- **Drug-induced confusion:**
  - **Behavioral toxicities of drugs include:**
    - ✓ Memory impairment.
    - ✓ Confusion: it is the state of being unclear in one's mind about something.
    - ✓ Disorientation: it is a cognitive disability in which the senses of time, direction, recognition of items (things), people and places become difficult to identify.
    - ✓ Mood changes.
    - ✓ Psychosis: abnormal condition of the mind described as involving a loss of contact with reality.

      Note: behavioral toxicity can be produced by both prescribed and abused drugs especially in elderly patients.
  - **Behavioral toxicity produced by a drug can be:**
    - ✓ Dose-related (very often): as you increase the dose → toxicity increases.
    - ✓ Dose-unrelated.
  - **Classes of drugs producing behavioral toxicity:**

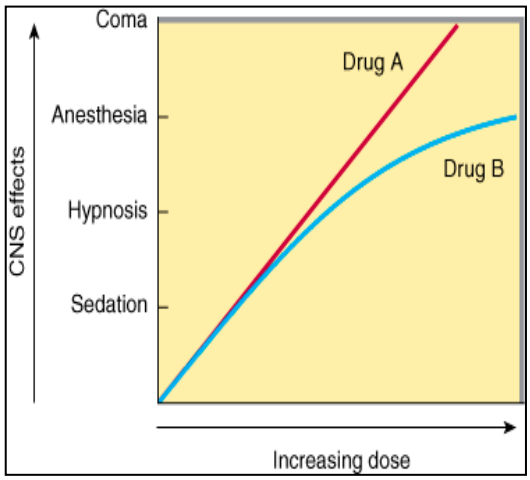
Drugs	Behavioral Toxicities
Benzodiazepines	Confusion, Amnesia
Anti-parkinsonian	Hallucination, Psychotic Symptoms
Digitalis	Apathy, Delirium
Diuretics	Confusion, Weakness
Psychotropics	Disorientation, Confusion
Salicylates	Confusion, Agitation
Corticosteroids	Euphoria, Depression, Hallucination.
General Anesthetics	Post-Anesthetic Confusion, Delirium

    - ✓ Note: in general anesthetics, delirium is mostly seen with "ketamine". Therefore, patient must be prepared with pre-anesthetics drugs which prevent similar effects.

- **Terminologies:**
  - **Sedative-hypnotics**: these are drugs which depress or slow down the body's function (they produce sedation). Barbiturate are considered as a good example but notice that they don't act as anti-anxiety drugs.
  - **Anti-anxiety (anxiolytics):** all of these drugs exert sedative effect.
- **Definitions of the above terminologies (in details):**
  - **Sedative**: a drug which suppresses responsiveness to a constant level of stimulation, with decreased spontaneous motor activity and mental function.
  - **Hypnotic**: a drug which produces drowsiness and encourages the onset and maintenance of a state of sleep that nearly resembles the natural sleep state.
  - **Anxiolytic**: a drug which reduces anxiety and exerts a calming effect with little or no effect on motor or mental function.

    Note: common features for the above 3 classes of drugs are:
    - ✓ Graded.
    - ✓ Dose-dependent.
    - ✓ Reversible depression of the central nervous system.

- **In the diagram:**
  - CNS depression starts with sedation (reduction of irritability) → hypnosis (sleep) → anesthesia (temporary state with one or more of the following: analgesia, paralysis, amnesia and unconsciousness) → coma (a state of unconsciousness in which the patient cannot be awakened).
  - Drug-induced coma might be irreversible!
  - **Drug-A**: as you increase the dose, there is a linear increase in CNS depression effect until reaching the state of coma (example: sedative-hypnotics).
  - **Drug-B**: it is safer and has a plateau (not reaching the state of coma).



- **Benzodiazepine receptor ligands:**
  - **Agonist:**
    - ✓ Causing positive allosteric modulation of omega(2)-receptor function.
    - ✓ Therefore, producing anxiolytic (reducing anxiety) and anticonvulsant effects.
    - ✓ Prototype: BZD (a prototype drug is the first form of a drug or medication that is used to create alternative forms and sates of drugs).
    - ✓ Endozepines: they are endogenous compounds with benzodiazepine-like effects.
  - **Antagonist:**
    - ✓ Blocking BZD but do not block barbiturates and ethanol.
    - ✓ Diazepam receptor binding inhibitor: flumazenil.
  - **Inverse agonist (it is the agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that of agonist):**
    - ✓ Causes negative allosteric modulation of omega(2)-receptor function.
    - ✓ Therefore, producing seizure and anxiety.
    - ✓ Example: β-Carbolines.
    - ✓ Blocking BZD.
- **Pharmacological effects of benzodiazepines and examples:**

Effect	Drug
Sedation/ anxiolytic	Buspirone
Hypnosis	Alprazolam: it has a rapid onset due to its rapid oral absorption and short duration of effect
Anesthesia	Midazolam (given IV)
Anticonvulsant	Lorazepam
Muscle relaxation	Chlordiazepoxide: also used to control withdrawal syndrome of alcoholic patients

- **Benzodiazepines: they are anti-anxiety, sedative-hypnotic drugs.**
  - **Kinetics**: moderate to extensive plasma protein binding (60-95%).
    - ✓ Enzyme induction → leads to development of tolerance.
    - ✓ Phase-1 reaction → phase-2 reaction (notice that only conjugation occurs in phase-2 reaction while multiple other reactions occur in phase-1 reaction).
    - ✓ Active metabolite(s):
      - ❖ Lorazepam has a short duration of action because it has no active metabolites.
      - ❖ Chlordiazepoxide has a long duration of action because it is producing multiple active metabolites (metabolites often have long elimination $t_{1/2}$). This is also the same for flurazepam.

- ❖ Cumulative effect: the state at which repeated administration of a drug may produce effects that are more pronounced than those produced by the first dose.
- ❖ Day-time sedation.

✓ Notice that diazepam is not administered IM because it will bind to muscle proteins.

✓ Zolpidem has not active metabolites and does not cause drug dependence.

- **Benzodiazepine receptors:**
  - ✓ 2 types:
    - ❖ *Omega(1)-receptor.*
    - ❖ *Omega(2)-receptor (being more important).*
  - ✓ Benzodiazepine receptors are part of GABA-receptors (which are pentameric subunits composed of: alpha, beta, gamma (and variants)) → this complex will lead to opening of chloride-channels and influx of Cl ions inside the pre-synaptic neurons resulting in their hyperpolarization (inhibition).
- **Adverse effects of benzodiazepines:**
  - ✓ Sedation, drowsiness, hangover (potentiating the effect of ethanol).
  - ✓ Impaired judgment and motor skills (example: cannot decide whether to stop the car or not when traffic light turns into yellow → this might lead to road traffic accidents).
  - ✓ Vary rarely can produce sexual fantasy in females (flunitrazepam: is a date-rape drug with no taste, flavor or odor which has been banned).
  - ✓ Weight gain and menstrual irregularities (because ovaries also have benzodiazepine receptors).
  - ✓ Elderly are more susceptible to amnesia and sedation.
  - ✓ Drug dependence and withdrawal syndrome.
  - ✓ Floppy-baby syndrome (characterized by decreased APGAR score and poor muscle tone).

- **Drugs for Alzheimer's disease:**
  - **Increasing the availability of Ach in the brain through:**
    - ✓ Cholinesterase inhibitors (mostly selective for the brain). examples include:
      - ❖ *Donepezil.*
      - ❖ *Galantamine.*
      - ❖ *Metrifonate.*
      - ❖ *Rivastigmine.*
      - ❖ *Huperzine-A.*

      Status:
      - ❖ *Limited efficacy in improving the quality of life.*
      - ❖ *Dose-limiting effect.*
      - ❖ *Variable adverse effects*: due to inhibition of cholinesterase in the periphery (mostly GI-related such as colicky pain and abdominal cramps and occasionally cardiovascular: AV-block).
    - ✓ Precursors for Ach biosynthesis: choline and phosphatidylcholine (lecithin)
      - ❖ *Status*: efficacy is doubtful!
  - **Slowing the progression of the disease:**
    - ✓ NMDA- glutamate receptor antagonist (example: memantine).