

- Diagram a dose/response curve. What would be the effect of adding an antagonist? Adding a non-competitive antagonist?
- Diagram a neuronal synapse. Describe how reuptake inhibitors influence this environment.
- Discuss the major structures of the brain that could be affected by drugs acting on the central nervous system.
- What is therapeutic index? How is it calculated? Give an example of a drug with a high therapeutic index. Give an example of a drug with a low therapeutic index.

13.5 Opioids (Natural, Synthetic and Semisynthetic)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 12.
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 23-24.
 - NHTSA: Methadone, morphine
- Study Questions
 - Differentiate between the terms opiate, opioid and narcotic.
 - Discuss the structure-activity relationship of morphine and its opiate analogs versus the opiate antagonist, naloxone.
 - Which of the following are used to synthesize opioids? Give specific products.
 - Morphine
 - Codeine
 - Papaverine
 - Noscopine
 - Thebaine
 - Discuss absorption, distribution, metabolism and elimination (ADME) of heroin.
 - Discuss the role of codeine and 6MAM in the determination of whether a death involved heroin.
 - What is the classical clinical presentation of acute opiate toxicity?
 - Discuss the pharmacologic CNS effects of opiates that would be relevant in a DUI case.

13.6 Cocaine/Benzoylgonine

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 13.

- NHTSA: Cocaine
- FSR: Cocaine
- Study Questions
 - What is contraction band necrosis?
 - What are the effects of cocaine on catecholamines?
 - What is neurotransmitter depletion? How is it related to cocaine use?
 - What are the effects of cocaine on drivers at the following concentrations?
 - Cocaine 0.02 mg/L, benzoylecgonine 0.3 mg/L
 - Cocaine ND, benzoylecgonine 2.0 mg/L

13.7 Cannabinoids

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 14.
 - FSR: Cannabinoids
 - NHTSA: Cannabinoids
- Study Questions
 - A Commonwealth Attorney calls to discuss the following cases. What would you say?
 - THC 0.001 mg/L, THCA 0.02 mg/L. Driver pulled over for bad driving, officer witnessed suspect throw joint out of window, failed all FSTs.
 - THC 0.001 mg/L, THCA 0.02 mg/L. Driver pulled over for broken tail light, defendant admitted to smoking a joint the night before, performed fairly well FSTs.
 - Is there an established relationship between THC blood concentration and driving impairment? Discuss why or why not.
 - What are the major metabolites of THC? Are they active/inactive? Which one does DFS analyze and why?
 - Describe ADME of THC.
 - THC has a broad spectrum of pharmacologic effects. Describe each. Can THC be classified in one drug category?
 - Describe the effects of THC on driving.

13.8 CNS Depressants (Benzodiazepines, Barbiturates, Carisoprodol, Zolpidem, GHB, etc.)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 11.

- Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 17.
- FSR: Benzodiazepines, GHB
- NHTSA: Carisoprodol, GHB, zolpidem
- Study Questions

Make a table listing major CNS depressant drugs analyzed in DUID cases. Include:

- Dosage form
- Therapeutic uses
- Therapeutic range
- Toxic concentrations
- Lethal concentrations
- Half-life
- Detection time in blood
- Detection time in urine
- Typical adverse side effects

13.9 Sympathomimetic Amines (Methamphetamine, Amphetamine, MDMA, Ephedrine, Methylphenidate)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 15.
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 10.
 - FSR: Methamphetamine
 - NHTSA: Methamphetamine, MDMA
- Study Questions
 - What are the common neurotransmitters involved in sympathomimetic pathways?
 - What are the common structural properties of these neurotransmitters?
 - How does hydroxylation affect their action?
 - Compare ADME for methamphetamine and MDMA. Include concentrations that contribute to observed effects and discuss tolerance.
 - What "rave" accessory is used to provide protection from a common MDMA side effect and why is it used?
 - Discuss the noted effects of methylone (or other novel psychoactive substances like methylone for which DFS provides testing).
 - Discuss the effects of methamphetamine and MDMA on driving.
 - Sympathomimetic amines are usually present in racemic mixtures. Describe the different properties of d and l methamphetamine and MDMA.

13.10 Hallucinogens (LSD, PCP, Ketamine, Psilocybin)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 16.
 - FSR: Ketamine
 - NHTSA: Ketamine, LSD, PCP
- Study Questions
 - Which neurotransmitters are responsible for the hallucinogenic properties of compounds?
 - Compare ADME of LSD and PCP. Include dosage and detection times.
 - Discuss significant adverse effects of hallucinogenic drugs on driving.
 - What are the lethal toxic effects of hallucinogenic drugs?
 - What is the prevalence of hallucinogenic drug use in the general population?

13.11 Neuroleptics (Antipsychotics)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 19.
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 18.
- Study Questions
 - Give 2 examples each of old and new generation neuroleptics.
 - Describe ADME for each.
 - What are some of the side effects of old and new generation neuroleptics?
 - What are some of the advantages of the new generation neuroleptics?

13.12 Antidepressants (MAO, TCA, SSRI)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 18.
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 19.
- Study Questions
 - What are some of the side effects that would result from tricyclic antidepressant combined concentrations of 0.1 mg/L amitriptyline and 0.5 mg/L nortriptyline?
 - Compare and contrast mechanisms of action, ADME and side effects of TCAs, SSRIs and MAOs.

13.13 Anticonvulsants (Phenytoin, Carbamazepine, Valproic acid, Gabapentin, Lamotrigine, Topiramate)

- Required Literature Reading
 - Levine Principles of Forensic Toxicology, Ch 17.
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 21.
- Study Questions
 - Drugs used to control seizures have varied chemical structures. Describe each.
 - Describe the neurological pathways of seizure control.
 - Describe lethal toxicities associated with seizure medications.
 - Describe the metabolism of carbamazepine and its significance.
 - Describe the adverse effects of seizure medication on driving.
 - In OCME cases, what is the most important reason for the analysis of seizure medications?

13.14 Antihistamines/NSAIDS (Diphenhydramine, Promethazine, Dextromethorphan, ASA, APAP)

- Required Literature Reading
 - Goodman and Gilman's The Pharmacological Basis of Therapeutics, Ch 25, 27
 - NHTSA: Diphenhydramine, dextromethorphan
- Study Questions
 - Make a table of histamine receptors including localization within the body, antagonists associated with each and the therapeutic uses, therapeutic/toxic levels, therapeutic effects and effects on driving for each antagonist.
 - Why do antihistamines have anticholinergic effects?
 - Describe postmortem redistribution of antihistamines.
 - What antihistamines can be used in a DFSA? What screening method is used to detect them? What is their detection time in blood and urine?

14 DATA REVIEW AND CASE EXAMINATION

14.1 Objectives

- To learn the process and documentation involved in data review.
- To learn the process and documentation involved in case examination and technical review.
- To learn the process for creating and releasing cases using LIMS.

14.2 Methods of Instruction

- Data review and case examination training is primarily learned by observing multiple certified examiners and performing training examinations that are critiqued by certified examiners
- Trainee will observe and take notes of data (batch) review process with at least two experienced data reviewers.
- Trainee will observe and take notes of case examination and review process with at least two experienced examiners.
- Trainee will observe and take notes on LIMS Certificate of Analysis creation, technical review and release with at least two experienced examiners.
- Trainee will review the Toxicology Procedures Manual (Ch. 2), Quality Manual (Ch. 17.1). ASCLD/LAB Supplemental- Section 4.13 Control of Records, ISO 17025 – Section 4.13 Control of Records, Technical Review Form (Form 100-F111).

14.3 Laboratory Exercises

- Perform data review on alcohol, immunoassay, drug screen, GC quantitation, GCMS quantitation, LC-MS-MS quantitation batches with at least two different examiners.
- Perform case examinations on 10 non-IMPLIED consent cases with at least two different examiners (total 20 cases minimum). Cases should be a variety and include homicide, drug overdose, sexual assault (at least one), positive ethanol/drugs manslaughter, and decomposition cases. Medical examiner ethanol only cases are not included.
- Perform 10 DUID/DUI case examinations with at least two different toxicologists/examiners (total 20 cases minimum). No more than 5 ethanol only cases and 2 negative tox cases can be included in the 20.
- The trainee should document the review at least five case files using the appropriate Technical Review Form (TRF). Case files should be generated by multiple examiners, if possible. The potential findings of the reviews shall be discussed with the Training Coordinator. Technical Review Forms generated in this capacity shall be marked as Training and retained in their Training File. The case files shall be technically reviewed by a qualified examiner pursuant to QM 17 prior to release.

14.4 Evaluation

- Non-IMPLIED Consent cases. Trainer will select 20 cases that have not had final case examination performed. Trainee will perform final case examination using a Toxicology Summary Worksheet marked as a training case and submit cases to trainer for evaluation.

- DUID/DUI cases. Trainer will select 20 DUID/DUI cases that have not had final case examination performed. Trainee will perform final case examination using a Toxicology Summary Worksheet marked as a training case and submit cases to trainer for evaluation. Alternately, the data from released cases may be used.

14.5 Study Questions

- What does the analyst date on the batch chain-of-custody indicate?
- How many controls must be acceptable in a drug quantitative batch?
- How is carryover monitored in a drug quantitation? What is the appropriate response when carryover is detected?
- Describe occasions when a drug may be reported as present.
- An OCME case history lists rule out heroin. The blood morphine quantitation is 0.10 mg/L, 6AM none detected. As final case examiner, is this case complete? What other questions might you consider?
- A methadone quantitation was performed on femoral blood and heart blood. Would you expect the methadone concentrations to be different and if so why?
- A sexual assault case has immunoassay blood benzodiazepine negative, urine benzodiazepine pending and benzodiazepine quantitation none detected. As final case examiner is benzodiazepine testing complete?
- Hospital blood and urine are submitted in a DUI manslaughter case. The blood alcohol was 0.10% on two separate aliquots. Would you order a urine alcohol and why or why not?

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15 UNCERTAINTY OF MEASUREMENT

15.1 Objectives

- To familiarize the trainee with traceability and its associated concepts.
- To familiarize the trainee with concepts of uncertainty of measurement.

15.2 Readings and Presentations

- Required
 - ASCLD/LAB Policy on Measurement Uncertainty (AL-PD-3060).
 - ASCLD/LAB Policy on Measurement Traceability (AL-PD-3057).
 - ASCLD/LAB Guidance on Measurement Traceability (AL-PD-3058).
 - ASCLD/LAB Guidance on Estimation of Measurement Uncertainty – Overview (AL-PD-3061).
 - ASCLD/LAB Guidance on Estimation of Measurement Uncertainty – ANNEX A: Details on the NIST 8 Step Process (AL-PD-3062).
 - ASCLD/LAB Guidance on Measurement Traceability – Measurement Assurance (AL-PD-3059).
 - ASCLD/LAB Guidance on the Estimation of Measurement Uncertainty – ANNEX D Toxicology Testing Discipline Example – Concentration of Ethanol in an Ante-Mortem Blood Specimen.
- Additional Resources
 - Presentations prepared by Dr. Wagner and DFS, available on the intranet.
 - Introducing the Concept of Uncertainty of Measurement in Testing in Association with the Application of the Standard ISO/IEC 17025 (ILAC-G17:2002).
 - Bell, S. A Beginner's Guide to Uncertainty of Measurement, Measurement Good Practice Guide No. 11 (Issue 2), ISSN 1368-6550.

15.3 Study Questions

- Define the following terms:
 - NIST
 - ASCLD/LAB
 - Mean
 - Median
 - Mode
 - Range
 - Accuracy
 - Precision
 - Gaussian distribution
 - Confidence Interval
 - Coverage Factor
 - Measurement

- Measurand
 - Type A evaluation
 - Type B evaluation
- Draw and explain what a Gaussian distribution is and how it relates to measurement uncertainty. Demonstrate two Gaussian distributions where one has high variability and one has low variability.
 - Obtain an uncertainty budget used in the toxicology section. Define the elements and from where the information is obtained.
 - Within the toxicology section, find a calibration standard that is traceable to NIST. Write a brief description of the traceability of that item.
 - Use the following information (Table 1) to calculate the expanded uncertainty at $k=2$ and $k=3$ and calculate the uncertainty of the measurement of alprazolam at 0.082mg/L. Report the measurement of alprazolam and its associated uncertainty at the 95.45% level of confidence.

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