						
Eszopiclone	Lunesta	1-3 mg	1	6-9	Active (less than parent)	Yes
Ramelteon	Rozerem	8 mg	0.5-1.5	1-2.6	Active (half-life 2-5 hours)	No
Zaleplon	Sonata	5-15 mg	1	1	Inactive	Limited
Zolpidem	Ambien	5-10 mg	1-2	1.5-4.5	Inactive	Limited
Zopiclone •	Immovane, Rhovane	3.75-7.5 mg	5-7	<2	Active (less than parent)	Yes

CLINICAL FEATURES OF OVERDOSE

Oral benzodiazepines (BZD) taken in overdose without a coingestant rarely cause significant toxicity

The classic presentation of a patient with an isolated BZD overdose consists of CNS depression with normal vital signs.

Many patients are arousable and able to provide an adequate history.

Of note, most intentional ingestions of BZDs involve a coingestant, the most common being ethanol.

Patients with a clinically apparent ingestion manifest slurred speech, ataxia, and altered (most commonly depressed) mental status. Respiratory compromise is uncommon with isolated oral ingestions,

but may be seen when patients ingest additional sedative hypnotic agents (such as ethanol) or when clinicians administer BZDs as one of several agents for procedural sedation.

The doses required to produce respiratory compromise are difficult to quantify and depend upon many factors, including tolerance, weight, age, coingestants, and genetics.

Patients with severe toxicity can present stuporous or comatose.

- One observational study found oxazepam to be the least and temazepam the most sedating BZD in intentional overdose

- The authors speculate that this is because temazepam is more rapidly absorbed and oxazepam more slowly absorbed than other BZDs.

- Another observational study found that alprazolam overdose resulted in significantly longer hospital stays, higher ICU admission rates, and a greater need for mechanical ventilation and the use of reversal agents (ie, flumazenil

Propylene glycol poisoning

Propylene glycol is the diluent used in parenteral formulations of diazepam and lorazepam and the cause of a unique complication related to the prolonged parenteral administration of these BZDs.

The potential effects of PG toxicity include skin and soft tissue necrosis (from extravasation), hemolysis, cardiac dysrhythmias, hypotension, lactic acidosis, seizure, coma, and multisystem organ failure.

PG toxicity is rare but may be considered when patients receiving large or continuous infusions of parenteral BZDs (eg, mechanical ventilation, severe sedative hypnotic or ethanol withdrawal syndromes, undifferentiated agitated delirium, management of chloroquine overdose) develop an anion gap metabolic acidosis.

The osmolal gap correlates with PG concentrations and can be used as a surrogate marker of PG toxicity

DIFFERENTIAL DIAGNOSIS

Altered mental status, a common finding in BZD overdose, is found in a wide range of medical and toxicologic conditions

BZD overdose is usually suspected on the basis of history and the clinical scenario. Any number of sedative-hypnotic medications share clinical features with BZDs in overdose, including ethanol, barbiturates, gamma hydroxybutyrate (GHB), and chloral hydrate

Common causes of delirium and confusional states

Drugs and toxins
Prescription medications (eg, opioids, sedative-hypnotics, antipsychotics, lithium, skeletal muscle relaxers, polyph
Non-prescription medications (eg, antihistamines)
Drugs of abuse (eg, ethanol, heroin, hallucinogens, nonmedicinal use of prescription medications)
Withdrawal states (eg, ethanol, benzodiazepines)
Medication side effects (eg, hyperammonemia from valproic acid, confusion from quinolones, serotonin syndrome)
Poisons:
Atypical alcohols (ethylene glycol, methanol)
Inhaled toxins (carbon monoxide, cyanide, hydrogen sulfide)
Plant-derived (eg, Jimson weed, Salvia)
Infections
Sepsis
Systemic infections; fever-related delirium
Metabolic derangements
Electrolyte disturbance (elevated or depressed): sodium, calcium, magnesium, phosphate
Endocrine disturbance (depressed or increased): thyroid, parathyroid, pancreas, pituitary, adrenal
Hypercarbia
Hyperglycemia and hypoglycemia
Hyperosmolar and hypoosmolar states
Hypoxemia
Inborn errors of metabolism: porphyria, Wilson's disease, etc

Brain disorders
CNS infections: encephalitis, meningitis, brain or epidural abscess
Epileptic seizures, especially nonconvulsive status epilepticus*
Head injury*
Hypertensive encephalopathy
Psychiatric disorders*
Systemic organ failure
Cardiac failure
Hematologic: thrombocytosis, hypereosinophilia, leukemic blast cell crisis, polycythemia
Liver failure: acute, chronic
Pulmonary disease, including hypercarbia and hypoxemia
Renal failure: acute, chronic
Physical disorders
Burns
Electrocution
Hyperthermia
Hypothermia
Trauma: with systemic inflammatory response syndrome, *head injury, fat embolism

Disorders that, while not truly systemic or "medical", may produce the clinical picture of delirium or confusional state in

Drugs believed to cause or prolong delirium or confusional states*

Analgesics
Nonsteroidal anti-inflammatory agents
Opioids (especially meperidine)
Antibiotics and antivirals
Acyclovir
Aminoglycosides
Amphotericin B
Antimalarials
Cephalosporins
Cycloserine
Fluoroquinolones
Isoniazid
Interferon
Linezolid
Macrolides
Metronidazole
Nalidixic acid
Penicillins
Rifampin
Sulfonamides

Corticosteroids
Dopamine agonists
Amantadine
Bromocriptine
Levodopa
Pergolide
Pramipexole
Ropinirole
Gastrointestinal agents
Antiemetics
Antispasmodics
Histamine-2 receptor blockers
Loperamide
Herbal preparations
Atropa belladonna extract
Henbane
Mandrake
Jimson weed
St. John's Wort
Valerian

Anticholinergics
Atropine
Benztropine
Diphenhydramine
Scopolamine
Trihexyphenidyl
Anticonvulsants
Carbamazepine
Levetiracetam
Phenytoin
Valproate
Vigabatrin
Antidepressants
Mirtazapine
Selective serotonin reuptake inhibitors
Tricyclic antidepressants
Cardiovascular and hypertension drugs
Antiarrhythmics
Beta blockers

Hypoglycemics
Hypnotics and sedatives
Barbiturates
Benzodiazepines
Muscle relaxants
Baclofen
Cyclobenzaprine
Other CNS-active agents
Disulfiram
Cholinesterase inhibitors (eg, donepezil)
Interleukin-2
Lithium
Phenothiazines

The sedative hypnotic toxidrome

depressed mental status, an unremarkable physical examination, and normal vital signs, hence the common description "coma with normal vitals.

" Ethanol and phenobarbital intoxication can be ruled out by obtaining serum concentrations.

Other life-threatening causes of depressed mental status must be considered in the differential diagnosis, including hypoglycemia and carbon monoxide exposure.

Stroke, meningitis and encephalitis, and head trauma can present with altered mental status and should be investigated as clinically indicated.

An isolated overdose with oral BZDs rarely causes profound respiratory depression requiring invasive airway management or cardiopulmonary instability.

In such cases, the presence of coingestants should be investigated.

LABORATORY EVALUATION

Benzodiazepines (BZDs) are themselves NOT detected in standard urine screening tests for drugs of abuse.

However, the most common BZD urine test identifies metabolites of 1,4-benzodiazepines, such as oxazepam .

This test may not detect clonazepam , lorazepam , midazolam , or alprazolam .

A number of factors, such as the amount of drug ingested, the presence of coingestants, and patient age and weight, can alter pharmacokinetics and affect urine drug tests.

In general, BZD metabolites can be detected as early as three hours after ingestion and may remain detectable for up to two weeks

Serum BZD concentrations are not routinely available in the emergency setting, correlate poorly with clinical findings, and do not aid management.

General diagnostic testing

Fingerstick glucose	• o rule out hypoglycemia as the cause of any alteration in mental status
Acetaminophen and salicylate levels	• to rule out these common coingestions
(ECG	• to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals
Pregnancy test	
serum ethanol concentration	

- Clinicians should obtain additional tests based upon clinical findings.
- As examples, altered mental status in association with fever raises concern for meningitis or other infections and warrants a thorough evaluation, including assessment of the cerebral spinal fluid.
- A head computed tomography scan should be obtained if there is external evidence or concern for head trauma.

MANAGEMENT

Initial treatment

- rapid assessment of the patient's airway, breathing, and circulation.
- Endotracheal intubation should not be delayed if needed.
- Oxygen is administered, intravenous access
- established, and continuous cardiac monitoring employed.
- A fingerstick serum glucose is immediately obtained.
- n cases of isolated BZD overdose, a history, physical examination (with particular attention paid to signs of respiratory dysfunction, trauma, and poisoning from coingestants), and regular monitoring are likely to be all that is necessary.

Decontamination

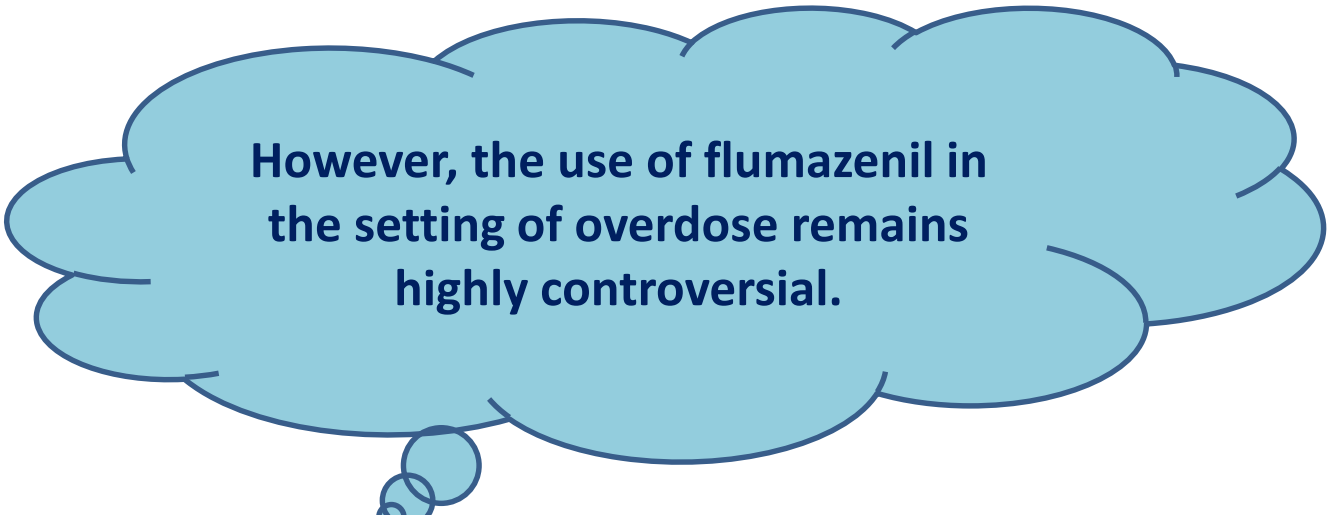
activated charcoal (AC) is usually of NO benefit in cases of isolated BZD ingestion and increases the risk of aspiration.

NOT be treated with AC, unless a life-threatening coingestant amenable to treatment with charcoal is suspected and the patient's airway is protected (naturally or with a tracheal tube).

Whole bowel irrigation is generally unnecessary because of the rarity of sustained release preparations

Antidote (flumazenil)

- Flumazenil is a nonspecific competitive antagonist of the BZD receptor.
- It can be used to reverse BZD-induced sedation following general anesthesia, procedural sedation, or overdose



Administration of flumazenil can precipitate withdrawal seizures in patients who have developed a tolerance to BZDs through chronic use or abuse.

Such risks may be further increased if the patient has taken coingestants with proconvulsant properties

Of note, flumazenil does NOT consistently reverse respiratory depression caused by BZD overdose

Because oral BZD overdose has a low rate of morbidity and mortality is rare, the risks of flumazenil treatment often outweigh its benefits.

- Flumazenil appears to be safe and effective when used to reverse the sedating effects of a BZD given for procedural sedation in patients who do not use BZDs chronically.

- In adults, the recommended initial dose is 0.2 mg given intravenously (IV) over 30 seconds.
- Repeated doses of 0.2 mg, to a maximum dose of 1 mg, can be given until the desired effect is achieved
- The peak effect of a single flumazenil dose occurs approximately 6 to 10 minutes after IV administration. For patients at greater risk of seizure or agitation with BZD reversal, a longer wait of several minutes between subsequent doses may be warranted.

- The duration of flumazenil is short (0.7 to 1.3 hours) and the duration of effect of a long-acting BZD or a large BZD dose can exceed that of flumazenil.

WITHDRAWAL

Any abrupt or overly rapid reduction in benzodiazepine (BZD) dose among chronic users can produce withdrawal.

Rapid recognition and treatment of BZD withdrawal is crucial because the syndrome can be life-threatening.

The symptoms and signs of BZD withdrawal can include tremors, anxiety, perceptual disturbances, dysphoria, psychosis, and seizures

Chronic ingestion of BZDs leads to conformational changes in the GABA receptor, which ultimately reduce the receptor's affinity for the agent and result in decreased GABA activity

This decreased activity manifests as tolerance to the agent.

When BZDs are no longer present or present at lower concentrations, this decreased GABA receptor activity has less inhibition of excitatory neurotransmitters, and thus, there is a pro-excitatory state.

- The onset of withdrawal varies according to the half-life of the BZD involved. Symptoms may be delayed up to three weeks in BZDs with long half-lives, but may appear as early as 24 to 48 hours after cessation of BZDs with short half-lives. The severity and duration of withdrawal is determined by many factors, including the period of BZD use, how rapidly use was tapered (if at all), and possibly patient genetics

- Withdrawal can usually be avoided or minimized through the use of BZDs with a long half-life, such as diazepam or chlordiazepoxide , and a gradual tapering of the patient's BZD dose over several months, depending upon the dosage and degree of dependency

Persistence

Persistence of a benzodiazepine (or an active metabolite) in the body governs the tempo of withdrawal onset in patients who have used benzodiazepines everyday for prolonged periods.

Benzodiazepines with shorter elimination half-lives are more likely to produce acute withdrawal on abrupt cessation after prolonged use.

In contrast, those with longer elimination half-lives usually produce more delayed and somewhat attenuated withdrawal symptoms.

In general, alprazolam , lorazepam , and oxazepam are more rapidly eliminated than are clorazepate , diazepam , flurazepam , and prazepam.

Clonazepam has a longer elimination half-life than alprazolam or lorazepam, so it is more appealing as a therapeutic agent in the treatment of withdrawal.

Abrupt discontinuation is not appropriate for benzodiazepine discontinuation after prolonged daily use, especially when high doses are used.

Short-acting benzodiazepines, when withdrawn gradually over several weeks or longer, do not produce more withdrawal symptoms than longer acting benzodiazepines

Short acting

- half-life of less than 12 hours
- triazolam oxazepam midazolam
- generally have few active metabolites, do not accumulate with repeated doses, and demonstrate clearance that is largely unaffected by age and liver disease
- Although midazolam possesses a short half-life, it has active metabolites that can accumulate with repeated dosing

Intermediate

- half-life between 12 and 24 hours
- lorazepam temazepam

Long

- half-life greater than 24 hours
- generally have pharmacologically active metabolites, accumulate in tissues after multiple doses, and demonstrate impaired clearance in older patients and those with liver disease
- diazepam chlordiazepoxide

Reinforcement

Reinforcement is the potential for medicines to be abused or "liked" by alcoholics and drug abusers. In controlled studies, benzodiazepines are not reinforcing or "liked" by subjects without a prior history of abuse of alcohol or other drugs

For example, normal and anxious subjects, given a choice between placebo and benzodiazepines, more often choose the placebo in double-blind acute dose experiments, regardless of the specific benzodiazepine given

In contrast, subjects with a history of addiction in double-blind studies prefer benzodiazepines, especially at high doses, to placebo.

Even for subjects with a history of substance abuse, the benzodiazepines are relatively weak reinforcers compared to other drugs

. People with a history of addiction show a greater preference for intermediate-acting barbiturates and stimulants, as well as narcotics, than for benzodiazepines [

This research confirms the common clinical observation that benzodiazepines are rarely drugs of choice for their euphoric effects among addicted people

Nevertheless, physicians working with patients addicted to alcohol and other drugs do commonly see patients who abuse benzodiazepines, and some of these patients use benzodiazepines as their primary drug of abuse

Withdrawal

- All medicines that influence the GABA system show cross-tolerance and similar withdrawal patterns.
- The sedative/hypnotics withdrawal syndrome includes the potential for withdrawal seizures and status epilepticus on abrupt discontinuation.
- These medications are potent antiepileptics that raise the seizure threshold. When abruptly discontinued, they produce a rebound drop in the seizure threshold that may cause seizures even in patients without a history of prior seizures.

Other symptoms of withdrawal include:

- Increased body temperature
- Elevated blood pressure
- Increased respiratory rate and heart rate
- Aroused level of consciousness or frank delirium
- Increased reflexes
- Disorientation
- Psychotic behavior including hallucinations.

Tolerance

- Tolerance develops rapidly, and is all but complete to the sedative and euphoric effects of the benzodiazepines on repeated oral administration at a steady dose for even a few days.
- The rapid development of tolerance for both sedation and euphoria/reward is seen clinically when these medicines are used to treat anxiety.
- Initial sedation or drowsiness often disappears within a few days of steady dosing.
- Tolerance to the anxiolytic effects of benzodiazepines, in contrast, is practically nonexistent.
- Non-addicted medical patients who use a benzodiazepine to treat chronic anxiety obtain beneficial effects at constant, standard, low doses.

Treatment

- BZD withdrawal is treated with a BZD that has a prolonged clinical effect, such as diazepam , given intravenously and titrated to effect.
- The goal is to eliminate withdrawal symptoms without causing excessive sedation or respiratory depression.
- Once symptoms are controlled, the BZD dose should then be tapered gradually over a period of months
- number of medications have been used to treat BZD withdrawal, but none has been found to be as effective as BZDs
- Beta blockers, antipsychotics, selective serotonin reuptake inhibitors, and antihistamines have all been shown to be inferior to standard treatment

Generic name	Trade name	Usual dose (oral)	Oral peak (hours)	Half-life (hours) parent	Metabolite activity*	CYP3A4 interactions
Alprazolam	Xanax	0.25-0.5 mg	1-2	6-27	Inactive	Yes
Clonazepam	Klonopin	0.25-0.5mg	1-2	18-50	Inactive	Limited
Chlordiazepoxide	Librium	5-25 mg	0.5-4	5-30	Active	Yes
Clorazepate	Tranxene	7.5-15 mg	1-2	Prodrug	Active	No
Diazepam	Valium	2-10 mg	0.5-1	20-50	Active	Limited
Lorazepam	Ativan	0.5-3 mg	2-4	10-20	Inactive	No
Flurazepam	Dalmane	15-30 mg	0.5-1	2-4	Active	Limited
Flunitrazepam •	Rohypnol	0.5-2 mg	1-2	16-35	Active	Limited
Midazolam	Versed	0.025-0.1 mg	1-2	1.5-3	Active	Yes
Oxazepam	Serax	10-30 mg	2-4	5-20	Inactive	No
Temazepam	Restoril	7.5-30 mg	1-2	3-19	Inactive	No
Triazolam	Halcion	0.125-0.25 mg	0.7-2	2-3	Inactive	Yes
Nonbenzodiazepine hypnotics						
Eszopiclone	Lunesta	1-3 mg	1	6-9	Active (less than parent)	Yes
Ramelteon	Rozerem	8 mg	0.5-1.5	1-2.6	Active (half-life 2-5 hours)	No
Zaleplon	Sonata	5-15 mg	1	1	Inactive	Limited
Zolpidem	Ambien	5-10 mg	1-2	1.5-4.5	Inactive	Limited
Zopiclone •	Immovane, Rhovane	3.75-7.5 mg	5-7	<2	Active (less than parent)	Yes