Pain Management and Compliance Toxicology

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Prescription Drug Abuse: A National Problem

- Prescription drug abuse is a growing issue nationwide
  - Opioid prescription deaths have exceeded deaths due to cocaine and heroin combined. *CDC, 2007.*
  - Prescription drugs now account for more deaths than illicit drugs. *TCMEO, 2012*
  - Prescription drugs now account for more deaths than motor vehicle accidents. *CDC, 2014.*
  - Patients receiving chronic opiate therapy demonstrated non-compliant urine drug tests results with a frequency of 32-48%. *Hariharin, Ives, Michna. 2006, 2007*
- Growing number accessibility to prescription drugs
  - Insurance enrollment
  - Intended and unintended access
  - Overprescribing
Prescription Drug Abuse: Why Test? Why Confirm?

- Growing number of prescriptions
- Government support
- Documentation of patient compliance
- Justification of continued treatment plan
- Justification of change in treatment plan
- Unrecognized drug use problems
- Drug diversion
- Risk management
- Accurate results
Four Major Toxicology Subfields

- Postmortem forensic toxicology
- Human performance toxicology
- Workplace drug testing toxicology
- Drug compliance toxicology
Most Common Drugs of Abuse

- Ethanol
- Marijuana
- Cocaine
- Methamphetamine
- Heroin
- Prescription drugs
Most Common Prescription Drugs of Abuse

- Hydrocodone
- Oxycodone
- Carisoprodol
- Alprazolam
- Morphine
- Codeine
- Hydromorphone
- Fentanyl
- Methadone
- Buprenorphine
- Meperidine
- Diazepam
- Clonazepam
- Lorazepam
- Oxazepam
- Quetiapine
- Amphetamine
- Methylphenidate
Scheduling of Drugs

- Schedule I through V
  - Potential for abuse
  - Medical use
  - Level of physical dependence as a result of abuse.
  - Level of psychological dependence as a result of abuse.
  - Risk to public health
  - Substance is an immediate precursor to a controlled substance.
Opioids and Synthetic Opiates

- Effects: Pain relief, CNS depression
- Synthetics used in treatment of opiate addiction
- Mechanism: Opiate receptor binding in CNS, inhibition of pain pathways

- Examples:
  - Heroin
  - Prescription Drugs
    - Hydrocodone (Vicodin)
    - Oxycodone (Oxycontin)
    - Oxymorphone (Opana)
    - Morphine (Kadian)
    - Codeine (Tylenol #3)
    - Hydromorphone (Diluadid)
    - Methadone (Dolophine)
    - Buprenorphine (Suboxone)
    - Fentanyl (Duragesic)
    - Meperidine (Demerol)
Behavioral

- Typically prescribed drugs
- Effects: mood stabilization, relief of depression and anxiety, sedation, relief of chronic and neurogenic pain
- Mechanism: Increase of 5HT and NE in CNS synapses, down regulation of other receptors
- Examples:
  - Tricyclic Antidepressants (TCAs)
  - 2nd and 3rd Gen Antidepressants
    - Trazodone
    - Quetiapine
    - Bupropion
    - Duloxetine
    - Sertraline
    - Venlafaxine
Benzodiazepines

- Typically prescribed drugs
- Effects: Sedation, anti-anxiety
- Mechanism: Increase effects of inhibitory neurotransmitters (GABA) by binding to receptors in CNS
- Examples:
  - Alprazolam (Xanax)
  - Diazepam (Valium)
  - Clonazepam (Klonopin)
  - Lorazepam (Ativan)
- International
  - Phenazepam (Russia)
  - Etizolam (Canada, UK)
Stimulants

- Effects: Increased energy, decreased appetite, mental alertness, stimulation of CNS, increases confidence
- Mechanism: Stimulation of the cerebral cortex, Release of 5HT, NE, and dopamine.
- Examples:
  - Cocaine
  - Methamphetamine
  - MDMA, Ecstasy
- Prescription Drugs
  - Amphetamine (Adderall)
  - Methylphenidate (Ritalin)
Muscle Relaxants

- Typically prescribed drugs
- Effects: Pain relief, treatment of muscle spasms, management of anxiety disorders
- Examples:
  - Carisoprodol (*Soma*)
  - Meprobamate (*Milltown*)
  - Cyclobenzaprine (*Flexeril*)

Note: TCA structure
Non-Benzodiazepine Hypnotics

- Typically prescribed drugs
- Effects: Sedation, drowsiness, induces sleep,
- Mechanism: Reacts with benzodiazepine GABA receptor complex
- Examples:
  - Zolpidem (*Ambien*)
  - Zopiclone (*Lunesta*)
  - Zaleplon (*Sonata*)
Typically prescribed drugs

Examples:
- Gabapentin (Neurontin)
  Use: Antiseizure, neuropathic pain relief, other off label uses
- Pregabalin (Lyrica)
- Primidone (Mysoline)
  Uses: Antiseizure, treatment of tremors
- Ketamine (Ketaset)
Other Illicit Drugs

- Not typically prescribed drugs
- Examples:
  - THC (*Marijuana*)
  - Phencyclidine (PCP)
  - “Bath Salts”
  - Synthetic Cannabinoids (*K2, Spice*)
  - Mitragynine (*Kratom*)

Cathinone (*Khat*)

Methylone

**Chemical Structures:**
- **THC:** ![THC Chemical Structure](image)
- **Cathinone:** ![Cathinone Chemical Structure](image)
- **Methylone:** ![Methylone Chemical Structure](image)
- **JWH-018 & JWH-250:** ![JWH Chemical Structures](image)
Toxicology Specimens
Fate of Drugs in Body

Absorption → Blood → Distribution → Excretion

Biotransformation (Metabolism)
Screen and Confirm

- Screening process
  - Narrow from many possibilities
  - Think funnel
- Confirmation
  - Provide proof to confirm “suspicion”
  - Drug quantitation
  - Evaluate against “Cutoffs”
Methods of analysis

- Immunoassay
  - Sensitive, poor quantitation
  - Ex. POCT Cup, AU 400
- LC/MS/MS
  - Ability to identify multiple drugs simultaneously
  - Very sensitive
Immunoassay

- Utilizes the antigen-antibody reaction
  - Target compound class
  - Exposure of host to antigen
  - Formation of antibody to “combat” foreign substance
  - Removal and mass production of antibody
- Susceptible to false positives
  - Confirmation necessary
Liquid Chromatography/Tandem Mass Spectrometry (LC-MSMS)
The Separation Process

- Column - the site of separation
The separation process

Compound A has a greater affinity for the stationary phase than compound B and, therefore, will take longer to elute (that is, have a greater retention time).
Liquid Chromatography/Tandem Mass Spectrometry (LC-MSMS)

- The technology
  - Liquid Chromatograph (LC)
    - Column Separation
  - Tandem Mass Spectrometry (MS-MS)
    - Fragmentation
    - Monitoring of Fragments
    - Identification
Tandem Mass Spectrometry

- The technology
  - Source
  - ESI
  - Q0-Focusing lens
  - Q1-Mass selection
  - Q2-Collision cell
  - Q3-Mass analysis
## 83 Drug Confirmation and Quantitation Method

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Confirmed Drug</th>
<th>Measured Drug</th>
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<tbody>
<tr>
<td>11-nor-9-carboxy-delta9-THC</td>
<td>Flurazepam</td>
<td>Norfentanyl</td>
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<tr>
<td>6-MAM</td>
<td>Gabapentin</td>
<td>Norhydrocodone</td>
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<td>7-Aminoclonazepam</td>
<td>Hydrocodone</td>
<td>Norketamine</td>
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<tr>
<td>7-Aminoflunitrazepam</td>
<td>Hydromorphone</td>
<td>Normeperidine</td>
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<td>7-hydroxyquetiapine</td>
<td>Imipramine</td>
<td>Noroxycodone</td>
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<tr>
<td>Alprazolam</td>
<td>Ketamine</td>
<td>Norpropoxyphene</td>
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<tr>
<td>Amitriptyline</td>
<td>Lorazepam</td>
<td>Nortriptyline</td>
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<tr>
<td>Amphetamine</td>
<td>MDA</td>
<td>O-Desmethyl-cis-Tramadol</td>
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<tr>
<td>a-OH-Alprazolam</td>
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<td>Desmethyldoxepin</td>
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<td>Zaleplon</td>
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<td>Flunitrazepam</td>
<td>Norbuprenorphine</td>
<td>Zolpidem-phenyl-4-carboxy</td>
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<tr>
<td></td>
<td>Nordiazepam</td>
<td>Zopiclone</td>
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Conclusions

- Prescription drug use is a growing problem
- Compliance monitoring is a tool
- LCMSMS technology allows for multiple drug identification and quantitation
- Results improve treatment plans, prevent drug diversion, and provide risk management
Sources

- CDC
- NIDA
Thank You

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