**Therapeutic Range and DUI**

**Definition: Therapeutic Range**
- The concentration of drug at which the patient will experience the desired clinical effect with a minimum of undesirable or adverse reactions.
- Size of range: determined by the toxicity of the drug.

**Therapeutic Index, Ratio, Concentrations**
- Therapeutic index = LD 50/ED 50.
- Where LD 50 if the lethal dose of the drug in 50% of the population and ED 50 is the effective dose of the drug in 50% of the population.

**A Reference Range Is Not the Same As a Therapeutic Range.**
- Alprazolam: therapeutic range: 10 – 50 ng/ml (NMS).
- Zolpidem: peak plasma concentrations following single oral 5 mg dose: 29 – 113 ng/ml.... (NMS). This is not a therapeutic range.
Quoted Therapeutic Range Will Vary From Source to Source

- Alprazolam (blood)
  - PacTox: 5 – 25 ng/ml
  - NMS labs: 10 – 40 ng/ml

- Carisoprodol/Meprobamate
  - PacTox: <20 / 5-20 ug/mL
  - NMS labs: <25/10-30 ug/mL

Absorption Phase

- Defined as the time required for uptake of the drug across various barrier sites and into certain tissues.
- Dependent on route of administration:
  - Patch: very slow.
  - Oral: slow.
  - Inhalation: faster.
  - Injection: fastest.

Distribution Phase

- Drug is distributed via the systemic circulation.
- Depends on several factors:
  - Blood flow to the tissue (cardiac output, arterial health, etc).
  - Partition coefficient between drug and tissue.
  - Chemistry of the drug (ionization).
  - Molecular size.
  - Protein binding.
Elimination Phase (Clearance)

- Most drugs metabolized by the liver.
- Purpose:
  - To detoxify.
  - To prepare for excretion.
- Excretion occurs via:
  - Kidneys.
  - Bile.
  - Lungs.
**Half-life**

- The amount of time it takes for the plasma concentration to decrease by 50%, given a first order process.

**Steady State**

- The level at which the amount of drug absorbed is equal to the amount being eliminated.
- The level of drug achieved after several constant dosages at constant intervals.
- The therapeutic range is usually steady state, but not necessarily visa-versa.
Narrow Therapeutic Range: Oxycodone

Wider Therapeutic Range: Methadone

Steady State

Effect of Increased Dosage

Lengthened Dosage Interval
From the PDR:
Until You Experience How This Medication Affects You, Do Not Drive a Car or Operate Heavy Machinery And Do Not Drive a Car or Operate Heavy Machinery Until Such Time You Feel It Is Safe to Do So

**DUI: The “Triad of Results” - I**
- Nature of the driving, including:
- Driving behaviors observed by police and/or witnesses.
- Nature of accident or incident.
- Accident reconstruction.
- Information from airbag system.
- Statements of witnesses to the accident.
DUI: The “Triad of Results” - II

- Driver’s condition, including:
- Police and witness descriptions of how the driver appeared and was doing after accident.
- Police interviews.
- FST’s and DRE’s.
- Admissions by the driver or passengers.

DUI: The “Triad of Results” - III

- Toxicology, including:
  - History of ingesting alcohol and/or drugs (prescription or non-prescription).
  - Pill bottles or prescriptions found in vehicle.
  - Blood and urine test results.
  - Medical records, if available.
  - Autopsy report and related documentation.

A Few Questions.....

Is the therapeutic dose or range defined by the manufacturer designed for optimal driving?

No, it is defined for a particular therapeutic benefit, such as pain relief.
Does a manufacturer even claim that a drug does not affect driving?

No, most centrally-acting drugs carry mfr’s warnings that they can adversely affect driving.

Does everyone even agree on what the therapeutic range actually is?

No, therapeutic ranges are in the eye of the beholder, even for the primary therapeutic effect, let alone for multiple indications.

Does a listed therapeutic range allow for the combined effects of other drugs and/or alcohol?

No, such ranges apply to only the drug as sole agent, taken at recommended doses.

Factors Which Affect How People Respond to Drugs in a Driving Situation

- √ Pharmacological nature of the drug (depressant, stimulant, etc.).
- √ Whether this is a new prescription.
- √ Degree to which the patient is tolerant.
- √ Dose, recency of dose, new prescription.
Factors, continued

- Other co-administered agents, including alcohol, similar drugs, antagonistic drugs, drugs or food that interfere with metabolism.
- Physical factors: Tired, sick, in pain.
- Miscellaneous factors: Distracted, UIC, bad weather, road conditions.
- How demanding is the driving situation?

Illustrative Cases – I

- **Nature of Accident**
  - Single car.
  - Left road and crashed.
  - Road unfamiliar to driver.

- **Driver Factors**
  - Taking Hyc for years in same doses.
  - Chronic back pain.
  - No prior DUI’s.
  - Drove thousands of miles per year.

Illustrative Cases – I (contd.)

- **Toxicology**
  - Postmortem Blood.
  - BAC = 0.11%.
  - Hyc = 29 ng/mL.
  - Reportedly takes ½ a 7.5 mg Hyc pill 1-3 X daily.
  - Max dose 30 mg/day.

- **Reference Ranges**
  - Therapeutic range (Plasma): 18-32 ng/mL.
  - WB/Pl ~ 1.
  - PMR ~ 1.

Illustrative Cases - II

- **Nature of Accident**
  - Rear impact collision into stopped vehicle.
  - Then crossed into opposing lane and struck another car.
  - Stopped when she hit a utility pole.

- **Driver Factors**
  - 37 year old female.
  - Partial DRE exam at hospital showed impairment by CNS depressants.
Illustrative Cases – II (contd.)
- **Toxicology**
  - Blood collect 4 hrs after accident.
  - Carisoprodol = ND.
  - Meprobamate = 28.4 ug/mL.
  - Hyc = 70 ng/mL.

- **Reference Ranges**
  - Chronic Therapy:
    - Carisoprodol: 3-15 ug/mL; Meprobamate: 5 – 30 ug/mL.
  - Therapeutic range Hyc (Plasma): 18-32 ng/mL.

Illustrative Cases - III
- **Nature of Accident**
  - Single car accident
  - Surface street.
  - Veered off road.
  - Struck bus stop.
  - Killed 4 people.

- **Driver Factors**
  - 34 year old female.
  - Eyes bloodshot, watery, glassy.
  - Dazed appearance.
  - Speech slurred, confused.
  - Failed FST’s.

Illustrative Cases – III (contd.)
- **Toxicology**
  - Blood collected 1 hour post-accident
  - Alprazolam = 100 ng/mL.

- **Reference Ranges**
  - Therap Ranges: 5-25; 10-40 ng/mL.
  - Peak concentration 1 hour after 1 mg dose ~ 12 ng/mL.
  - Steady state after 3 mg daily dose ~ 29 ng/mL.
  - WB/Pl ~ 0.8

Illustrative Cases - IV
- **Nature of Accident**
  - Hit bicyclist.
  - Surface street.
  - Failed to stop and render aid.
  - Left scene.
  - Later said she knew she “hit something”.

- **Driver Factors**
  - 44 year old female.
  - Unsteady gait.
  - Slurred speech.
  - Droopy eyelids.
  - Food on face, clothing.
  - Failed FST’s.
Illustrative Cases – IV (contd.)

- **Toxicology**
  - Blood collected X hours after accident.
  - Carisoprodol = 4.6 ug/mL.
  - Meprobamate = 27.1 ug/mL.
  - Codeine = 150 ng/mL.

- **Reference Ranges**
  - Chronic Therapy: Carisoprodol: 3-15 ug/mL; Meprobamate: 5 – 30 ug/mL.
  - Peak level 0.5-1.5 hours after a single 60 mg dose for Codeine: 110 – 230 ng/mL.

Illustrative Cases – V

- **Nature of Accident**
  - Turning left at intersection.
  - Surface street.
  - Hit motorcyclist.

- **Driver Factors**
  - 42 year old male.
  - Poor balance & coord.
  - Speech slow, slurred.
  - Constricted pupils slow to react to light.
  - Eyes B/S, watery.
  - Failed FST’s

Illustrative Cases – V (contd.)

- **Toxicology**
  - Blood collect 5 hours after the accident.
  - Fluox/NF = 480/280 ng/mL.
  - Caris/Mepro = 1.1/2.7 ug/mL.
  - Trazodone = 220
  - Norpropoxy = 470

- **Reference Ranges**
  - 60 mg/ day for 1 week, F: 200-531; NF: 103-465 ng/mL.
  - Chronic, Caris: 3-15, Mepro: 5-30 ug/mL.
  - Single 100 mg dose, Trazodone: 1300-1900
  - SS, 195 mg/day, NP: 600-3000 ng/mL.

Illustrative Cases - VI

- **Nature of Accident**
  - Veered into oncoming lane.
  - Surface street.
  - Speed too fast for conditions.

- **Driver Factors**
  - 39 year old male.
  - “Appeared to be asleep at the wheel” before the accident.
  - Meth + paraphernalia.
  - HR 100, BP 120/80
  - Probable meth W/D.
Illustrative Cases – VI (contd.)

- **Toxicology**
  - Blood collected 5 hours post-accident.
  - Methamphetamine = 785 ng/mL.
  - Amphetamine = 45 ng/mL.

- **Reference Ranges**
  - Therapeutic range for methamphetamine (ADHD or narcolepsy): <50 ng/mL.
  - Typical range for active drug effects in abuse: >100 ng/mL.

Illustrative Cases- VII

- **Nature of Accident**
  - Rear-end collision.
  - Freeway.
  - Another car caused accident by driving erratically.
  - Unable to stop in time when 2 cars came into lane.

- **Driver Factors**
  - 47 year old male.
  - Police: Condition “Apparently Normal”.
  - No DRE, No FST.
  - No biological samples collected immediately post-accident for toxicology.

Illustrative Cases – VII (contd.)

- **Toxicology**
  - Urine collected 2 days after the accident.
  - BZE = 20000 ng/mL.

- **Reference Ranges**
  - Urine level of BZE roughly consistent with a same day dose of 40 – 120 mg.

Summary

- Therapeutic or other reference ranges can be accepted as a rough guide only.
- Drivers with blood levels in the therapeutic range can still be impaired for driving.
- Some people may be unimpaired at elevated drug levels.
- Drug impairment is not a “quantum” phenomenon.
Summary (contd.)

- Some cases will have insufficient information to form a forensically sound opinion on impairment.