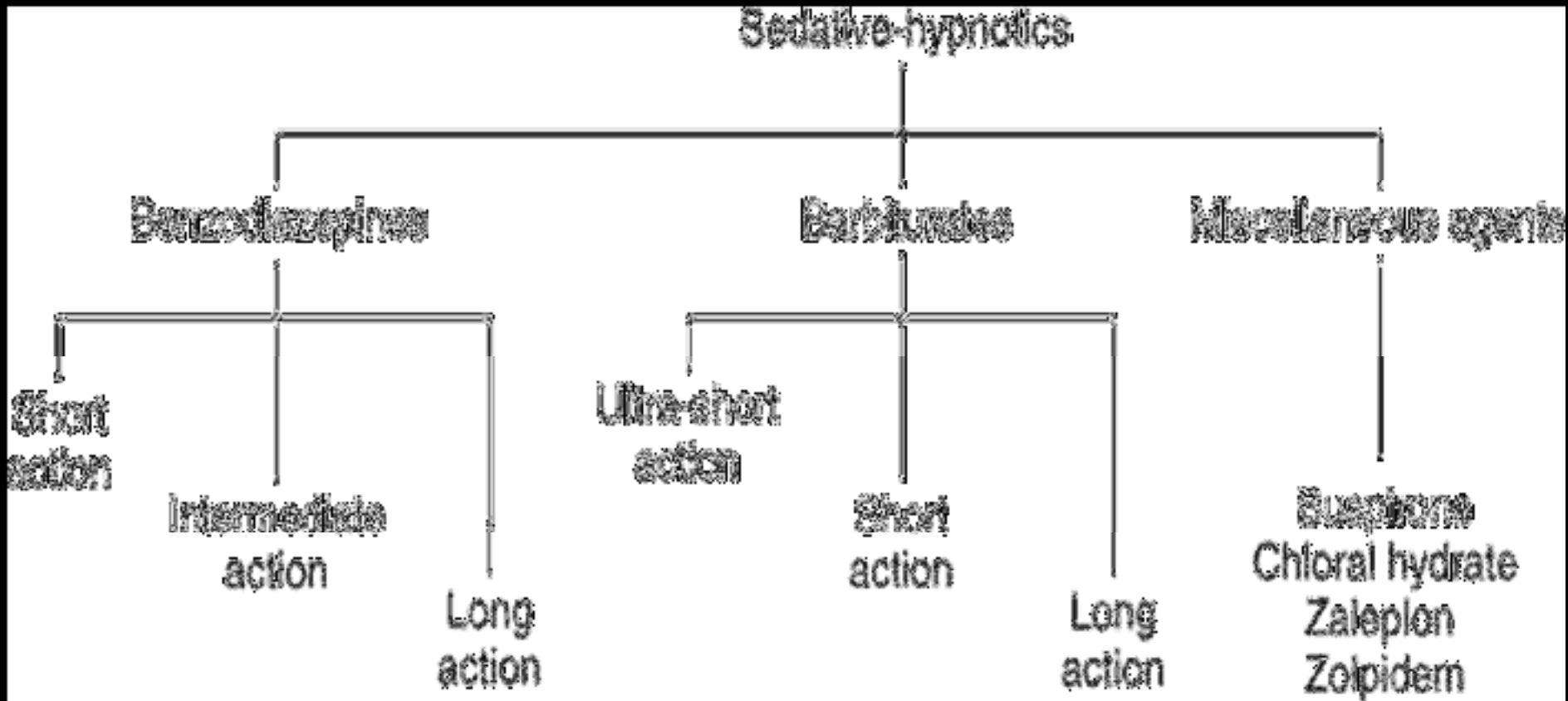
Barbiturates and benzodiazepines

By Dr. Swathi Swaroopa . B

Introduction

Barbiturate	Benzodiazepine
Derivatives of barbituric acid (2,4,6-trioxohexahydropyrimidine) Extensively used as sedative hypnotics till the 1960s when the benzodiazepines arrived and quickly displaced them.	Benzodiazepines are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring



Source: Panus PC, Jobst EE, Masters SB, Katzung B, Tinsley CL, Trevor AJ: *Pharmacology for the Physical Therapist*: http://www.accessphysiotherapy.com

Drugs

Barbiturate	Benzodiazepine
Long acting (duration of action 6–12 hrs) a. Mephobarbitone b. Phenobarbitone. 2. Intermediate acting (duration of action 3–6 hrs) a. Amobarbitone b. Aprobarbitone c. Butobarbitone. 3. Short acting (duration of action < 3 hrs) a. Hexobarbitone b. Pentobarbitone c. Secobarbitone. 4. Ultra-short acting (duration of action <15–20 min) a. Thiopentone b. Methohexitone	Alprazolam, brotizolam, chlordiazepoxide, chlorazepate, clobazam, clonazepam, diazepam, estazolam, flunitrazepam, flurazepam, halazepam, lorazepam, lormetazepam, medazepam, midazolam, nitrazepam, oxazepam, pinazepam, prazepam, quazepam, temazepam, triazolam and zolazepam

DURATION OF ACTION	BARBITURATE	METABOLISM AND ACTIVITY
Ultrashort-acting	Methohexital (Brevital) Thiopental (Pentothal)	Highly lipid soluble with rapid CNS penetration
Short-acting	Pentobarbital (Nembutal) Secobarbital (Seconal)	Highly lipid soluble with rapid CNS penetration
Intermediate-acting	Amobarbital (Amytal) Aprobarbital (Alurate) Butabarbital (Butisol) Butalbital (Florinal)	Intermediate CNS penetration (30-60 min)
Long-acting	Barbital (Veronal) Mephobarbital (Mebaral) Phenobarbital (Solfoton, Luminal) Primidone (Mysoline)	Metabolized slowly in liver; greater fraction excreted unchanged by kidney; undergoes enterohepatic recirculation

CNS, Central nervous system; *MDAC*, multiple-dose activated charcoal.

Classifications of Benzodiazepines

are classified according to duration of action into:

Short acting (3-8 hours): triazolam- Oxazepam

Intermediate (10-20 hours): "ALET"

Alprazolam - Lorazepam

Estazolam - Temazepam

Long acting: (24-72 hours)

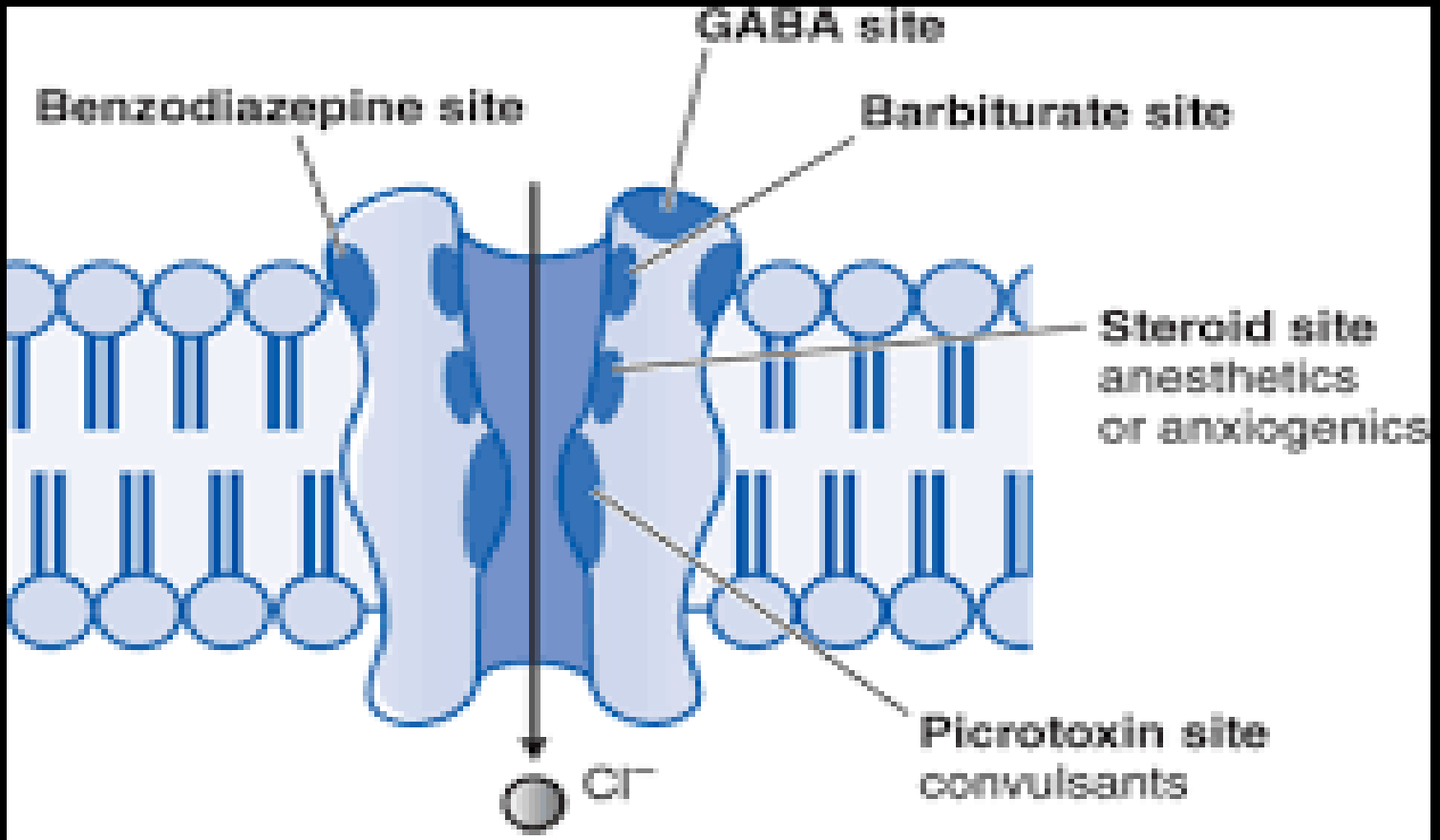
Diazepam - Chlordiazepoxide - Flurazepam

Uses

Barbiturate	Benzodiazepine
1.Sedative-hypnotic. 2. Pre-operative sedation. 3. Treatment of seizure disorders.	Anxiety disorders 2. Seizure disorders 3. Insomnia 4. Movement disorders (adjunctive therapy) 5. Mania (adjunctive therapy) 6. Some of these drugs are also used for inducing skeletal muscle relaxation, as pre-anaesthetic medication, and for the treatment of alcohol withdrawal.

Mechanism of toxicity

Barbiturates	Benzodiazepines
Barbiturates bind to specific sites on gamma-aminobutyric acid (GABA)–sensitive ion channels found in the central nervous system (CNS), where they allow an influx of chloride into cell membranes and, subsequently, hyperpolarize the postsynaptic neuron.	BZDs bind to a specific receptor on the GABA A receptor complex and thereby facilitate the binding of GABA to its specific receptor site. BZD binding causes increased frequency of opening of the chloride channel complexed with the GABA A receptor. Chloride channel opening results in membrane hyperpolarization, which inhibits cellular excitation.



Source: Douglas E. Rollins, Donald K. Blumenthal: Workbook and Casebook for Goodman and Gilman's The Pharmacological Basis of Therapeutics, www.accesspharmacy.com

Mechanism of action

Barbiturate+GABA

↓

Activation of GABA receptor

↓

Opening of chloride channel

↓

Increase the duration of GABA gated channel opening

↓

Hyperpolarisation of cells

↓

Depression of CNS

MODE OF ACTION:

Benzodiazepines

↓

Stimulating GABA b receptors

↓

Opening up the chloride ion channel in the receptor complex

↓

↑se conductance of chloride ion across the nerve cell membrane

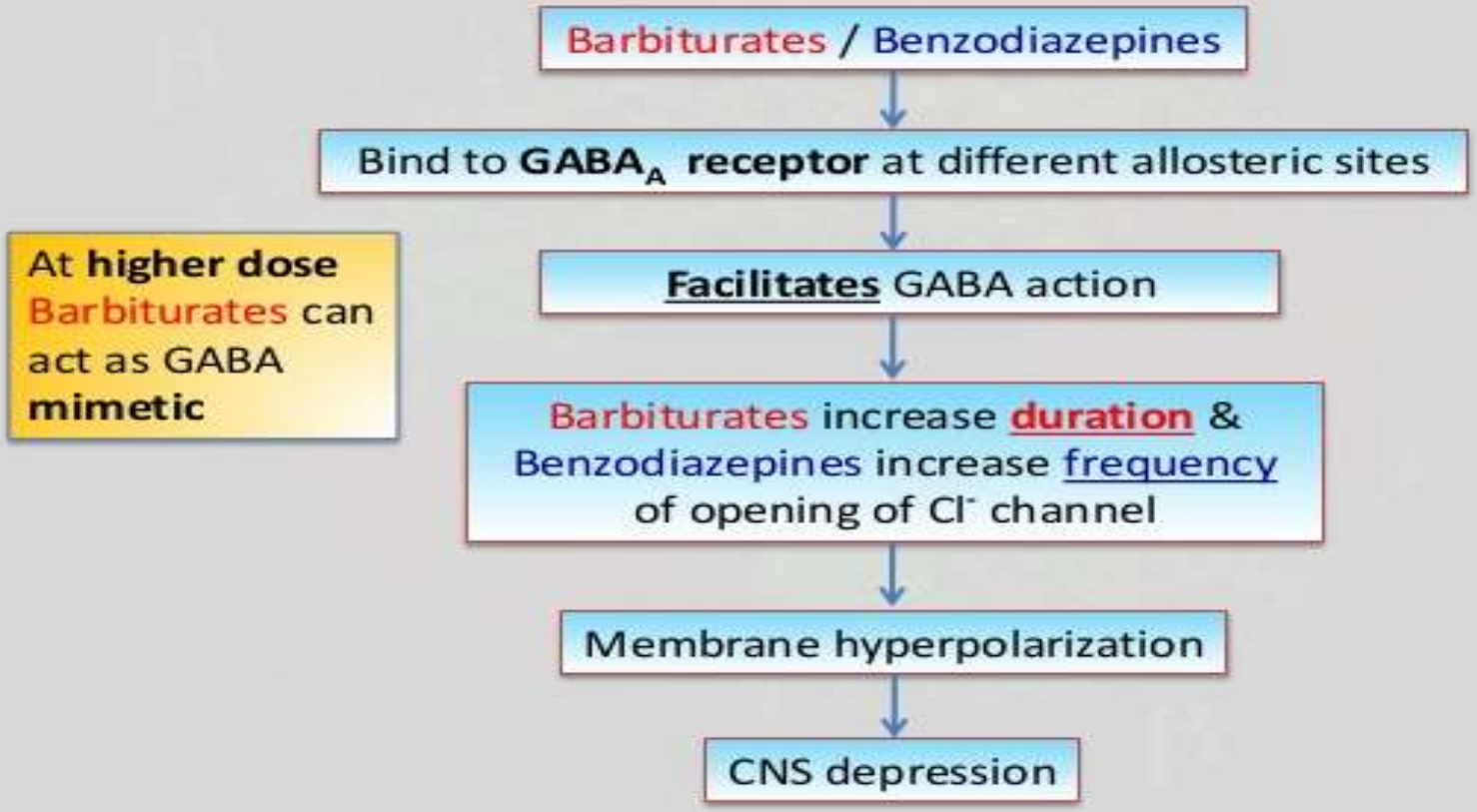
↓

Lowers the potential difference btwn the interior & exterior of the cell

↓

Blocking the ability of the cell to conduct nerve impulses

Mechanism of Action



- Although the clinical effects of barbiturates and benzodiazepines are similar and result from hyperpolarization of the neuron, there are subtle differences in terms of receptor binding.

- Barbiturates increase the duration of Cl ion channel opening at the GABA receptor, which, in turn, increases the efficacy of GABA.

- Benzodiazepines, on the other hand, increase the frequency of Cl ion channel openings at the GABA receptor, which, in turn, increases the potency of GABA. [7]

Usual fatal dose

Barbiturate	Benzodiazepine
Usual Fatal Dose Phenobarbitone: 6 to 10 grams. ■ Amobarbitone, pentobarbitone, secobarbitone: 2 to 3 grams. ■ Lethal blood level for short- and intermediate-acting barbiturates varies from 3 to 4 mg/100 ml, for phenobarbitone it ranges from 8 to 15 mg/100 ml	Uncertain for most benzodiazepines. Even ingestion of up to 2000 mg diazepam has not resulted in death, or for that matter, even serious morbidity. However, several cases of fatality due to triazolam and flunitrazepam overdose have been described.

BARBITURATES vs BENZODIAZEPINES

BOTH HAVE SIMILAR EFFECTS ON THE **CNS**

- DEPRESSANT

PSYCHOACTIVE -

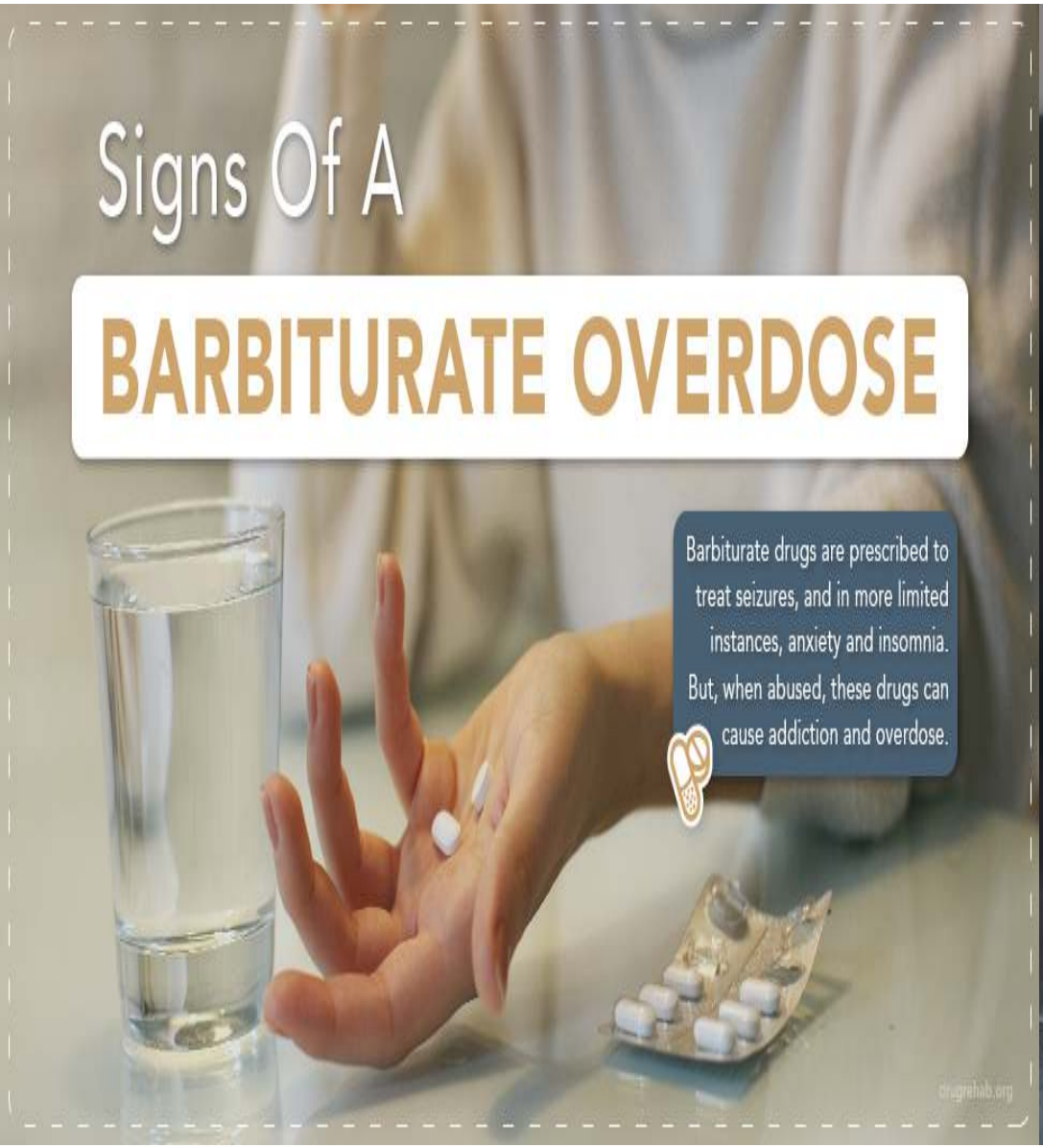
THE BIGGEST DIFFERENCE IS THEIR *FATALITY* RATE

- HIGHER DOSES OF BARBITURATES CAN LEAD TO DEATH

TAKEN ALONE - BENZOS ARE RARELY THE CAUSE OF DEATH

Toxicokinetics

Barbiturate	Benzodiazepine
As sedative-hypnotics are administered orally. Intravenous route is usually reserved for status epilepticus or induction/maintenance of general anaesthesia. ■ barbiturates are distributed widely. The long acting barbiturates have a plasma half-life of about 80 hours. ■ Metabolism of most of these drugs occurs by oxidation in the liver resulting in the formation of alcohols, ketones, phenols, or carboxylic acids which are excreted in the urine as such or in the form of glucuronic acid conjugates. Metabolism of barbiturates is more rapid in children and is slower in the elderly	Administered orally or by IV injection. Intramuscular injection may lead to erratic absorption lorazepam and midazolam are exceptions to this and can be given IM. Following absorption, all benzodiazepines are bound to plasma proteins to the extent of 70 to 99%. metabolised extensively by different microsomal enzyme systems in the liver. Metabolites are invariably as active as the parent compound. **Benzodiazepines** are **excreted** in urine.


Signs Of A
BARBITURATE OVERDOSE
Barbiturate drugs are prescribed to treat seizures, and in more limited instances, anxiety and insomnia. But, when abused, these drugs can cause addiction and overdose.
drugrehab.org


SIGNS OF A
BENZODIAZEPINE
OVERDOSE
Benzodiazepine abuse and addiction can cause significant harm, and may result in fatal overdose.
drugrehab.org

Adverse effects

Barbiturate	Benzodiazepine
Residual depression after the main effect of the drug has passed off. ■ Paradoxical excitement (especially in the elderly). Hypersensitivity reaction—localised swelling of eyelid, cheek, or lip, erythematous or exfoliative dermatitis. ■ Synergistic action with ethanol and antihistamines. ■ Barbiturates are contraindicated in patients with acute intermittent porphyria since they enhance porphyrin synthesis.	Weakness, headache, amnesia, vertigo,diplopia, nausea, diarrhoea, and rarely chest pain. ■ Paradoxical effects (disinhibition or dyscontrol reaction) may sometimes occur characterised by restlessness, agitation, and hallucinations. ■ Flurazepam has been associated with nightmares and hallucinations. Allergic, hepatotoxic, and haematological reactions are rare.

Barbiturates

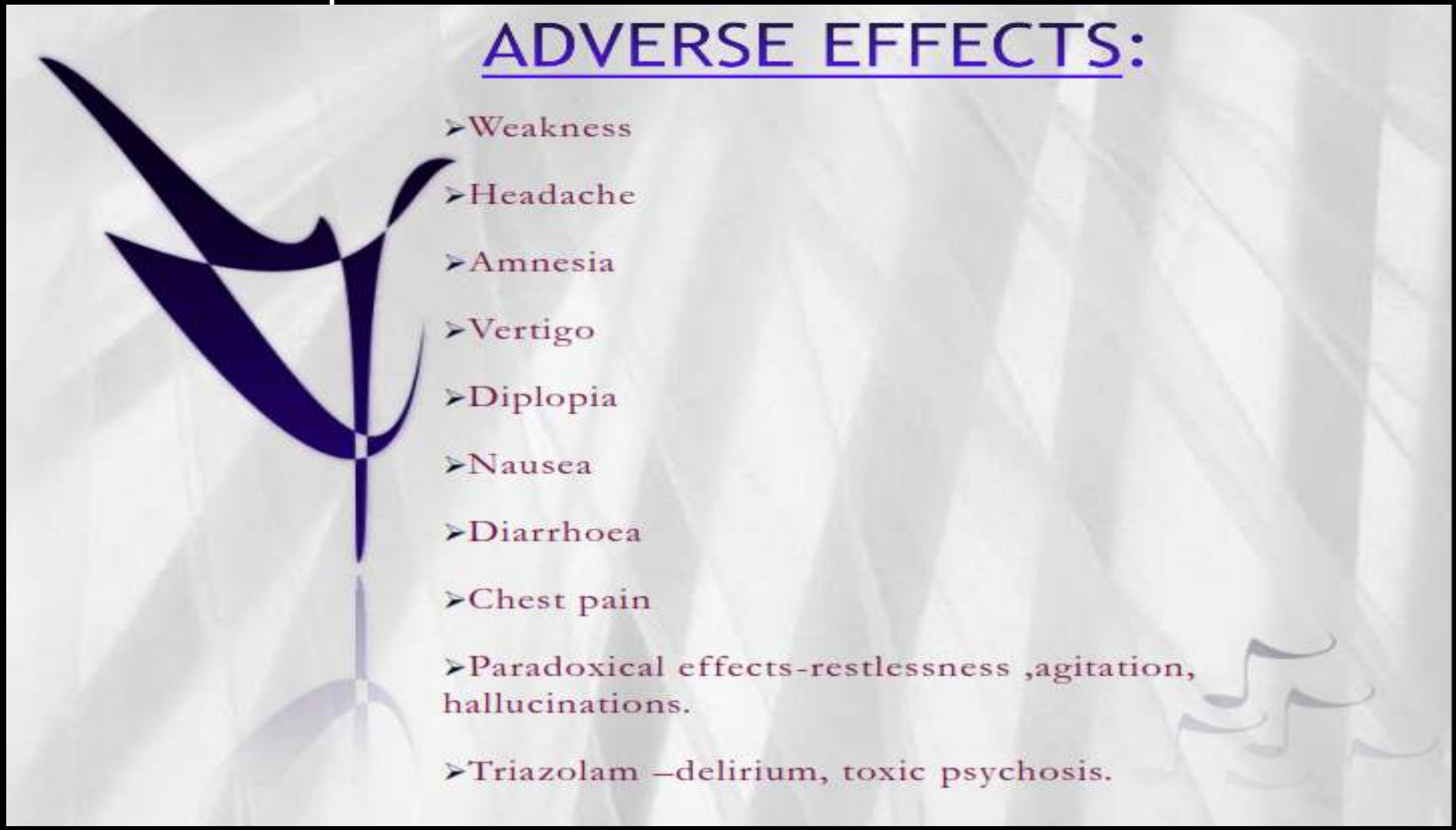
ADVERSE EFFECTS:

- Residual depression.
- Paradoxical excitement.
- Hypersensitivity reactions localised swelling of eye lid,cheek or lip , erythematous or exfoliative dermatitis.
- Synergistic action with ethanol & antihistamines.

TOXIC EFFECTS:

- Slurred speech , ataxia, lethargy, confusion , headache , nystagmus .
- CNS depression,coma,shock.
- Pupils –first contricted , later dilate because of hypoxia.
- Hypothermia
- Cutaneous bullae (blisters)
- Death due to respiratory arrest or cardio vascular collapse.

Benzodiazepiness



Toxic features

Barbiturates	Benzodiazepines
Slurred speech, ataxia, lethargy, confusion, headache, nystagmus. 2. CNS depression, coma, shock. 3. Pupils are at first constricted, but later dilate because of hypoxia. 4. Hypothermia. Cutaneous bullae (“barb burns”, barbiturate blisters) Death may occur from respiratory arrest or cardiovascular collapse. Chronic barbiturate (ab)use is associated with the development of tolerance which is responsible for decreasing the therapeutic to toxic index. An addict may obtain therapeutic benefit only with 5 to 6 times the normal dose	Benzodiazepines are remarkably safe drugs and rarely produce serious toxic effects even with substantial ingestion Mild—Drowsiness, ataxia, weakness Moderate to Severe Vertigo, slurred speech, nystagmus, partial ptosis, lethargy, coma. Hypotension and respiratory depression Both miosis and mydriasis, Nystagmus may also occur. The incidence of coma indicate that short acting benzodiazepines (midazolam and triazolam) and intermediate acting (flunitrazepam) have a higher acute toxicity, as compared to diazepam, lorazepam and nitrazepam Flurazepam and temazepam may also have greater toxicity.

Toxic features

Barbiturates	Benzodiazepines
Abrupt withdrawal results in anorexia, tremor, insomnia, cramps, seizures, delirium, and orthostatic hypotension.	Long-term use of benzodiazepines is associated with the development of tolerance Abrupt cessation provokes a mild withdrawal reaction characterised by anxiety, insomnia, headache,tremor, and paraesthesia. Restlessness, encephalopathy, and hallucinations may occur after abrupt withdrawal from high daily doses. Convulsions may occur after a lapse of 3 to 10 days Newer benzodiazepines such as alprazolam, triazolam, and temazepam are associated with fatalities

Diagnosis

Barbiturates	Benzodiazepines
Serial plasma levels may be useful in the management of phenobarbitone overdose. Plasma levels exceeding 8 mg/ dL (80 mcg/mL) (344 mcmol/L) are generally associated with some degree of coma. In the absence of tolerance, plasma levels exceeding 2 to 3 mg/dL may be associated with CNS depression. 2. EEG: alpha coma* indicates poor prognosis.	Estimation of plasma levels of benzodiazepines is usually not Necessary Qualitative testing for presence of benzodiazepine is helpful to confirm presence, especially when overdose history Blisters of skin (bullae) can occur following overdose with nitrazepam, oxazepam, and temazepam.

Marilyn Monroe died due to barbiturate overdose at the age of 36years

Barbiturates

- Monitor CBC, serum electrolytes, glucose, blood urea nitrogen, creatinine, and urine myoglobin in patients with significant intoxication.

- The onset of toxic effects is usually within 2 hours, but peak toxicity may not occur for 18 or more hours.

Treatment

Barbiturates	Benzodiazepines
Gastric lavage (preferably with a large-bore, double-lumen tube), can be done with benefit up to 12 to 24 hours post ingestion.	**Acute poisoning** Decontamination Stomach wash may be helpful if the patient is seen within 6 to 12 hours after the ingestion
Activated charcoal in the usual dose or in Multiple dose	Activated charcoal is beneficial
Forced alkaline diuresis • Useful in phenobarbitone poisoning • It should be considered only in severe barbiturate toxicity with life-threatening signs and symptoms. • Less effective than multiple dose activated charcoal • No value in the treatment of short acting	Forced diuresis and haemodialysis are ineffective

Treatment

Barbiturates	Benzodiazepines
Haemodialysis or charcoal haemoperfusion Managing severe barbiturate intoxication, Reserved for patients with haemodynamic compromise refractory to aggressive supportive care Exchange transfusion may be beneficial in severe cases For hypotension: First administer 10 to 20 ml/kg of isotonic intravenous fluids and place in Trendelenburg position Repeat boluses of isotonic intravenous fluids If the patient is unresponsive administer	Hypotension Begin by infusing 10 to 20 ml/kg of isotonic fluid, and place patient in Trendelenburg position. if no response administer dopamine or noradrenaline

Treatment

Barbiturates	Benzodiazepines
Supportive measures: supplemental oxygen, intubation, assisted ventilation, IV fluids.	Establish clear airway. Oxygen and assisted ventilation are often necessary. IV fluids (Ringer's lactate at a rate of 150 ml/hr for adults). **Antidote** Flumazenil is effective in reversing the coma induced by benzodiazepines as well as zolpidem by competitive antagonism. Effect is short-lived, and flumazenil also has the tendency to induce a withdrawal reaction in benzodiazepine-dependant patients.

Treatment

Barbiturates	Benzodiazepines
	Most patients achieve complete reversal of benzodiazepine effect with a total slow IV dose of just 1 mg Some investigators suggest that flumazenil is better administered in a series of smaller doses in an incremental manner beginning with 0.2 mg and progressively increasing by 0.1to 0.2 mg every minute until a cumulative total dose of 3.5 mg is reached However, resedation occurs within ½ hour to 2 hours Patients must be carefully monitored for resedation and subsequent doses of flumazenil should be administered as needed.

Treatment

Barbiturates	Benzodiazepines
	The use of continuous flumazenil maintenance infusion over 5 to 24 hours seems useful for resedation after initial response Flumazenil has also been reported to reverse cardiovascular depression Flumazenil does not reverse respiratory depression very well Flumazenil is contraindicated in mixed ingestions involving tricyclic antidepressants and drugs which induce seizures

Treatment

Barbiturates	Benzodiazepines
	Flumazenil may cause the following adverse effects: fatigue, nausea, vomiting, hypertension, tachycardia, anxiety, confusion, restlessness, aggression, and rarely convulsions and cardiac arrhythmias
Withdrawal symptoms Reinstitute phenobarbitone, and a programme of gradual reduction over three weeks(10 percent decrease in every 3 days).	**Chronic Poisoning:** Phenobarbitone-substitution technique is recommended for benzodiazepine withdrawal and propranolol should be added along for acute somatic symptoms. Replacement of a short half-life benzodiazepine (such as alprazolam) with a long half-life benzodiazepine (such as clonazepam), before initiating a taper and final discontinuation.

Thank you