ANXIOLYTICS, SLEEP AGENTS, AND STIMULANTS

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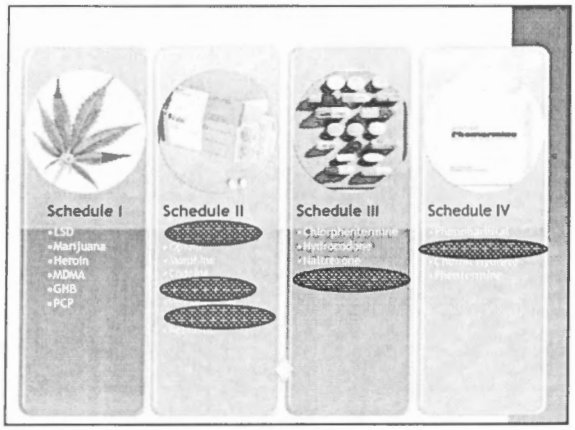
DEA CLASSIFICATION

High Abuse Potential	No accepted use for medical treatment in the U.S.A	CAN be used for research
High Abuse Potential	Severe Physical Dependence Liability	Severe Psychological Dependence Liability	NO REFILLS. NO TELEPHONE PRESCRIPTIONS.
Abuse potential less than levels I and II	Moderate or Low Physical Dependence Liability	High Psychological Dependence	Prescriptions must be rewritten after 6 months
Low Abuse Potential	Limited Physical Dependence	Limited Psychological Dependence	Prescriptions must be rewritten after 6 months.
Lowest abuse potential of all controlled substances.			



ANTIDEPRESSANTS

- Mentioned in previous lectures
- Have a role in the chronic treatment of anxiety disorders—many are FIRST LINE treatment!
- All may increase anxiety when they are started.
  - Warn patients
  - Start a benzodiazepine for short-term usage.

BENZODIAZEPINES

- Approved for the following:
  - Acute Anxiety
  - Chronic Anxiety
  - Insomnia
- Avoid in the following:
  - Patients with a history of drug use.
  - Patients with a history of alcohol use.
- Almost all patients will develop some physical dependency.
- 60% of patients with panic disorder will stay on benzodiazepines indefinitely.

SIDE EFFECTS OF BENZODIAZEPINES

- Daytime sedation
- Ataxia
  - Can lead to dangerous falls
  - Big concern for the elderly
- Accident proneness
  - Motor Vehicle Accidents
- Headaches
- Memory problems
  - Short-term memory problems
  - Brief periods of profound memory loss
- Paradoxical excitement or anxiety

PROBLEMS WITH BENZO USE

- The short half-life of some benzodiazepines can facilitate medication tolerance and dependence.
- Powerful reinforcement for avoidance and numbing coping mechanisms.
- Become a safety signal and a significant obstacle to exposure treatments.
  - Prohibits extinction learning in CBT.
- Benzodiazepines have not been found efficacious in treating PTSD.

BENZODIAZEPINE WITHDRAWAL

- Increased Blood Pressure
- Increased Heart Rate
- Shaking, redness, agitation
- Possible psychosis and delirium
- Seizure and death

ANTIADRENERGIC AGENTS

- Reduce re-experiencing of traumatic events in PTSD.
- May decrease physical symptoms of a panic attack.
- Still being studied in research.
- Most commonly used:
  - Clonidine
  - Propanolol

BUSPAR

- Serotonin$_{1A}$ receptor partial agonist.
- Typically dosed three times daily.
- No motor, memory, or concentration impairments.
- No abuse potential.
- Will not cause dependency or withdrawal.
- No drug interactions.
- Disadvantages:
  - Takes 3 weeks to mitigate anxiety.
  - Decreased response in severe anxiety
    - Especially patients who have received benzos in the past
  - Stimulates the locus coeruleus
    - Paradoxical increase in anxiety in some patients.

SLEEP AGENTS

- Trazodone
  - Discussed in previous lectures
- Zolpidem (Ambien)
- Lunesta
- Rozerem
- Seroquel
  - Is NOT NOT NOT NOT a sleep agent.

SLEEP AGENTS

Generic	Trade	Half-Life	Onset	Adult Dose	Mechanism
Zolpidem	Ambien	1.5-2.4	Fast	5-10	GABA-A Agonist
Zaleplon	Sonata	1	Fast	5-10	GABA-A Agonist
Eszopiclone	Lunesta	5-7	Medium	2-3	GABA-A Agonist
Ramelteon	Rozerem	1-2.6	Fast	8	Melatonin Agonist

NON-BENZO SLEEP AGENTS

- Less risk of misuse
- Less risk of rebound insomnia
- No Withdrawal symptoms
- Can generally be given to recovering addicts
- May cause "hangovers" if taken too late at night.
- Trazodone (desryl)

ZOLPIDEM

- GABA-A Receptor Agonist
- Can be taken in doses larger than prescribed
- Is available in a controlled-release preparation
- Can cause parasomnias

RAMELTEON (ROZEREM)

- Selective Melatonin Agonist
- Does not bind to GABA
- No activity within brain reward system
- Rapid onset of action.
- Reportedly "addiction proof."

STIMULANTS

Treatment of ADHD:
Amphetamine Behavioral Stimulants

- Methylphenidate (Ritalin, Concerta, Metadate)
- Used in treatment of ADHD to calm hyperactivity and improve attention (prescribed in 90% of cases)
- Narcolepsy
- Half-life = 2-4 hours
- Variable absorption rates, but generally a rapid onset with short duration (multiple administrations needed over the course of a day)
- Long acting forms now available

Treatment of ADHD:
Amphetamine Behavioral Stimulants

- Methylphenidate (continued)
- + Abuse potential
- Increases synaptic conc. of DA by blocking the presynaptic DA transporter (like cocaine) and increases the release of DA (like amphetamine)
- Contraindicated in pts with HTN, anxiety, CAD

Treatment of ADHD:
Amphetamine Behavioral Stimulants

- Other drugs:
- Dexedrine, Adderall, Vyvanse

Treatment of ADHD:
Non-Amphetamine Behavioral Stimulants

- Strattera (Atomoxetine) NE reuptake inhibitor
- Less abuse potential
- Not scheduled as a controlled substance
- Provigil (Modafinil)
- Potentiates glutamate neurotransmission, and inhibits activity of GABA neurons in the nucleus accumbens and cerebral cortex-- probably
- Used in treatment of ADHD, narcolepsy, "shift-worker" medicine

Intoxication with Stimulants

- Euphoria
- Elevated HR
- Dilated pupils
- Increased Anxiety
- Decreased appetite
- Possible cardiotoxicity in overdose

Withdrawal from Stimulants

- Fatigue
- Depression
- Increased appetite
- Excessive sleep
- Can progress to extreme depression with psychosis

SEDATIVE–HYPNOTICS

TABLE 5-30 Sedative–Hypnotics

Generic (Brand)	Dose (Ativan-eq)	Half-Life (hr)	Onset	Active Metabolites (Half-Life, hr)	Administration	Metabolism	Dose (mg/day)
Benzodiazepines							
Alprazolam (Xanax, XR)	0.5	6–27	Fast to intermediate	No (6–27)	PO	Hepatic	0.75–5.00
Chlordiazepoxide (Librium, Mitran)	10	8–28	Intermediate	Yes (3–200)	PO	Hepatic	15–100
Clonazepam (Klonopin)	0.5	18–50	Slow	No (19–50)	PO	Hepatic	0.5–4.0
Clorazepate (Tranxene)	7.5	30–200	Fast	Yes (3–200)	PO	Hepatic	15–60
Diazepam (Valium)	5	20–50	Fast	Yes (3–200)	PO, IV	Hepatic	4–40
Flurazepam (Dalmane)	15	40–114	Fast	Yes (36–120)	PO	Hepatic	15–30
Lorazepam (Ativan)	1.0 (comparator)	10–20	Intermediate	No (13–16)	PO, IV, IM	Hepatic and renal	1–10
Midazolam (Versed)	2	1–4	Fast	No	IV, IM	—	—
Benzodiazepines							
Oxazepam (Serax)	15	5–15	Slow to intermediate	No	PO	Hepatic and renal	30–120
Temazepam (Restoril)		3.5–18.5	Fast	No	PO	Hepatic and renal	15–30
Triazolam (Halcion)		1.5–5.5	Fast	No	PO	Hepatic	0.125–0.5
Other Hypnotics							
Eszopiclone[a] (Lunesta)		3–6	Fast	No	PO	Hepatic	1–3
Ramelteon[b] (Rozerem)		1–3	Fast	No	PO	Hepatic	8–16
Zaleplon[a] (Sonata)		1	Fast	Yes	PO	Hepatic	5–20
Zolpidem[a] (Ambien, -CR, Stilnox)		1.5–4.5	Fast	No	PO	Hepatic	5–10 CR: 6.25–12.5

[a]Benzodiazepine receptor agonists. May afford less tolerance and dependence; similar impairments of memory or performance; and lack the anxiolytic, anticonvulsant, and muscle-relaxant properties of benzodiazepines. Use is restricted to 35 days.
[b]Melatonin-receptor agonist; approved for adults with difficulty initiating sleep.
IM, intramuscular; IV, intravenous; PO, oral.

TABLE 5-31 Other Sedating Drugs

Generic (Brand)	Action	Dose (mg/day)	Side Effects and Contraindications
Diphenhydramine (Benadryl)	Antihistamine	25–300 PO or IM (divided)	CNS depressant May be clinically dangerous with emphysema, COPD, glaucoma, BPH
Benztropine (Cogentin)	Anticholinergic	0.5–2	Use caution in patients with glaucoma, tachycardia, BPH
Hydroxyzine (Vistaril, Atarax)	Antihistamine	50–100 PO or IM	Dry mouth, drowsiness Avoid long-term use in patients with anxiety
Promethazine (Phenergan)	Phenothiazine	12.5–50	High risk of typical EPS May produce fatal respiratory depression Use caution in patients with glaucoma, ulcer, obstructions, hepatic disorders, marrow dysfunction or depressants, epilepsy
Melatonin (unbranded)	Hormone	0.5–10	Use caution in patients with bleeding and those using anticoagulants, NSAIDs, antiplatelet or antidiabetic agents

COPD, chronic obstructive pulmonary disease; EPS, extrapyramidal side effects; BPH, benign prostatic hypertrophy; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug; PO, oral.

TABLE 5-32 Herbal Medications Used in Psychiatry

Agent	Indications	Dose (mg/day)	Adverse Risks	Efficacy
St. John's Wort	Mild to moderate depression	300–1800 (divided)	Serotonin syndrome with SSRIs; may induce CYP3A4 9 and lower OCPs, cyclosporin, digoxin, Indinavir, Irinotecan, warfarin levels); mania, phototoxicity, dry mouth, dizziness, constipation anxiety, fatigue, headache, sexual dysfunction	Poor evidence in severe MDD One RCT in moderate MDD

(*continued*)

TABLE 5-32 Herbal Medications Used in Psychiatry (*continued*)

Agent	Indications	Dose (mg/day)	Adverse Risks	Efficacy
SAMe	Depression; may augment antidepressants	400–1600	May increase mania or anxiety in bipolar disorder, mild insomnia, decreased appetite, constipation, nausea, dry mouth; sweating, dizziness	May be effective if given IV; RCTs about PO administration are ambiguous; sometimes used to augment SSRIs or SNRIs
Folate	Depression; may augment antidepressants; may help in mild dementia	.4 (RDA age 19 years and older)	High doses may provoke vitamin B12 deficiency; may interact with methotrexate; may increase seizure risk at high doses and with anticonvulsants; may cause allergic reactions	Decreased folate levels are linked with decreased response to antidepressant treatment
Omega-3 fatty acids	Depression > mania in bipolar disorder	1000–2000 (EPA + DHA)	GI distress, fishy taste, may induce mania, may increase bleeding with anticoagulants	May be effective in bipolar depression for long-term use (off-label use); may augment antidepressants

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GI, gastrointestinal; IV, intravenous; MDD, major depressive disorder; OCP, oral contraceptive pills; PO, oral; RCT, randomized, controlled trial; RDA, recommended daily allowance; SAMe, S-adenosyl methionine; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

General Guidelines for the Management of Non-Emergent Side Effects

- Educate patients about common, serious, and transient side effects before initiating a new medication
- Begin with the lowest effective dose and gradually titrate upward ("start low; go slow")
- Reassure and wait when side effects are likely to abate with ongoing therapy.
- Consider adjunctive agents rather than switching to another agent, which may delay the therapeutic response