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Using Controlled Substances for Pediatric Behavioral Health

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Speaker Disclosure

- I have no personal disclosures
- I will be discussing non-FDA approved uses of medications
  - These will be clearly identified as such

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Learning Objectives

1-Apply the current evidence for the use of controlled psychopharmacotherapeutic agents in pediatric behavioral healthcare.

2- Discuss the clinical implications for the use of controlled psychopharmacotherapeutic agents in pediatric behavioral healthcare.

3- Incorporate knowledge of monitoring parameters required when using controlled pharmacotherapeutic agents in pediatric behavioral healthcare.

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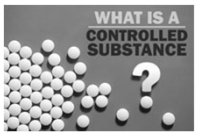
What Are Controlled Substances?



- According to the DEA (Controlled Substance Act of 1970), controlled substances are classified as such because of:
  - Its actual or relative potential for abuse.
  - Scientific evidence of its pharmacological effect, if known.
  - The state of current scientific knowledge regarding the drug or other substance.

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What Are Controlled Substances?

- Its history and current pattern of abuse.
- The scope, duration, and significance of abuse.
- What, if any, risk there is to the public health.
- Its psychic or physiological dependence liability.
- Whether the substance is an immediate precursor of a substance already controlled under this subchapter.

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https://www.dea.gov/drug-information/csa

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DSM Schedules

- Range from I to V
  - Schedule I- "highest risk of abuse with no recognized medical use in the US"- "these may not be prescribed, dispensed, or administered"
    - Ex: marijuana, MDMA, heroin, mescaline (peyote), LSD
  - Schedule II- have "high abuse potential with severe psychological or physical dependence"
    - Cannot have refills
    - Ex: oxycodone, morphine, **methylphenidate**, **amphetamine salts**, hydromorphone

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DSM Schedules

- Schedule III- "intermediate abuse potential"
  - Can be prescribed over the phone, can only be refilled 5 times
  - Ex: anabolic steroids, **ketamine,** testosterone
- Schedule IV- "Abuse potential less than Schedule II but more than Schedule V"
  - Can be prescribed over the phone and have as many as 5 refills per 6 months
  - Ex: diazepam, **alprazolam**, tramadol, **clonazepam,** codeine preparations with higher codeine concentrations
- Schedule V – "least potential for abuse"
  - Can be prescribed over the phone, have a "partial fill" which is equivalent to a refill
  - Ex: Pregabalin, codeine preparations with lower codeine concentrations (cough medicines)

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Should Monitor for Misuse

- Examples of misuse
  - Taking too much
  - Taking too often
  - Incorrect dose
  - Incorrect route
  - Sharing with others/using medications prescribed for others

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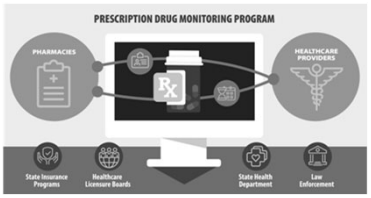

Prescription Drug Monitoring Program (PMDP)

- Is an electronic database that tracks controlled substance prescriptions within a state
- Allows for real-time ability to identify prescription dispensing
- NPs can access and staff in office can be delegates to access information
- Not all states are equal

https://www.cdc.gov/drugoverdose/pdmp/index.html

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When Using Controlled Substances, Think About Abuse Potential

- Immediate release is often more likely to give a "high" than an extended release
- Prodrugs like lisdexamphetamine have lower abuse potential (theoretically)
- Patches versus oral- patches can still be abused!!!!!!
- Always consider using non-controlled substances as options for treatment
  - SSRI for anxiety
  - Alpha adrenergic agent, antipsychotic for aggression

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Why Is This An Issue In Pediatrics?

- Brain development continues until the mid 20s
  - Particularly pruning and remodeling of the cortex and mesolimbic structures occurs in adolescence
  - Once described as "use it or lose it" (Giedd, 2004)- if used regularly they are shored up and strengthened, if not used, they are pruned and remodeled

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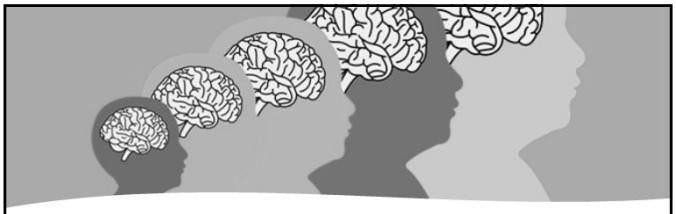

Why Is This An Issue In Pediatrics?

- One of the largest areas remodeled is the prefrontal cortex- the decision brain. Many if not most of the controlled substances are active in this portion of the brain
  - Believed to be why teens have increased novelty seeking and risk taking

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Psychostimulants

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Psychostimulants

- Best evidence and response for treatment of ADHD
- NIMH Multi-Modal Treatment of ADHD study- 80% response, general response in trials 70-90%
- Two stimulant groups- methylphenidate (MPH) (ex Concerta, Ritalin, Focalin, Daytrana, Quillivant) and amphetamine/dextroamphetamine (AMPH) (ex Adderall, Vyvanse)
- Do not use stimulants under 6 without a trial of behavioral interventions- MPH is drug of choice for age 4-6 (Wolraich et al., 2018)
  - Stimulants may cause mood reactivity/dysphoria in preschoolers
- Titrate dose to maximum effect with minimum s/e

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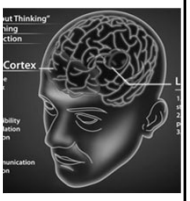
How do they work? MPH

- Increases Nepi and dopamine by blocking reuptake
- Enhances dopamine and NEpi actions in dorsolateral prefrontal cortex (PFC). This area is responsible for working memory, attention, impulse control and planning. May improve attention, concentration, executive function, wakefulness
- Improves basal ganglia dopaminergic activity which may affect hyperactivity
- Enhances dopamine and NEpi in other areas which may affect depression, fatigue, and somnolence



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How do they work? AMPH

- Primarily work to block dopamine and NEpi reuptake and facilitate their release- means higher concentrations available
- Affects vesicular monoamine transporter 2 and monoamine oxidase activity
- Enhances dopamine and NEpi actions in dorsolateral prefrontal cortex (PFC). This area is responsible for working memory, attention, impulse control and planning. May improve attention, concentration, executive function, wakefulness
- Improves basal ganglia dopaminergic activity which may affect hyperactivity
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Concerns with Use

- Common adverse effects
  - Insomnia (less than 1 hour/night). Evidence for melatonin up to 3 mg
  - Anorexia while active
  - GI upset
  - Headache
  - Irritability
  - Tachycardia (1-4 bpm)
  - Hypertension (1-4 mm Hg systolic, 1-2 mm Hg diastolic
- Contraindications: Glaucoma, HTN, hyperthyroidism, Symptomatic cardiovascular disease, unstable psychiatric disease

Concerns with Use

- Decreased growth (1-2 cm from predicted height- mostly first 3 years- catch-up growth happens). Is dose related
- Some evidence for decreased bone density, especially in males- unclear if clinical significance (Fu, et al., 2022)
- Tics- Commonly comorbid, fears of stimulants precipitating tics
  - Cochrane Review entitled "Pharmacologic treatment for attention deficit hyperactivity disorder (ADHD) in children with comorbid tic disorders (2018)
  - Treatment with MPH, clonidine, MPH + clonidine, guanfacine and desipramine improve tic symptoms
  - Of stimulants, only high dose dextroamphetamine appeared to worsen tics (1 study)
  - General clinical practice is that stimulants are preferred

Stimulants and Psychosis

- Is inattention part of ADHD or prodrome for psychosis?
- Observational studies remain mixed
- Gallagher et al (2022) conducted a systemic review
  - Examined both AMPH and MPH
  - 8 studies included (n = 232,567 patients): 4 retrospective cohort studies, 1 nested case-control study, 2 self-controlled case series, and 1 prospective cohort study
  - No significant evidence of risk of psychosis with MPH, 1 study showed evidence in AMPH but limited studies available so unable to draw conclusion and more research needed

Concern for Cardiovascular Instability

- Lead to black box warnings in 2004 due to concern for sudden unexplained death
  - Originally amphetamine then also concern for methylphenidate
- New guidelines "Although concerns have been raised about sudden cardiac death among children and adolescents using stimulant medications, it is an extremely rare occurrence" and did not result in actual deaths. (Wolraich, et al, 2019, p.14)

Mandatory Cardiac Pre-Screening

Screen all children for:

Cardiac symptoms	Family history of sudden death, CV sx, Wolff-Parkinson-White, hypertrophic cardiomyopathy, and long QT syndrome.

Symptoms or concerning history merit referral to pediatric cardiology before using medications.

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When to Stop

- Dose adjustment or discontinuation needed for agitation, significant H/A or GI distress, psychosis, hallucinations, increased irritability, marked somnolence, worsening anxiety/depression

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Monitoring

- Baseline BP, pulse, height and weight to rule out contraindications and for growth monitoring
- Annual VS assessment
- Assess weight and objective measurement of loss of appetite at each visit.
- Screen for insomnia, headaches, social withdrawal, and tics
  - Look for behavioral problems on medications (anger, irritability, "meltdowns")
- 40% will respond to both types, 40% will respond to only one
- Are they taking medication daily- if not adjust Rx!

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Selecting the Correct Medication

- Meta-analysis of stimulant effects Cortes et al. *Lancet Psychiatry* 2018: 5: 727-38
  - Included 133 RCTs
  - AMPH is the most efficacious in children but have a higher side effect profile and are tolerated less well than MPH, they also significantly increase DBP.
  - MPH is the only drug with better acceptability than placebo.
  - They conclude MPH as first choice in children and adolescents

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Selecting the Right Dose

- Farhat et al (2022) conducted a meta-analysis of 65 RCTs involving 7877 children and adolescents
  - Higher drug S/E and higher discontinuation with higher doses
  - Concluded there was limited incremental benefit beyond 30 mg MPH and 20 mg AMPH in fixed-dose trials
  - Flexible dosing (considering symptoms, tolerance) allows for higher dosing, improved symptoms, and decreased adverse effects and discontinuation

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Selecting the Right Dose

- Some debate over what dose should be started
  - Evidence suggests low dose (0.3 mg/kg/dose) best to enhance cognitive function (inattention) while higher doses (0.6mg/kg/dose) are more effective for behavioral control (hyperactivity/impulsivity
- **Doses should not exceed 2 mg/kg/d for MPH and 1 mg/kg/day for AMP**
- 3rd doses (if used) should be ~ half or less of 1st and 2nd doses to minimize rebound effects and insomnia

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Selecting the Right Formulation

- There are short and long acting formulations, osmotic release systems (OROS), and prodrugs (lisdexamphetamine (Vyvanse), dexmethylphenidate + serdexmethylphenidate (Azstarys)
- Longer acting formulations are better tolerated and less likely to have rebound/withdrawal effects
- Shorter acting formulations are more flexible for adjuvant dosing and titration
- Are patches, chewable and liquid formulations commercially available

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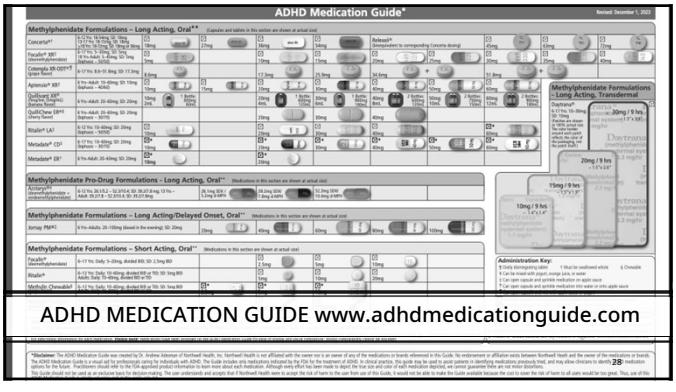

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Dosing Options

- Concerta (MPH) is in indigestible vehicle so can't crush (Write OROS if generic)
- Quillivant XR (MPH), Adzenys ER (AMPH), Dynavel XR (AMPH) come in liquid form so good for those who can't swallow pills
- Chewable versions MPH (short acting and Quillichew ER MPH)
- ODT MPH (Contempla XR), ODT AMPH (Adzeyns XR-ODT, Eveko ODT versions as well
- Daytrana MPH patches

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What Do I Do?

- Caveat!!!!!
- Journay- rare
- Concerta- common. OROS formulation if generic
- Focalin- common
- Quillivant- rare for chewable and liquid preparation
- Vyvanse- common
- Adderall- uncommon

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Shortages in 2024

- National stimulant shortages are noted and ascribed to increased diagnoses and increased demand for medication worldwide, supply chain issues including manufacturing and raw supply shortages (CBS news)
- DEA sets annual quotas on stimulant production
- Is affecting generic brand more than brand name medications
- Education
  - Refill at 14 days
  - Review refill policies- how long it takes to process, etc.
  - Support families!

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Ketamine

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Ketamine

- Ketamine is a N-methyl-D-aspartate-receptor (NMDAR) antagonist, it is a derivative of phencyclidine (PCP)
- Esketamine is the version used for use in psychiatry
- It is a nonselective NMDA receptor channel inhibitor that causes glutamate release
- It may also cause opioid signaling; affect monoamine pathways, the adrenergic system, and the cholinergic system; and cause neuromodulatory effects that result in its antidepressive effects (Ryan & Hosanager, 2023)

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Ketamine

- Is indicated for adjunctive treatment resistant depression in adults and for acute depression in adults with suicidal behavior
- It is important to note the safety and efficacy for use in pediatrics IS NOT established
  - Data are VERY limited
- AACAP stated in 2018 "Therefore, esketamine is not proven to be safe or indicated in children and adolescents, and AACAP's Psychopharmacology Committee does not currently recommend its use in this population." https://www.aacap.org/AACAP/Latest_News/statement_ketmamine.aspx

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What Is Known?

- Esketamine commonly causes dissociation and sedation and has been associated with significant hypertension
- Typically administered over an induction phase of 1-4 weeks twice a week, maintenance for weeks 5-8 once weekly, then every 2 weeks beginning week 9.
- Is administered IV or with a nasal kit that is FDA approved for use via a REMS program
- It can precipitate psychosis because of its dissociative properties
- No clear protocols regarding use of concomitant psychotherapy

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Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. (Dwyer et al., 2021)

- Authors conducted a single double-blind, case crossover, clinical trial of 17, 13-17 year-old adolescents with MDD
  - Received a single IV dose of ketamine or midazolam
  - Crossover to other drug occurred two weeks later
  - Depression scores were measured with the Montgomery-Asberg Depression Rating Scale (MADRS)
  - MADRS decrease significantly higher in ketamine-treated youth vs. midazolam (− 17.66 in ketamine vs − 8.97 in midazolam) after 24 h ($p = 0.036$, effect size of 0.78). 13 of 17 (78%) responded (> 50% MADRS ↓) to ketamine in 3 days post-treatment. Effects lasted 14 days as measured by MADRS
    - At 6-week mark, 3 patients were in remission, at 6 months- 2 were in remission

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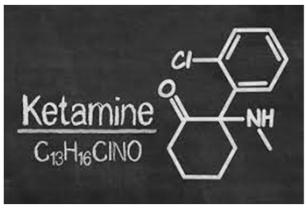
What is Known?

- Anti-suicidal properties of ketamine are not established in youth
  - Only lithium and ECT have clear suicide protective evidence (Ryan & Hosanagar, 2023)
- Interest in use for PTSD, eating disorders, substance use disorders, and disorders with complex aggression



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Benzodiazepines

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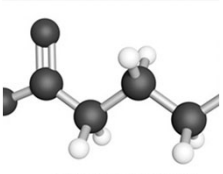
How Do They Work?

- Are central nervous system depressants
- Enhances GABA activity binding to GABA receptors in the CNS
  - Highest concentrations in the reticular activating system, cerebellum, and cerebral cortex
- Inhibit neuronal activity in the fear centers of the amygdala- thus creating anti-anxiety effects
- Half-lives between drugs vary widely from less than 24 hours to over 48 hours



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Issues With Benzos

- Tolerance and dependence are known issues- as quickly as two weeks
- Sedation is a large problem
  - Ataxia- staggering gait
  - Confusion
  - Antegrade amnesia- difficulty forming new memories
  - Impaired judgment
- Withdrawal symptoms are common and vary from anxiety, insomnia, nightmares, psychosis, hyperpyrexia, seizures

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Uses In Pediatric Behavioral Health

- Limited at best
  - Rapid decrease of pre-procedural anxiety
  - Safety and efficacy for use in panic disorder is limited
  - Resolving insomnia of mania
  - Sedation for acute aggression/risk of harm to others
    - Risk with olanzapine
  - NMDA receptor encephalitis- limited

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Uses In Pediatric Behavioral Health

- May worsen suicidal ideation
- Good evidence for use when treating catatonia
- Must be used with caution with delirium- can reduce survival and precipitate cognitive impairment
- Note that youth with ASD and ID are much more likely to have a paradoxical reaction to BZDs

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Benzodiazepine

Name	Dose	Half-life	Notes
clonazepam	0.01-0.03 mg/kg to max 0.05 mg/kg/d	30-40 hours	Taper by 0.25 mg every 3 days- may need to go much slower May require tapering over months (1% q3days)
diazepam	0.12-0.8 mg/kg/day divided q6-8h up to age 12	20-50 hours	Taper by no more than 2 mg every 3 days
alprazolam	0.125-0.25 mg PO TID to max 3.5 mg/day in 7+ yo	12-15 hours	Risk of sz is highest 1st 3 days after D/C Taper no faster than 0.5 mg/day every 3 days

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