Sedative, Hypnotic, Anxiolytic Related Disorder

Introduction

Sedative-hypnotic agents are classified in this section as follows:

- (1) Benzodiazepines and functionally related drugs.
- (2) Barbiturates.
- (3) Miscellaneous sedative-hypnotic drugs.
- Anxiolytic drugs cover a wide spectrum of pharmacological agents, and the terminology implies more specificity than actually exists.
- The broad group of drugs that historically has been included in that class exhibits considerable variation in clinical use, toxicity, risk for addiction, and potential for diversion and misuse.

CLASSIFICATION

- Short acting (< 5hr) = Midazolam , Triazolam
- Intermediate acting (5-24hr) = Alprazolam, Clonazepam, Oxazepam, Lorazepam
- Long acting (24hr) = Chlordiazepoxide, diazepam

Etiology & Neuropharmacology

- Their primary effects on the γ-aminobutyric acid type A ($GABA_A$) receptor complex.
- Neuroadaptive changes that occur with prolonged drug exposure affect not only the $GABA_A$ receptor but other neurotransmitters, the hypothalamic pituitary axis, and calcium modulated systems.
- GABA is the major inhibitory neurotransmitter in the brain.
- GABA type A receptors are a family of ligand-gated ion channels responsible for inhibitory regulation of the CNS.

Etiology & Neuropharmacology

- Chronic exposure to benzodiazepines leads to alterations of GABAergic neurotransmission, which are manifested as the symptoms of tolerance, dependence & withdrawal.

- The mechanism of these changes is unclear.

- May involve alterations in the expression of individual $GABA_A$ receptor subtypes, but is known to be linked to the dose and duration of benzodiazepine use.

- While the direct effects of benzodiazepines are GABA-related, the withdrawal syndrome may be in part be mediated by **calcium channel** and **glutamatergic mechanisms**.

Etiology & Neuropharmacology

- In neuroendocrine pathways, including regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis, may be involved in the mechanism of benzodiazepine dependence.
- Agonists that interact with the benzodiazepine receptor produce alterations in the structure of the $GABA_A$ receptors, which can enhance the affinity of these receptors for GABA and direct receptor agonists, and are often referred to as positive modulators, to differentiate them from direct agonists, such as GABA and muscimol.
- The benzodiazepine-induced allosteric changes in the $GABA_A$ receptor complex result in an increase in the frequency of opening of the chloride channel located in the centre of $GABA_A$ receptor complex.

Etiology & Neuropharmacology

- Barbiturates share some similarity in their actions with those of benzodiazepines.

- At low concentrations, barbiturates act at a receptor site other than the GABA binding site on the $GABA_A$ receptor complex to positively modulate the actions of GABA via an allosteric mechanism.
- At higher concentrations barbiturates act as $GABA_A$ receptor agonists, directly increasing the activity of these receptors.

- $GABA_A$ receptors that contain the β2 or β3 subunit show greater sensitivity to the effects of pentobarbital than receptors with the β1 subunit.

Etiology & Neuropharmacology

- Barbiturates also may have actions on neurons that involve mechanisms other than inhibition of the $GABA_A$ receptor activity.
- At least in the hippocampus, pentobarbital may inhibit the activity of Dl-α-amino-3- hydroxy-5-methylisoxazole-4-propionic acid (**AMPA**) receptors.
- These receptors are involved in the mediation of some of the effects of excitatory neurotransmitter glutamate.
- Barbiturates also may inhibit the release of neurotransmitters by blocking voltage-sensitive calcium channels.

Etiology & Neuropharmacology

- Diazepam and other classical benzodiazepines appear to bind with equal affinity to benzodiazepine-sensitive receptors with different subunit composition.

Misuse liability

- Rates of benzodiazepines misuse by pts dependent on alcohol or other drugs may be higher than individuals with anxiety or insomnia without a h/o of substance use problems.
- Long-term use is high among pts with psychiatric d/o & the elderly.
- One approach to assessing misuse liability is by measuring the reinforcing properties of the drug.
- If its pharmacological effects increase behavior (i.e., self-administration of a dose or the work required to permit self-administration), then the drug is a positive reinforcer and has abuse liability.

Misuse liability

- Animal and human studies have assessed the reinforcing properties of BDZs.

Animal studies

- Animal studies have demonstrated that a withdrawal syndrome occurs on abrupt discontinuation of benzodiazepines and related sedative hypnotics.
- The animal models using the social interaction test and social conflict paradigms, along with isolation-induced ultrasonic vocalizations recordings, indicate that abrupt discontinuation of benzodiazepine tranquilizers may induce numerous anxiogenic responses, including decreased social interaction and increased aggressive behaviors.
- Studies shows that use of a competitive benzodiazepine receptor antagonist, such as flumazenil, to precipitate withdrawal, have also demonstrated the development of a withdrawal syndrome using electrophysiological measures.

Survey of medical use in clinical population

A survey of unsupervised changes in dosage indicated –

- 12% of pts had decreased their anxiolytic dosage
- 6 % had increased it.
- 9 % of pts taking hypnotics decreased their dosage
- 8 % increased it.

Survey of medical use in clinical population

- Surveys of psychiatric patients have demonstrated high rates of benzodiazepine prescription but almost uniformly low rates of misuse.
- In one study of 2,719 outpatients, none of the 178 pts who had received benzodiazepines was diagnosed with a sedative-hypnotic use disorder.
- Studies of psychiatric inpatients suggest that the rate of BUDs ranges from 0.4 to 13.0 % of admissions.

Survey of special clinical population

- Substantial evidence indicates that patients who abuse benzodiazepines frequently have a h/o of misusing other drugs.

- Results from the TEDS, which compiles national information about individuals admitted to publicly funded programs, indicate that benzodiazepines are rarely the primary drug of abuse.

- The number of substance abuse t/t admissions reporting both benzodiazepine and narcotic pain reliever misuse increased 569.7 % from 5,032 admissions in 2000 to 33,701 admissions in 2010, while the number of all other admissions decreased by 9.6 % during the same period.

Survey of special clinical population

- The concurrent use of opioids and benzodiazepines is ubiquitous around the world.
- There were no buprenorphine–benzodiazepine deaths, while exposure to methadone–benzodiazepine resulted in 16 deaths.
- The data suggest that nonmedical use of benzodiazepines with methadone is associated with higher morbidity and mortality as compared to nonmedical use of benzodiazepines with buprenorphine.

Survey of special clinical population

- BUD is a serious clinical problem in the methadone maintenance t/t population.

- Estimates of the prevalence of BUDs among methadone maintenance t/t pts range from 21 % - 66 %, with roughly 1/2 of pts starting benzodiazepine use after entering methadone maintenance t/t.

Pattern of abuse

ORAL :

Occasional use pattern:

- Young persons who take it for specific effects like relaxation for an evening, intensification of sexual activities and a short lived mild euphoria

Regular use pattern:

- Middle aged, middle class who usually obtain the substance from the family physician as a prescription for insomnia or anxiety
- Have prescriptions from several physicians and the pattern of abuse may go undetected until obvious signs of withdrawal or dependence are noticed by family members or co workers

Pattern of abuse

INTRAVENOUS USE:

- Severe form
- Young adults
- HIV, cellulitis, vascular complications, infections, allergic reactions
- Rapid and profound tolerance, dependence and a severe withdrawal syndrome

ACUTE INTOXICATION

ICD-10 RESEARCH CRITERIA	DSM-5
A. General criterion of acute intoxication must be met.	Recent use of sedative hypnotic, Anxiolytic
B. There is dysfunctional behavior as evidence by at least **one** of the following: 1. Euphoria and disinhibition: 2. Apathy and sedation 3. Abusiveness or aggression 4. Lability of mood 5. Impaired attention 6. Anterograde amnesia 7. Impaired psychomotor performance 8. Interference with personal functioning.	Clinically significant maladaptive behavioral or psychological changes (e.g. inappropriate sexual or aggressive behavior, mood lability, impaired judgement, impaired social or occupational functioning) that developed during or shortly after sedative & hypnotic or anxiolytic use.

C. At least one of the following signs must be present- **1. Unsteady gait** **2. Difficulty in standing** **3. Slurred speech** **4. Nystagmus** **5. Decreased level of consciousness** **6. Erythematous skin lesions or blisters.**	**One (or more) of the following sign, developing during or shortly after sedative, hypnotic or anxiolytic use;** **1. Slurred speech** **2. Incoordination** **3. Unsteady gait** **4. Nystagmus** **5. Impairment in attention or memory** **6. Stupor or coma**
	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

WITHDRAWAL STATE

ICD-10 RESEARCH CRITERIA	DSM-5
A. General criterion for withdrawal must be met.	Cessation of (or reduction in) sedative -hypnotic or anxiolytic use that has been heavy and prolonged.
B. Any three of the following signs must be present: 1. Tremors of the tongue, eyelids or outstretched hands 2. Nausea or vomiting. 3. Tachycardia 4. Postural hypotension 5. Grand mal convulsions 6. Headache 7. Insomnia 8. Malaise or weakness 9. Transient visual, tactile or auditory hallucination or illusions. 10. Paranoid ideation 11 . Psychomotor agitation	Two (or more) of the following developing within several hours to a few days after criterion A : 1. Autonomic hyperactivity (eg. sweating or a pulse rate greater than 100 beats/min. 2. Increased hand tremors 3. Nausea or vomiting 4. Insomnia 5. Transient visual, tactile or auditory hallucinations or illusions 6. Psychomotor agitation 7. Anxiety 8. Grand mal seizures

ICD-10 RESEARCH CRITERIA	DSM-5
	The symptoms in criteria B cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
	The symptoms are not due to general medical condition and are not better accounted by another mental illness. Specify if: **Any perceptual disturbances**

Benzodiazepines

- Benzodiazepines have become the primary drugs used to treat anxiety and insomnia, largely replacing barbiturates and other sedative-hypnotic agents.
- Zolpidem, an hypnotic drug, is chemically distinct from the benzodiazepines but has similar clinical effects and acts at the $GABA_A1$ benzodiazepine receptor complex.
- At present it has the largest market share of hypnotic prescriptions in the United States; other hypnotics acting at the$GABA_{A1}$ receptor, such as zaleplon and eszopiclone, also have effects very much like classical benzodiazepines.
- The benzodiazepines have lower abuse liability than most barbiturates, pose a much lower risk when taken in overdose, and have fewer interactions with other drugs.
- The advantages of the benzodiazepines must be weighed against the risk of abuse and physiological dependence.

Intoxication

- It can be associated with behavioral disinhibition, potentially resulting in hostile or aggressive behaviour.
- The effect is perhaps most common when benzodiazepines are taken in combination with alcohol.
- Benzodiazepine intoxication is associated with less respiratory depression than barbiturate intoxication.

Withdrawal syndrome

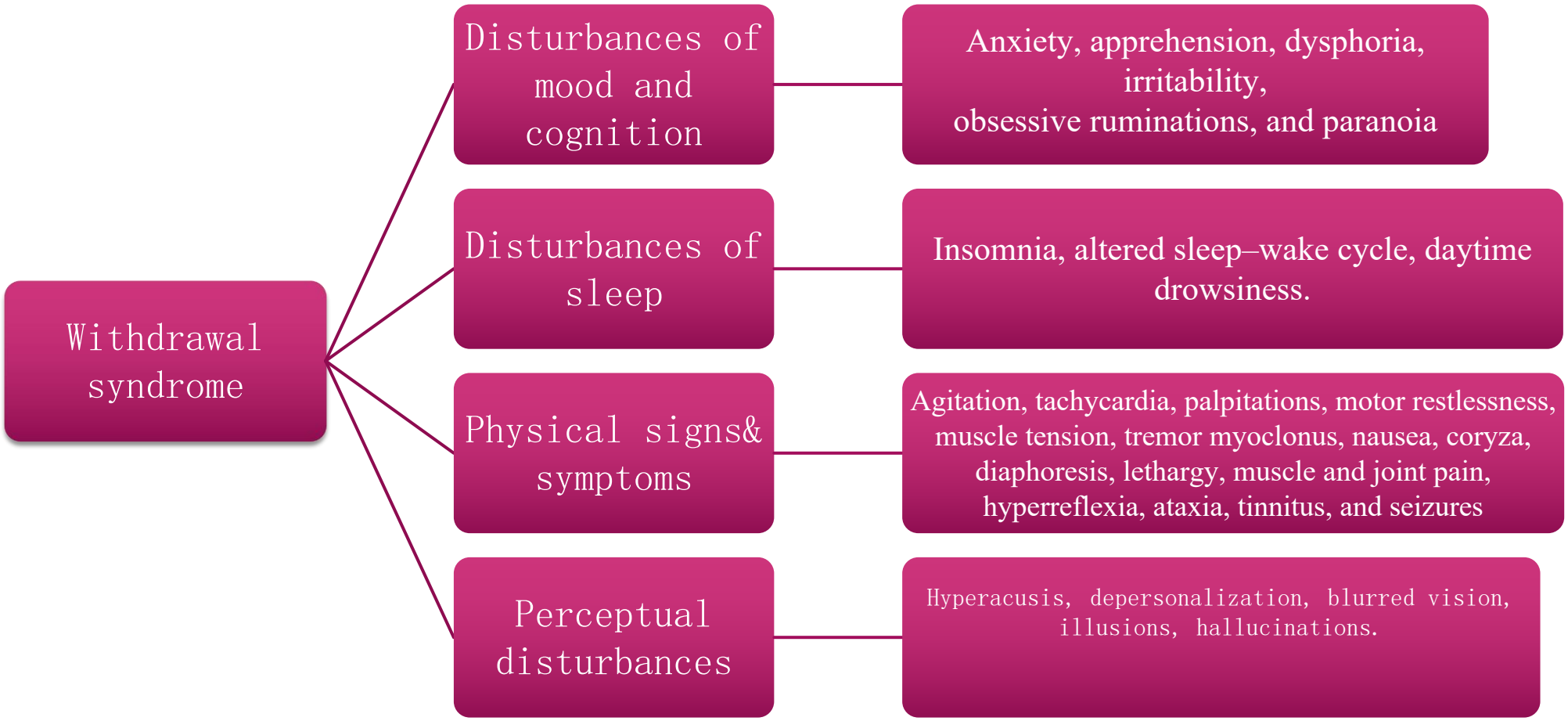
Sign and symptoms:-

- Abrupt discontinuation of high doses of chlordiazepoxide or diazepam could lead to a withdrawal syndrome.
- More recent studies show that therapeutic doses given for weeks to months may also be associated with withdrawal syndrome.
- The discontinuance syndrome may also be divided into symptoms of **rebound, recurrence, and withdrawal.**

Withdrawal syndrome

- *Rebound symptoms* are those for which the benzodiazepine was originally prescribed that return in a more severe form than they had before t/t.
- They have a rapid onset after termination of therapy and a brief duration.
- *Recurrence* refers to return of the original symptoms at or below their original intensity.
- The pattern and course of these symptoms reflect the anxiety disorder for which treatment was originally instituted.

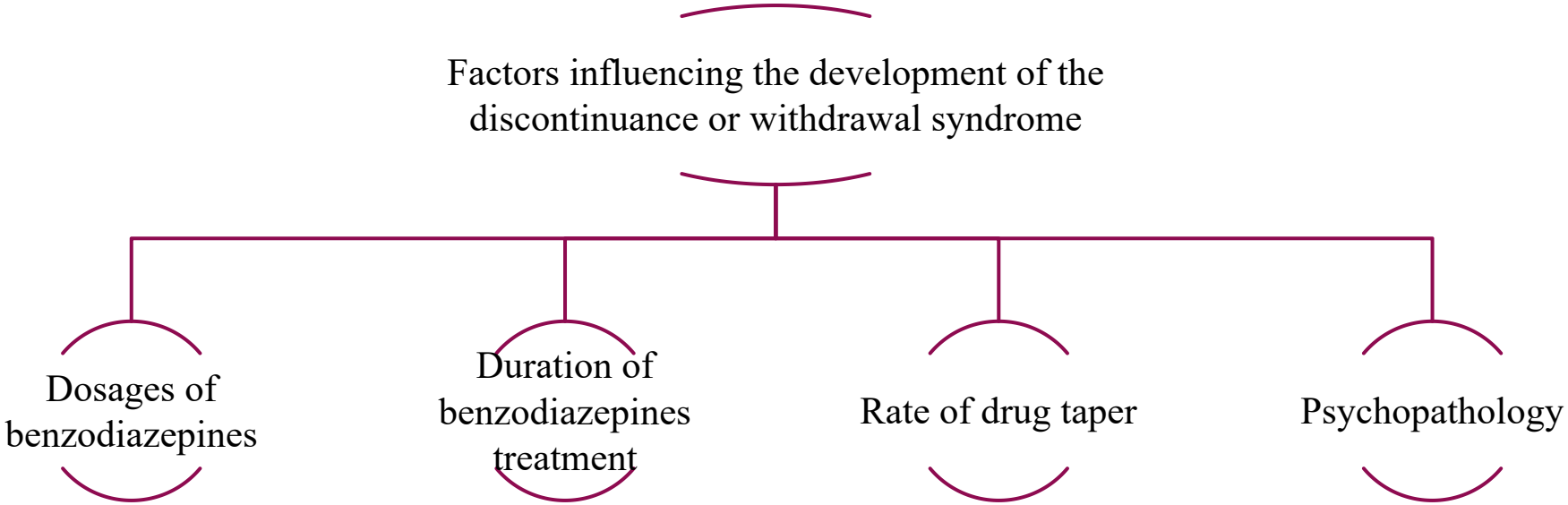
Withdrawal syndrome



Withdrawal syndrome

- The temporal sequence of symptom development is not well established.
- On the abrupt cessation of benzodiazepines with short elimination half-lives, symptoms may appear within 24 hours and peak at 48 hours.
- Symptoms arising from abrupt discontinuance of benzodiazepines with long half-lives may not peak until 2 weeks later.

Risk factors



- According to one study, withdrawal symptoms are related to t/t duration when the length of the t/t is < 8 months but not when it is 1 year or longer.
- Mild withdrawal symptoms may occur with abrupt discontinuation of therapeutic doses after 4 weeks of benzodiazepine t/t.
- There is a risk of rebound insomnia after a few days to 1 week of t/t with benzodiazepine hypnotic drugs with short elimination half-lives.
- Benzodiazepine hypnotics with longer elimination half-lives are less likely to induce rebound insomnia on abrupt discontinuation.

Overdose

- The benzodiazepines have a large margin of safety when taken in overdoses than barbiturates and the barbiturate-like substances.
- The ratio of lethal to effective dose is approximately 200 to 1 or higher because of the minimal respiratory depression associated with the benzodiazepines.
- When grossly excessive amounts (more than 2 g) are taken in suicide attempts, the symptoms include only drowsiness, lethargy, ataxia, some confusion, and mild depression of the user's vital signs.

Overdose

- A serious condition prevails when benzodiazepines are taken in overdose in combination with other sedative-hypnotic substances, such as alcohol.

- In such cases, small doses of benzodiazepines can cause death.

Barbiturates

- Phenobarbital is still prescribed as an anticonvulsant and as a sedative, especially for children.
- It is also a common component of many combination products and reduces the stimulating effects of sympathomimetic agents.
- Butalbital is an intermediate-acting barbiturate found in a widely used combination product that also contains acetaminophen and caffeine and is approved for the treatment of muscle contraction headaches.
- A major disadvantage of the use of the barbiturates is the development of pharmacokinetic and pharmacodynamic tolerance.

Intoxication

- When barbiturates and barbiturate-like substances are taken in relatively low doses, the clinical syndrome of intoxication is indistinguishable from that associated with alcohol intoxication.
- Symptoms include **sluggishness, incoordination, difficulty in thinking, poor memory, slowness of speech and comprehension, faulty judgment, disinhibition of sexual and aggressive impulses, a narrowed range of attention, emotional lability, and exaggeration of basic personality traits**.
- The sluggishness usually resolves after a few hours, but the impaired judgment, distorted mood, and impaired motor skills may remain for **12 to 24 hours**, depending primarily on the half-life of the abused substance.

Barbiturates and other sedative hypnotics

Generic Name	Trade Name	Dose (mg)
Amobarbital	Amytal	100
Aprobarbital	Alurate	40
Butabarbital	Butisol	100
Butalbital	Many combination products (e.g., Fioricet)	100
Pentobarbital	Nembutal	100
Secobarbital	Seconal	100
Chloral hydrate	Aquachloral Supprettes	500
Ethchlorvynol	Placidyl	500
Glutethimide	Doriden	250
Meprobamate	Miltown	400

Note: The substitution technique for sedative-hypnotic withdrawal requires calculation of equivalent doses of phenobarbital to replace the sedative–hypnotic agent that the patient is taking. The above are doses of various sedative-hypnotic agents for which a 30-mg dose of phenobarbital should provide adequate coverage of a withdrawal syndrome. Daily doses of phenobarbital should rarely exceed 600 mg using this protocol.

Dependence & withdrawal

- Physiological dependence may develop after a daily dose of 400 mg of pentobarbital for 3 months; abrupt discontinuation results in paroxysmal abnormalities on the EEG in approximately 30 % of pts.

- At a daily dose of 600 mg of pentobarbital for 1 to 2 months, a withdrawal syndrome characterized by anxiety, insomnia, anorexia, tremor, and EEG changes occurs in approximately 1/2 of patients.

- 10 % may have a single seizure.

Dependence & withdrawal

At higher dosages of 800 to 2,200 mg per day for several weeks to months, abrupt discontinuation leads to minor symptoms-

- Apprehension and uneasiness
- Insomnia
- Muscular weakness, twitches
- Coarse tremors, myoclonic jerks
- Postural faintness and orthostatic hypotension
- Anorexia, vomiting
- EEG changes, within 24 hours of the last dose
- Minor symptoms may persist as long as 2 weeks.

Dependence & withdrawal

- 75 % of pts may have grand mal seizures on the 2nd or 3rd day after withdrawal, and 2/3rd have more than one seizure.
- 2/3rd of these patients develop delirium b/w the 3rd and 8th days of withdrawal, which is sometimes accompanied by hypothermia, which may be fatal.
- Disorientation, visual hallucinations, and frightening dreams may precede the onset of full delirium.
- Delirium may be exceedingly difficult to reverse, even with large doses of a barbiturate; thus, clinicians should never wait for the appearance of withdrawal symptoms before instituting therapy.
- The duration of the withdrawal syndrome is between 3 and 14 days; most end by the day 8.

Overdose

- Barbiturates are lethal when taken in overdose because they induce respiratory depression.
- In addition to intentional suicide attempts, accidental or unintentional overdoses are common.
- Barbiturates in home medicine cabinets are a common cause of fatal drug overdoses in children.
- As with benzodiazepines, the lethal effects of barbiturates are additive to those of other sedative-hypnotic drugs, including alcohol and benzodiazepines.
- Barbiturate overdose is characterized by induction of coma, respiratory arrest, cardiovascular failure, and death.

Overdose

- The ratio of lethal to effective dose ranges between 3 to 1 and 30 to 1.
- Dependent users often take an average daily dose of 1.5 g of a short-acting barbiturate,
- Some have been reported to take as much as 2.5 g per day for months.
- The lethal dose is not much greater for the long-term abuser than it is for the neophyte.

- Miscellaneous sedative-hypnotic drugs

Meprobamate, Carisoprodol

- It is a carbamate derivative, has weak efficacy as an antianxiety agent.
- At clinical doses in humans, it has minimal muscle-relaxant effects, but it may have a mild analgesic effect in musculoskeletal pain and may potentiate analgesics.
- Typical daily doses are b/w 1,200 and 1,600 mg, with a maximum of 2,400 mg, in three or four divided daily doses.
- A discontinuance syndrome occurs after several weeks of treatment with a daily dose of 2,400 mg, and mild symptoms may be seen with long-term therapy at doses of 1,600 mg daily.

Meprobamate, Carisoprodol

- Onset of the discontinuance syndrome occurs within 12 - 48 hours after abrupt discontinuation and lasts for an additional 12 - 48 hours.
- Seizures may be common in withdrawal from meprobamate.
- Reports published in the 1970s suggest that serious withdrawal symptoms are more common with meprobamate than with barbiturates.
- Meprobamate induces microsomal enzymes and may exacerbate intermittent porphyria.

Meprobamate, Carisoprodol

Blood concentration	
5 to 20 µg/mL	Normal range with recommended doses
30 to 100 µg/mL	Mild-to-moderate overdose, with patients in stupor or light coma
100 to 200 µg/mL	Serious overdose, deeper coma, and fatalities
Greater than 200 µg/mL	More fatalities than survivals.

Carisoprodol

- Carisoprodol is a commonly prescribed muscle relaxant that is metabolized to meprobamate, hydroxyl meprobamate, and hydroxyl carisoprodol.

- has been associated with abuse, dependence, and impairment of driving ability.

Chloral hydrate

- Chloral hydrate is used as a hypnotic in doses of .5 to 2.0 g.
- After oral administration, it is rapidly transformed to trichloroethanol, the metabolite responsible for its pharmacological activity.
- It is also effective in blocking experimentally induced seizures.

- Anticonvulsive and hypnotic doses are similar in humans, making the benzodiazepines and barbiturates better choices for anticonvulsive medications.

Chloral hydrate

- At high doses, chloral hydrate may produce respiratory depression, hypotension, gastric necrosis, depressed cardiac contractility, and a shortened refractory period.
- Even at therapeutic doses, it is associated with gastric distress and flatulence.
- Somnambulism, disorientation, and paranoid ideation may occur.
- Tolerance and physiological dependence develop with long-term use, and the withdrawal syndrome is similar to the barbiturate abstinence syndrome.
- Fatalities from overdose may occur with as little as 4 g, although patients have survived after taking 30 g.

Ethchlorvynol

- Ethchlorvynol is a rapidly acting sedative-hypnotic agent with anticonvulsant and muscle-relaxant properties.
- Recommended doses are 500 to 1,000 mg.
- Initial effects (which may include euphoria) occur 15 to 30 minutes after an oral dose, and plasma levels peak at 1 to 1.5 hours.
- The elimination half-life of the parent compound is 10 to 20 hours.
- The duration of the hypnotic effect is approximately 5 hours.
- Long-term use of ethchlorvynol has been associated with toxic amblyopia, scotoma, nystagmus, and peripheral neuropathy, which are usually reversible on drug discontinuation.

Ethchlorvynol

- IV self-administration may cause pulmonary edema.
- Lethal doses are typically between 10 - 25 g;
- One person was reported to have died after taking 2.5 g with ethanol.
- One patient survived but was in a coma for 7 days after taking 50 g.

Glutethimide and Methyprylon

- Glutethimide and methyprylon (no longer marketed in the United States) are piperidinedione sedative-hypnotic drugs that have high liability for abuse.
- Glutethimide resembles the barbiturates in most respects but differs from them in having significant anticholinergic activity.
- An overdose can cause ileus, bladder atony, mydriasis, hyperpyrexia, myoclonic jerks, and convulsions.
- A lethal dose is b/w 10 - 20 g; intoxication may be seen at a dose of 5 g.
- An unusual characteristic of glutethimide is that a withdrawal syndrome can occur in patients taking therapeutic doses (0.5 to 3.0 g daily), even when they have not stopped taking the drug.

Glutethimide and Methyprylon

- The abstinence syndrome includes tremulousness, nausea, tachycardia, fever, tonic muscle spasms, and grand mal seizures.
- Withdrawal from a combination of glutethimide and antihistamine has caused catatonia and dyskinesia.
- When glutethimide is taken with codeine (the street name is a *load*), a euphoria similar to that with heroin results.
- In these patients, detoxification may require opioid withdrawal and sedative withdrawal.

Methaqualone

- Methaqualone is a quinazoline with sedative, anticonvulsive, local anesthetic and antispasmodic activity.
- It has antitussive effects comparable to those of codeine and weak antihistaminic activity.
- During the 1960s and 1970s, those in the drug culture considered it to provide the ultimate high of all sedative-hypnotic agents, producing euphoria comparable to that from heroin.
- Usually taken orally, often with alcohol, which was referred to as **"luuding out."**
- Chronic users may take daily oral doses between 75 mg and 2 g, with an average daily dose of 775 mg.
- Onset of effects after oral dosing occurs after 30 minutes and lasts 2 to 4 hours.

Methaqualone

- Oral dosing was most common in the United States and Europe, methaqualone is smoked in South Africa and India, frequently used in a preparation of crushed methaqualone tablets, cannabis, and tobacco, referred to as “white pipe.”

- Onset of euphoria is rapid by the smoked route and is followed by a relaxed state lasting up to 6 hours.
- A/E include peripheral neuropathy, nightmares, somnambulism, gastric discomfort, and urticaria.
- Death has been reported after 8 g, but one report attributed most deaths under the influence of methaqualone to accidents due to impairment produced by the drug.

Methaqualone

- Tolerance and physiological dependence are seen with chronic dosing.
- An overdose of methaqualone may result in restlessness, delirium, hypertonia, muscle spasms, convulsions, and (in high doses) death.
- Unlike barbiturates, methaqualone rarely causes severe cardiovascular or respiratory depression, and most fatalities result from combining methaqualone with alcohol.

Gamma hydroxybutyrate

- Gamma hydroxybutyrate (GHB) was used for decades in Europe with a limited number of reported adverse effects and abuse.
- By the early 1990s, concern that GHB was developing into a popular drug of abuse and evidence that GHB was being used as a recreational club drug led to FDA removal of GHB from the market.
- The FDA has now approved GHB as a treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy.
- It is synthesized in the brain from GABA via deamination to succinic semialdehyde (SSA) by GABA aminotransferase.

Gamma hydroxybutyrate

- Abrupt discontinuation of chronic high doses have been associated with anxiety, restlessness, insomnia, nausea, lethargy, tachycardia, sweating, tremors, muscle cramps, and psychosis.
- 6-month open label clinical trials of clinical doses of sodium oxybate have not shown tolerance.
- GHB in combination with other CNS depressants, especially ethanol, creates amplified CNS depression and has been found to result in acute intoxication, often requiring medical attention.
- Also known as – **Date Rape Drug.**

Investigations

- Arterial blood gas (ABG) if respiratory depression is present.
- Serum electrolytes
- Glucose
- BUN
- Serum creatine
- Obtain a chest x-ray if respiratory compromise is present to evaluate for aspiration and ARDS
- ECG

Guidelines for T/T of Benzodiazepine Withdrawal

- Evaluate and treat concomitant medical and psychiatric conditions.
- Obtain drug history and urine and blood sample for drug and ethanol assay.
- Determine required dose of benzodiazepine or barbiturate for stabilization, guided by history, clinical presentation, drug-ethanol assay, and (in some cases) challenge dose.
- Detoxification from supra therapeutic dosages:
  - Hospitalize if there are medical or psychiatric indications, poor social supports, polysubstance dependence or the patient is unreliable.

Guidelines for T/T of Benzodiazepine Withdrawal

- Some clinicians recommend switching to longer-acting benzodiazepine for withdrawal (e.g., diazepam, clonazepam); others recommend stabilizing on the drug that patient was taking or on phenobarbital.
- After stabilization reduce dosage by 30% on the 2nd or 3rd day and evaluate the response, keeping in mind that symptoms that occur after decreases in benzodiazepines with short elimination half-lives (e.g., lorazepam) appear sooner than with those with longer elimination half-lives (e.g., diazepam)
- Reduce dosage further by 10 - 25% every few days if tolerated.
- Use adjunctive medications (if necessary carbamazepine, valproate, clonidine, and sedative antidepressants have been used but their efficacy in the treatment of the benzodiazepine abstinence syndrome has not been established).

Guidelines for T/T of Benzodiazepine Withdrawal

- Detoxification from therapeutic dosages:
  - Initiate 10 to 25 % dose reduction and evaluate response.
  - Dose, duration of therapy, and severity of anxiety influence the rate of taper and need for adjunctive medications.
  - Most patients taking therapeutic doses have uncomplicated discontinuation.
- Psychological interventions may assist patients in detoxification from benzodiazepines and in the long-term management of anxiety.

Equivalent doses of benzodiazepines

Approximate Therapeutic Equivalent Doses of Benzodiazepines

Generic Name	Trade Name	Dose (mg)
Alprazolam	Xanax	1
Chlordiazepoxide	Librium	25
Clonazepam	Klonopin	0.5–1.0
Clorazepate	Tranxene	15
Diazepam	Valium	10
Estazolam	ProSom	1
Flurazepam	Dalmane	30
Lorazepam	Ativan	2
Oxazepam	Serax	30
Temazepam	Restoril	20
Triazolam	Halcion	.25
Quazepam	Doral	15
Zolpidem	Ambien	10
Zaleplon	Sonata	10

Adjunctive Medications:

Carbamazepine

- May partially attenuate the withdrawal syndrome from benzodiazepines.
- Initial dosages are 200 mg twice a day, although some clinicians recommend a single dose of 400 mg at bedtime to take advantage of the sedative effect.
- Carbamazepine is increased to 600 mg on the 2^{nd} or 3^{rd} day.
- Can be tapered quickly 2 to 4 weeks after the last benzodiazepine dose.
- Carbamazepine may not be successful in withdrawing patients with panic disorder because it is ineffective in blocking panic attacks

Adjunctive Medications:

Divalproex :

- Used in starting dosages of 500 to 1,000 mg divided into 2 or 3 daily doses.
- For patients who abuse alcohol and benzodiazepines, valproate should be avoided when liver enzyme activities are 3 times their normal values.

Gabapentin

- May also reduce benzodiazepine withdrawal symptoms, but experience is limited.
- Other anticonvulsants, such as **levetiracetam and topiramate.**
- Are also being studied to treat benzodiazepine withdrawal.

Adjunctive Medications:

Propranolol:

- In doses of 60 to 120 mg

- May reduce the symptoms of benzodiazepine withdrawal, although tachycardia and elevated blood pressure are the primary symptoms reduced, whereas the subjective sense of discomfort and dysphoria persists.
- The α-blockers do not have prophylactic effects against seizures and should not be used in monotherapy for withdrawal.

Adjunctive Medications:

Clonidine

- 0.1 mg twice a day to 0.2 mg three times a day or as a patch, has been used in the treatment of low-dose benzodiazepine withdrawal with variable results.

- does not provide protection against withdrawal seizures.

- may be effective only when used before withdrawal symptoms develop.

ADJUNCTIVE MEDICATIONS:

Antidepressants:

- ✓ Agents with well-established anti panic and sedative effects may be useful adjunctive medications for patients whose anxiety recurs during taper or after drug discontinuation.

Psychological treatment

- Cognitive behavioural strategies
- Self-help cognitive behavioural therapy (which incorporates education, planned sage reductions, engaging patients in their taper schedule, and medical support).
- Cognitive restructuring teaches patients about the withdrawal syndrome and helps them identify and relabel withdrawal symptoms as anxiety.
- Thus permitting the implementation of adaptive coping strategies, which include systematic desensitization, in vivo graded exposure, and group problem solving.

Psychological treatment

- Using a diary to record mood states and their precipitants sometimes helps cognitive restructuring.

- A diary may also alert the clinician to maladaptive responses to benzodiazepine withdrawal, such as increased alcohol consumption.

Barbiturates

- There are three common methods of establishing the barbiturate dosage required for safe withdrawal:
- (1) administration of a test dose of pentobarbital to determine tolerance.
- (2) calculation of required doses based on estimated equivalencies.
- (3) administration of phenobarbital loading doses.

Barbiturates

- In 1st method, the initial step is to determine tolerance.
- Once intoxication has subsided but before withdrawal symptoms have developed, an oral dose of 200 mg of pentobarbital is administered on an empty stomach, and the effects are observed after 1 hour to determine the stabilization dose.
- If no changes, the test is repeated 3 hours later using 300 mg.
- If there is still no response, the total requirement may exceed 1,600 mg per day.
- The calculated daily dose is divided and given every 4 to 6 hours for a 2- to 3-day stabilization period.
- Daily dose reductions are usually 10 % of the stabilization dose, but withdrawal regimens must be individualized. Phenobarbital may be substituted for pentobarbital for stabilization and withdrawal at 1/3rd of the dose.

Barbiturates

- 2nd method of barbiturate detoxification requires calculating the equivalent hypnotic dose of phenobarbital on the basis of the dosage of barbiturate or other sedatives the patient reports taking, also taking into consideration any alcohol consumed.
- A dose of 30 mg of phenobarbital is substituted for an equivalent hypnotic dose of the sedative.
- Pt is stabilized for the period of peak vulnerability to withdrawal, 2 to 3 days for sedative-hypnotic agents with short half-lives, and reductions of 30 to 60 mg of phenobarbital are made every 2 or 3 days.
- Only rarely are doses of phenobarbital greater than 600 mg required.

Barbiturates

- Final method for medical withdrawal from barbiturates involves using loading doses of phenobarbital.

- According to the original protocol, 120-mg doses are administered every 1 to 2 hours until three of five signs are present—**nystagmus, drowsiness, ataxia, dysarthria**, or **emotional lability**—or, if patients are in withdrawal, until abstinence symptoms abate.

- No additional drug is administered, because of its long half-life, the drug self-tapers.

Barbiturates

- Protocol to use doses of 60 mg every 1 to 2 hours and to use a gradual taper rather than abrupt discontinuation.
- The originators of the protocol reported a mean loading dose of 1,440 mg, with hourly doses sometimes required for 15 to 20 hours.
- They have also administered phenobarbital IV at 0.3 mg/kg per minute, with close medical supervision, for medically ill patients.
- A loading dose procedure for withdrawal from butalbital containing headache remedies has also been described.

Barbiturates

- Since patients do not always reliably report drug intake, an alternative strategy is to use a loading dose of 120 mg of phenobarbital hourly guided by a rating scale to document effects on nystagmus, dysarthria, ataxia, and drowsiness.
- One study found that the mean number of phenobarbital doses required was 9.7 (range 7 to 14) and withdrawal was completed in less than 24 hours.

OUT PATIENT DETOX PROTOCOL

- Create a rapport with the patient. Discuss with the patient the plan to discontinue the abused drug.
- Ask the patient to maintain chart of their abused drug.
- Review the chart with the patient. Determine the maximum dose taken each day as well as the average dose taken each day.
- Ask the patient to continue the charting while taking the average daily dose as a fixed daily dose.
- Ask the patient to maintain a log of symptoms that are observed on days when patient feels like having a higher dose.
- After long-term benzodiazepines use, a minimum of 6 months duration for completion of the taper is recommended.
- Treat the symptoms, which the patient observed either pharmacologically or via other modalities.

OUT PATIENT DETOX PROTOCOL

- Ensure that the patient is taking the daily dose in divided doses.
- **Three times a day dosing schedule** is a reasonable starting point, this will result in diminished withdrawal symptoms at any time of day during the course of the taper.
- Educate the patient.
- Taper of medication
- **If patient is taking 1 mg of sedatives 3 times a day.**
- **Taper as follows.**
- **I Month 0.75 mg, 1 mg, 1 mg**
- **II Month decrease** the patient's dose by **another quarter milligram,** removing the amount at the time for which the patient reports the least symptoms but also make sure that the 3 doses are roughly equivalent to each other

BZDs in pregnancy

- Most commonly anxiolytic drugs among women of reproductive age and to pregnant women for reducing anxiety and managing preeclampsia or eclampsia in the latter part of pregnancy.
- All major classes of benzodiazepine compounds can be assumed to be excreted into milk or to diffuse readily across the placenta to the fetus.
- The amount of a drug excreted depends on the characteristics of the particular drug—plasma protein binding, ionization, degree of lipophilicity, molecular weight, half-life, maternal blood concentrations, oral bioavailability, pharmacokinetics.

BZDs in pregnancy

- Many possible risks to the fetus whenever anxiolytic medications are prescribed to pregnant women.
- The onset of teratogenic effects may be immediate or delayed.
- Possible effects include **abortion, malformation, intrauterine growth retardation, functional deficits, carcinogenesis, and mutagenesis**.
- If a woman is prescribed benzodiazepines and found to be pregnant, the prescription should be gradually withdrawn over as short a time as possible, being mindful of the risk of withdrawal seizures and the potential consequences for the pregnant woman and foetus.

BZDs in children & adolescent

- To control seizures in young children.
- Diazepam(status epilepticus, cerebral convulsions), clonazepam, lorazepam are most common.
- Short term courses (6-12 weeks).
- Benzodiazepine receptor agonists, sedating antidepressants, antihistamines, and melatonin agonists.
- **Benzodiazepine receptor agonists** (BRAs), which include traditional bzds (e.g., temazepam, flrazepam) and **nonbenzodiazepine hypnotics** (e.g., zolpidem, eszopiclone, and zaleplon) also acting on the GABA receptor complex, have been extensively evaluated in controlled clinical trials in adults (Walsh *et al*., 2005).

BZDs in children & adolescent

- A trial of zolpidem failed to improve polysomnographically measured sleep in 6–17-year-olds who met diagnostic criteria for insomnia associated with ADHD (Blumer *et al*., 2009).

- Seibt and colleagues (2008) investigated the impact of Zolpidem on the development of the visual system in kittens 28–41 days old.
- Zolpidem increased NREM sleep by 27% and increased total sleep over the 8-hour period.

BZDs in Elderly:

- What should we do?

Benzodiazepines should be prescribed with -

- Caution
- At low doses
- For short periods

BZDs in Elderly:

Short half life BZDs like oxazepam, triazolam, alprazolam can be prescribed because

- These agents do not accumulate in the blood,
- Are rapidly cleared from circulation,
- Offer greater dosage flexibility
- But they are associated with risk of withdrawl symptoms and have higher abuse potential.

BZDs in Elderly:

DOs	DONT
✓ Daily dose should be limited. ✓ Duration of use should not exceed more than 2 months. ✓ Start with low dose. ✓ Titrate dosage gradually. ✓ Monitor BZDs use in each follow up. ✓ Identify the possibility of Abuse and dependence. ✓ Gradually taper in dependent patient to avoid withdrawal symptoms ✓ Consider patient's comorbid medical conditions ✓ Adjust dosage for renal and hepatic impairment	✓ Avoid higher dosage from the beginning. ✓ Avoid BZDs for conditions not indicated. ✓ Avoid BZDs together with psychotropic drugs having sedative properties. ✓ Avoid long acting BZDs. ✓ Avoid prescribing for longer duration without indication. ✓ Avoid drugs having interactions with BZDs [metabolism]. ✓ Avoid BZDs having high abuse potential. ✓ Avoid abrupt cessation of BZD continued for long duration

PROGNOSIS

- Only a handful of studies have looked into long-term success of benzodiazepine discontinuation programs.
- Most studies indicate a high relapse state; however, outcome is more favorable in those individuals who manage to complete a discontinuation program
- Outcome is better in individuals with good social support, absence of psychiatric co-morbidity or remission of preexisting psychiatric symptoms, and absence of dependence on other drugs.

Conclusion

- In children, adolescents & elderly age group, we should use BZDs for short course & low dose.
- Particular care should be taken in prescribing benzodiazepines for vulnerable patients such as those with alcohol or drug dependence, and doctors should be aware that prescriptions may enter the illicit market.
- Low dose Benzodiazepine Withdrawal No special treatment is needed.
- Most patient experience only mild to moderate symptom rebound that disappears after few days to weeks.

References

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