Chapter 7

Abuse and Addiction to Benzodiazepines and Similar Agents

Benzodiazepines (BZs)

- Medical uses:
  - BZs were developed as a safer sedative/hypnotic alternative to barbiturates
  - Relatively large therapeutic windows
  - Though largely replaced with newer, long-term anxiolytic, still used for short-term acute anxiety and generalized anxiety disorder (GAD)

Pharmacology of BZs

- Various BZs classified by duration of action and pharmacological characteristics
  - More lipid-solubility will effect absorption and slower elimination
  - Allows some choice in which BZ to use depending upon desired effect
- Though often compared to barbiturates, the mechanism of action is more specific for BZs.

Subjective effects of BZs at normal levels

- Users report reduction in anxiety and gentle relaxation
- Used as an hypnotic, reduces sleep latency and reports or restful sleep
- BZs are involved in 1/3 of prescription drug deaths
- When used alone, relativity nontoxic, but when combined with other depressants, the margin of safety is greatly reduced

Side effects of BZs at normal levels

- Usually prescribed as anti-anxiety agents.
- Between 4% and 9% of patients will experience some degree of sedation but reduces with tolerance
- Cross-tolerance with alcohol
- Potential for anterograde amnesia “blackouts”
- There are rare reports of benzodiazepine-induced suicidal thinking in patients who did not demonstrate such thoughts prior to starting these medications

Neuroadaptation, abuse, and addiction to BZ

- BZ abusers fall into one of two groups
  - Small group who uses BZ to achieve euphoria
    - Intravenous BZ abusers
    - Polydrug abusers
  - Second more common group abuse BZ by taking more of it or for longer than was prescribed in reaction to development of tolerance

Neuroadaptation, abuse, and addiction to BZ

- Discontinuation syndrome from neuroadaptation meaning stopping BZ disrupt newly adjusted balance.
  - Based on:
    - Duration of use
    - Dose used
    - Half-life of BZ used
    - Individual expectations

BZ abuse

- Use these compounds to enhance the effects of the primary drug of choice
- Control some of the unwanted side effects of the primary drug of abuse
- Help control the effects of the withdrawal process from their primary drug of abuse
- Patients who are recovering from *any* SUD are “at risk” for a reactivation of their addiction if they should receive a prescription for a BZ

Drug Interactions involving BZ

- Cimetidine can increase BZ blood levels
- Disulfiram can reduce the biotransformation of BZs
- BZ use can alter the blood levels of many antipsychotic medications such as haloperidol
- St. John’s Wort may reduce effectiveness of BZ
- Due to synergistic effects, BZ not be mixed with other CNS depressants

Long term consequences of chronic BZ use

- Although originally hailed as safe and non-addicting, both assertion has not born out
- Potential for psychological dependence
  - “clock watching” for next dose
- Only recommended for second tier, short-term treatment for insomnia as sleep-inducing hypnotic effect diminishes rapidly and may result in REM suppression

BZ receptor antagonists (BRAs)

- Buspirone
  - Marketed in 1986 under the name of BuSpar was introduced as an anti-anxiety agent
  - New class of compounds, *azapirones*
  - Mechanism of action not well understood
  - Side-effects
  - Interacts with MAO Inhibitors

BZ receptor antagonists (BRAs)

- Zolpidem
  - Hypnotic introduced in 1993 as Ambien
  - Unlike the BZs, Zolpidem causes only a minor reduction in REM sleep when used at normal levels, and it does not interfere with the normal progression through the stages of sleep, allowing for a more restful night's sleep
  - Adverse effects:
    - Nightmares, headache, GI upset, agitation and some degree of residual drowsiness
    - Does cause some cognitive performance problems
    - Sleepwalking has been reported

BZ receptor antagonists (BRAs)

- Abuse potential of Zolpidem
  - Since its introduction, evidence has emerged that its abuse potential might be higher than originally thought
  - Abuse potential seems to be about the same as BZs
  - Reports of users resisting hypnotic effects to achieve sense of euphoria

BZ receptor antagonists (BRAs)

- Zaleplon
  - Name brand Sonata
  - Approved in the US only for hypnotic use
  - Little evidence of a “hangover” effect
  - Various side effects:
  - Tolerance to hypnotic effects develop quickly so only good for short-term
  - Abuse potential is the same for BZs

Lunesta®

- Not a member of the BZ family but is a hypnotic meant to treat short-term insomnia
- Does have abuse potential
- Reported side effects include “hangover” effect, GI upset, cognitive problems
- Implicated in amnesia with higher doses
- Synergistic effect with other CNS depressants

Ramelteon

- Brand name Bozerem is a novel hypnotic agent that binds at the melatonin receptor
- Thought to enhance the effects of melatonin
- Only 2% reaches the brain

Rohypnol

- BZ that is not legally sold in the U.S (schedule IV)
- Used by physicians in other countries as a pre-surgical medication, muscle relaxant, and as a hypnotic
- Know in US as a “date rape” drug
- Its pharmacological characteristics, especially when mixed with alcohol, could induce a state of anterograde amnesia that would last for 8-24 hours

Sedative, hypnotic, or anxiolytic use disorders and the DSM-V

- Sedative, hypnotic, or anxiolytic use disorder
- Sedative, hypnotic, or anxiolytic intoxication
- Sedative, hypnotic, or anxiolytic withdrawal
- Other sedative, hypnotic, or anxiolytic-induced disorders

Rohypnol

- Estimated to be 10 times as potent as diazepam
- Hard to detect with standard urine toxicology tests
- It is a member of the benzodiazepine family of drugs, the effects are similar to those seen with other BZs in use in this country
- It is capable of causing a pharmacological state of dependence
- Unlikely to ever be legalized in the US