Drug Trends: The Opioid Epidemic

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Drug Trends: The Opioid Epidemic

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Objectives

- Understand what is the opioid epidemic.
- Appreciate the significance of the patient's right to pain relief.
- Brief review of the opioids.
- Understand the biotransformation of the opioids.
- Understand the pharmacological and toxicological effects of opioids.
- Appreciate the concentration ranges for the opioids.

Objectives

- Understand how to toxicologically evaluate an overdose or a DUI case involving opioids.
- Know what is needed for a toxicologist to review.
- Apply the "3 prong" approach (actions, assessment and toxicology) to your forensic evidence.
- Know where to get the toxicological references you need.
- Apply this knowledge to some actual forensic cases.

The Opioid Epidemic

- Epidemic: a rapid spread or increase in the occurrence of something
  : a temporary prevalence of a disease
- The opioid epidemic is the increase in the prescription and use of opiates to treat pain and the prevalence of resulting opiate addiction.

The Opioid Epidemic in Tennessee

- There were more opioid prescriptions than people in TN in 2015.
- 1.18 opioid prescription for every man, woman and child.
- TN is second only behind AL in the prescription of drugs per capita.
- More Tennesseans (1,263) died in 2014 from opioid overdose than car accidents or firearms.

The Opioid Epidemic

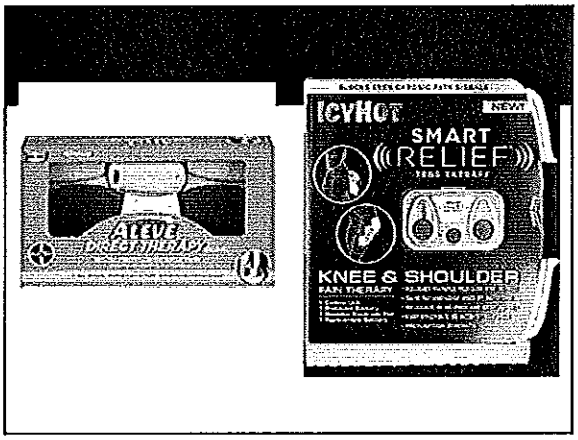
- Why the increase in opioid prescriptions?
- The Federal Government and numerous states have passed laws protecting and promoting the patient's right to pain relief.
- Pharmaceutical companies have developed sustained release opioid pain medications to meet the needs of patients with chronic pain.
- Pain management has become a medical specialty.

The Opioid Epidemic

- What do patients expect from their physicians?
- It is treatment of their medical condition and if that includes any pain, they expect relief of that pain.
- There are many tools physicians can use to relieve pain, drugs are only one such tool.

Pain Management

- Pain can be classified in severity as minor to severe, and in duration as acute to chronic.
- Pain can be relieved by:
  - physical rehab & electrotherapy
  - acupuncture
  - light therapy
  - cognitive/ behavioral therapy/ hypnosis
  - steroids / nerve blocks



Pain Management

- Other causes of pain can be relieved by:
  - muscle relaxants (benzodiazepines and carbamates).
  - neuritic pain (fibromyalgia, diabetic nerve pain) with gabapentin.
  - local anesthetics / topicals
  - anticonvulsants ("off label use")
  - antidepressants (SSRIs, TCAs, SNRIs)
  - marihuana / cannabinoids

Pain Management

- Moderate to severe pain of any duration may require pharmacotherapy.
- Acetaminophen or a NSAID such as ibuprofen should be used first.
- Opiates/opioids/combination medications with immediate release such as tramadol, codeine, morphine, or oxycodone should be used next.
- If the pain is of short duration (a few days) then a short prescription for a minimal number of tablets should be used.

Pain Management

- If the pain is moderate to severe and of a chronic nature (recurring for an extended period) then sustained release opiates should be used such as OxyContin, MS Contin, Zohydro, Opana, or Exalgo, with immediate release opioids for break through pain.
- The medical conditions producing this type of pain are often debilitating and require these drugs/formulations for relief.

Chronic Opioids

- Chronic administration of opioids leads to tolerance.
- Tolerance is an increased need for more drug, more often, to achieve effectiveness (relief of pain as well as the toxic effects).
- Increased and chronic use of opioids leads to addiction.
- Addiction is the chronic need and use of a drug to maintain normal function and avoid withdrawal.

Dependence on Opioids

- Continued used of opioids will lead to *physical dependence* or *addiction (substance dependence).*
- Persons are addicted when
  - their bodies need the drug for normal physiological function.
  - they have pronounced drug-seeking behavior.
  - cessation of drug use produces a *withdrawal* or *abstinence syndrome.*

Dependence on Opioids

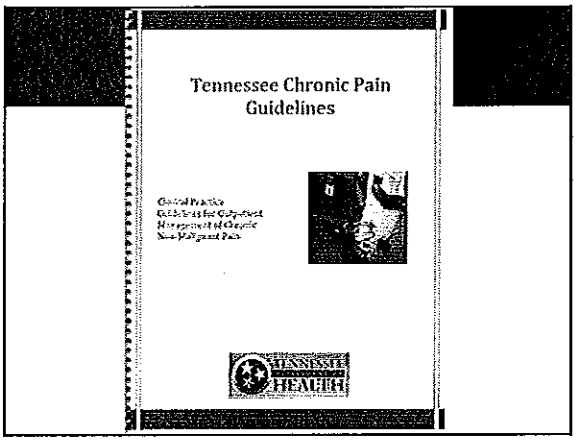
- Opioids will also produce a strong compulsion to use the drug to maintain a feeling of well-being. This is termed *psychological dependence* or *habituation.*
- *Tolerance* is a decreased response to the effects of a drug, thus requiring larger doses to achieve the same effect.

Dependence on Drugs

- Tolerance may be due to:
  - metabolic tolerance : increased biotransformation of a drug after its chronic use.
  - behavioral tolerance : ability to compensate for a drug's effect.
  - functional tolerance : compensatory changes in a drug's receptor.

The Opioid Epidemic in Tennessee

- The TN Department of Health has developed new guidelines to help reduce the use of opioids.
- The number of opioid prescriptions has declined each year in TN since 2013.
- Morphine milligram equivalents dispensed in TN has decreased each year since 2012.



Prescription Drug Abuse In Tennessee

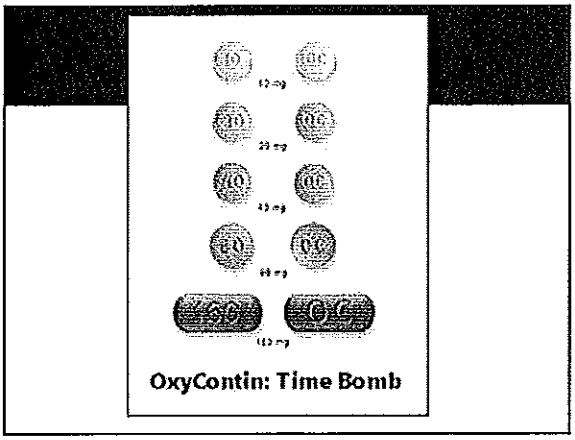
- Controlled Substance Monitoring Act of 2002. Monitors dispensing of all schedule II –V drugs.
- Controlled Substance Monitoring Database (CSMD) and Prescription Safety Act (2012).
- Physicians are required to check the CSMD before giving opioids or benzodiazepines to their patients as a new course of treatment lasting more than 7 days.
- Physicians must report patients who deceive them or attempt to get controlled substances within 5 days to law enforcement.

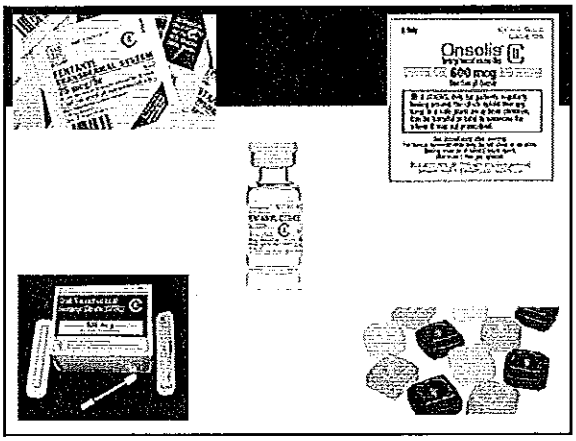
Prescription Drug Abuse In Tennessee

- The increased control of prescription medications is a means to reduce drug diversion.
- Increased education to disposal removes potential for abuse.
- Reduced accessibility and availability to opioids increases the pressure and the market for illicit opioids like heroin.

Opioids

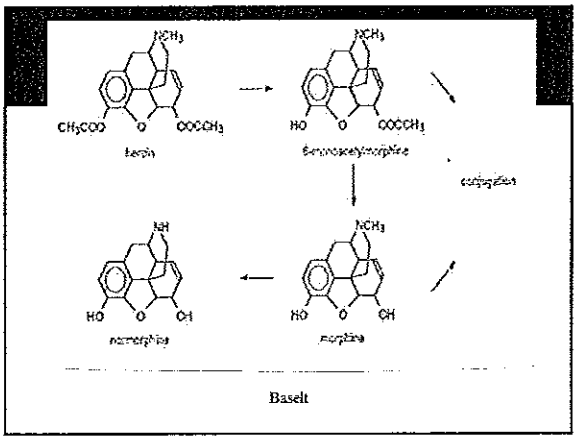
- Heroin (diacetylmorphine)
- Morphine (Kadian, MS Contin)
- Codeine
- Hydrocodone (Lortab, Vicodin, Zohydro, Hysingla)
- Hydromorphone (Dilaudid, Exalgo)
- Dihydrocodeine (Synalgos-DC)
- Oxymorphone (Numorphan, Opana)
- Oxycodone (Percodan, Roxicodone, Oxycontin)
- Fentanyl derivatives
  - Fentanyl (Duragesic, Sublimaze, Innovar)
  - Alfentanil (Alfenta)
  - Sufentanil (Sufenta)
  - Remifentanil (Ultiva)
- Synthetic fentanyls (acetylfentanyl, furanylfentanyl)
- Propoxyphene (Darvon)
- Methadone (Dolophine)
- Meperidine (Demerol)
- Tramadol (Ultram)

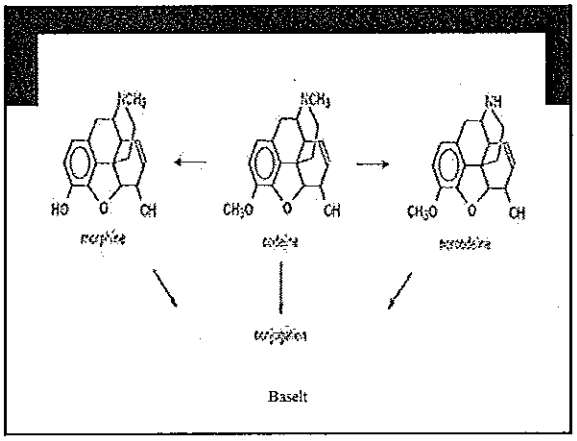


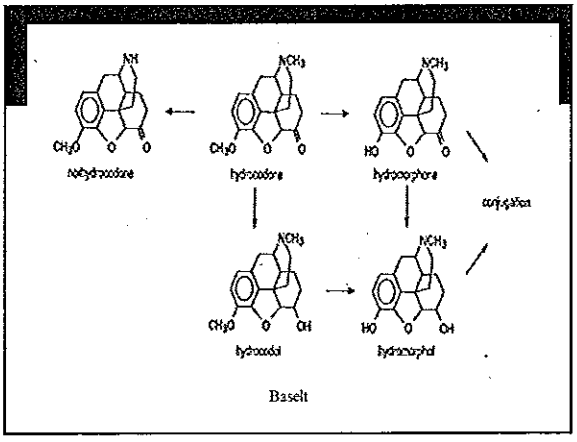


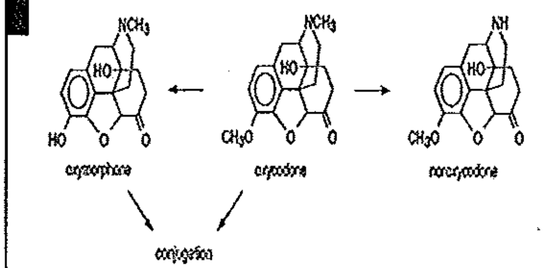
Biotransformation of Opioids

- All of the opioids are metabolized to active metabolites.
- Identification of the different opioids can help prove which drugs were used/abused.
- Often times if the subject is addicted to opiates they will use multiple drugs in this class.









Baselt

Pharmacological and Toxicological Effects

- Opioids bind to opiate receptors in the central nervous system (CNS).
- Used as analgesics to relieve pain and some as adjuncts for surgical anesthesia.
- Abused for their ability to produce euphoria and decrease consciousness.
- Very potent drugs (minimal doses produce extremely low blood concentrations but tremendous responses).

Drug Recognition Expert Matrix

	CNS Depressants	CNS Stimulants	Hallucinogens	PCP	Narcotic Analgesics	Inhalants	Cannabis
HGN	Present	None	None	Present	None	Present	None
Vertical Nystagmus	(High Dose) Present	None	None	Present	None	(High Dose) Present	None
Lack of Convergence	Present	None	None	Present	None	Present	Present
Pupil Size	Normal (1)	Dilated	Dilated	Normal	Constricted	Normal (4)	Dilated (6)
Reaction to Light	Slow	Slow	Normal (3)	Normal	Little or None Visible	Slow	Normal
Pulse Rate	Down (2)	Up	Up	Up	Down	Up	Up
Blood Pressure	Down	Up	Up	Up	Down	Up/Down (5)	Up
Body Temperature	Normal	Up	Up	Up	Down	Up/Down Normal	Normal
Muscle Tone	Flaccid	Rigid	Rigid	Rigid	Flaccid	Flaccid	Normal

1 [illegible]
2 [illegible]
3 [illegible]
4 Normal, but may be dilated
5 [illegible]
6 Pupil size possibly normal

Clinical Toxicology

- Clinical presentation of the opioid effects can include:
  - apathy, drowsiness, dizziness, confusion
  - impairment of cognition and motor control
  - constipation and urinary retention.

Clinical Toxicology

- Clinical presentation of the opioid effects can also include:
  - lethargy, small to pinpoint pupils, low blood pressure and heart rate, decreased body temperature, diminished bowel sounds and flaccid muscles
  - respiratory depression, apnea, pulmonary edema
  - seizures with some synthetics (meperidine, propoxyphene and tramadol).

Drugs of Abuse: Opioids

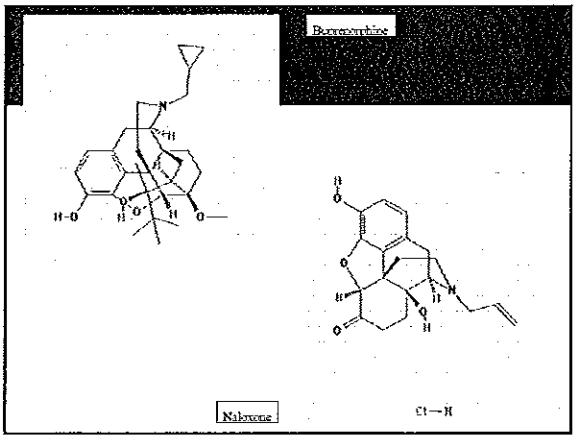
- Rapid development of tolerance.
- Strong physical dependence.
- Psychological dependence.
- Chronic use leads to addiction.
- Frequent concomitant use of other drugs (especially other opioids and benzodiazepines).
- Antagonist (naloxone) produces acute abstinence syndrome.
- Methadone maintenance for withdrawal therapy.
- Suboxone (buprenorphine & naloxone) for addiction therapy.

Drugs of Abuse: Opioids

- More cases of drug abuse of opioids are linked to drug diversion (prescription sources) than use of illicit opioids (heroin).
- Many cases related to chronic pain management.
- Methadone and buprenorphine can be used in pain management as well as addiction therapy.

Treatment of Opioid Addiction

- Subutex and Suboxone are used to treat opioid addiction.
- Subutex only contains buprenorphine, a partial opiate agonist/antagonist.
- Suboxone contains buprenorphine and naloxone. Naloxone is a pure opiate antagonist.
- Addiction therapists will use either Subutex or Suboxone during their course of therapy.



Withdrawal From Opioids

- Muscle aches
- Restlessness
- Anxiety
- Lacrimation & rhinitis
- Excessive sweating
- Insomnia
- Frequent yawning
- Diarrhea
- Abdominal cramps
- Goose bumps
- Nausea & vomiting
- Dilated pupils / blurred vision
- Tachycardia
- Hypertension

Withdrawal From Opioids Neonatal Abstinence Syndrome

- Babies born to addicted mothers while pregnant will experience withdrawal.
- Digestive issues
- Poor feeding
- Dehydration
- Vomiting
- Seizures

Withdrawal From Opioids

- Adult opioid withdrawal is not life threatening in adults (like ethanol or benzodiazepines) .
- Neonatal opioid withdrawal is prolonged and extremely costly.
- Neonatal opioid withdrawal can be life threatening and we do not know the potential damage it may produce to these children.

Opioid Overdose

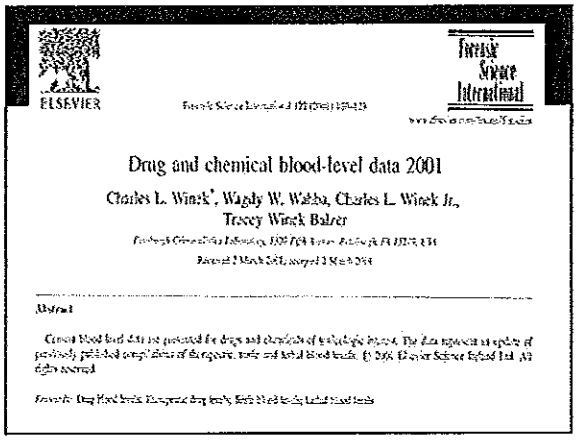
- Opioid overdose produces severe respiratory and central nervous system depression.
- Death is due to anoxia.
- Naloxone (Narcan) is a pure opiate receptor competitive antagonist. It is the antidote to opioid overdose.
- The overdosed patient needs to be dosed the effect.

The Opioid Epidemic in Tennessee

- To appreciate the extent of the opioid epidemic in Tennessee, we must acknowledge how it is changing our lives.
- Naloxone Rescue Act of Tennessee and associated Good Samaritan Protection (https://www.etsu.edu/com/cme/documents/119469%20Kirschke%203-page.pdf) .
- Incorporate overdose prevention education and naloxone rescue kits into medical and pharmacy practice by educating patients about overdose risk reduction and furnishing naloxone rescue kits.

Interpretation of Blood Concentrations

- Blood concentrations are divided into four categories:
  - -subtherapeutic is less than needed to produce a response
  - - therapeutic range is produced by therapeutic effective dosage
  - - toxic is associated with serious toxic symptoms
  - - lethal range has been reported to produce death.
- Blood concentrations presented as therapeutic, toxic, and lethal.

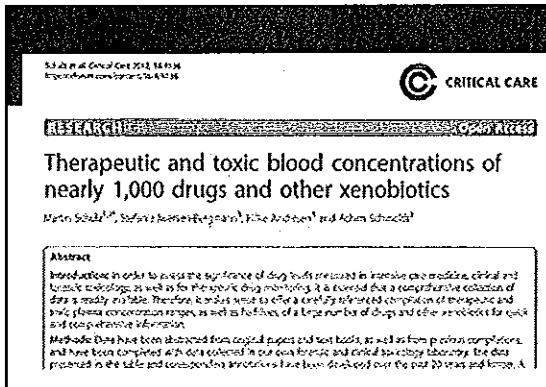

ELSEVIER

Forensic Science International

Drug and chemical blood-level data 2001

Charles L. Winek*, Wagdy W. Wahba, Charles L. Winek Jr., Tracey Winek Balzer

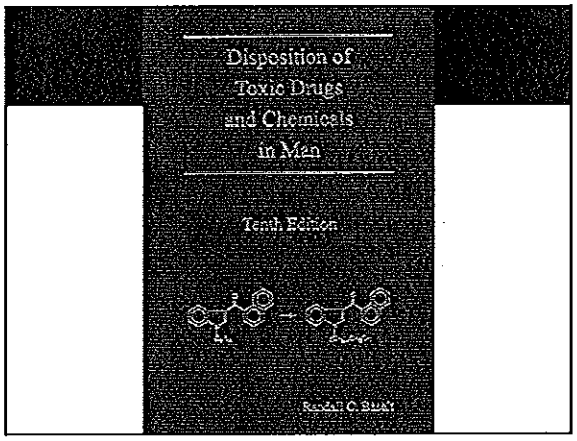
Abstract


CRITICAL CARE

RESEARCH

Therapeutic and toxic blood concentrations of nearly 1,000 drugs and other xenobiotics

Abstract


Disposition of Toxic Drugs and Chemicals in Man

Tenth Edition

Randall C. Baker

Interpretation of Blood Concentrations

- Morphine – up to 0.1 ug/ml, unreported, 0.05 to 4 ug/ml
- Codeine – 0.03 to 0.34 ug/ml, unreported, greater than 1.6 ug/ml
- Hydrocodone – 0.002 to 0.024 ug/ml, 0.13 to 0.19 ug/ml, 0.12 to 7 ug/ml
- Hydromorphone – 0.008 to 0.049 ug/ml, unreported, 0.3 ug/ml

Interpretation of Blood Concentrations

- Oxycodone – 0.01 to 0.1 ug/ml, 0.2 to 5 ug/ml, 0.1 to 14 ug/ml
- Oxymorphone – 0.0011 to 0.0046 ug/ml, unreported, 0.02 to 0.69 ug/ml
- Fentanyl – 0.01 to 0.1 ug/ml, unreported, 0.003 to 0.028 ug/ml
- Tramadol – 0.1 to 1.047 ug/ml, 0.05 to 0.536 ug/ml, 1.4 to 11ug/ml

Interpretation of Blood Concentrations

- Buprenorphine and norbuprenorphine - therapeutic 0.00025 to 0.008 ug/ml, toxic up to 0.032 to 0.045 ug/ml, and lethal 0.0011 to 0.029 ug/ml.
- Note the efficacy and the overlap of therapeutic and lethal concentrations.

Interpretation of Blood Concentrations

- Parent drug / metabolite ratios can help determine if a drug has been used acutely or chronically.
- Chronic use can lead to a greater degree of tolerance and less impairment.
- Multiple opiates can produce additive effects.

Interpretation of Blood Concentrations

- Even therapeutic concentrations of these drugs can produce impairment.
- Concentrations of drugs that produce euphoria and loss of consciousness (anesthesia) as their therapeutic response do not need to be toxic to impair psychomotor performance.

Interpretation of Blood Concentrations

- Methadone – 0.075 to 1.1 ug/ml, 0.2 to 2 ug/ml, 0.4 to 1.8 ug/ml.
- Concentration ranges overlap due to biological variation in response and development of tolerance.
- Therapeutic concentrations do not impair psychomotor performance in the chronic user (tolerance).

Toxicological Evaluation of Opioids in a DUI Case

- Each case is unique, but each is the same. It can be approached in a uniform, logical manner.
- No two cases will have the same situations and /or evidence.
- Determine if your blood concentration is therapeutic, toxic or potentially lethal.
- Correlate the concentration with the effects noted and other information in the case.

Toxicological Evaluation of Opioids in a DUI Case

- Determine if you have multiple opioids or is a drug & metabolites present.
- Try to determine if the person just began using this drug or has used it chronically.
- Why are they using the drug, therapeutic or abuse.
- Beware of interpretation of blood concentrations alone.

Toxicological Evaluation of Opioids in a DUI Case

- Check the TBI report. The first test is an EMIT screen for the presence of opiates. If it is not reported as negative an opioid may be present.
- If no specific opioid is reported then the lab may not have been able to confirm and/or quantitate the opioid.
- Additional specific testing may be needed.

Toxicological Evaluation of Opioids in a DUI Case

- Case specific information is helpful in identifying the presence of opioids.
- Relay information to the lab on drugs(s) which may be suspected.
- Specific tests can be performed if known and/or requested (e.g. fentanyl, hydrocodone, suboxone).
- Understand what the lab is telling you with a concentration less than 0.1 ug/ml.

What the Toxicologist Needs to Review?

- You need to provide all the evidence you have to substantiate the "3 prongs":
  - misoperation of the vehicle
  - psychomotor impairment
  - drug concentrations which would produce effects noted.

Misoperation of the Vehicle

- Misoperation can be substantiated with the affidavit of complaint, crash report and/or reconstruction.
- Video of misoperation is very useful.
- Witness statements.
- Need to establish time of crash or incident.

Psychomotor Impairment

- Psychomotor impairment can be substantiated by the affidavit of complaint.
- Standard Field Sobriety Tests results are very useful especially if scored.
- Video of SFST needs to be reviewed if available.
- Clinical records or evaluations.
- Need to determine degree of impairment.

Drug Concentrations

- Must have complete toxicological reports from TBI.
- If clinical treatment is provided, need to see clinical lab reports.
- Compare toxicology reports to other evidence of drugs involved in the case.
- Make sure to differentiate blood and urine drug results.

Evaluate Opioids First!

- Know what opioids are present, concentration ranges and effects.
- Determine if the opioids alone are sufficient to produce the effects noted.
- Determine if there are other CNS depressants present which may produce additive/synergistic effects.

Drug Interactions with Opioids

- Numerous other CNS depressants can produce additive/synergistic effects with opioids:
  - antidepressants
  - antihistamines
  - antipsychotics
  - anesthetics
  - barbiturates
  - benzodiazepines
  - carbamates
  - ethanol
  - inhalants
  - sedative/hypnotics

PolyDrugs in 2016

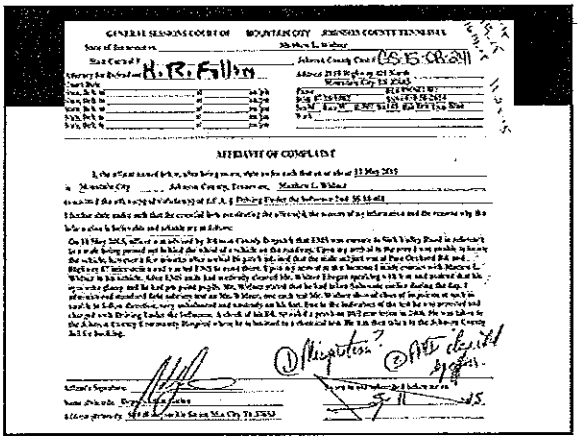
- Review of our autopsy cases (314) from January through July revealed:
- 120 cases with polydrugs, $\geq$ 3 drugs (38%)
- 81 cases with opioids (26%)
- 76 cases with benzodiazepines (24%)
- 58 cases with ethanol (18%)
- 24 cases with buprenorphine (7%)
- 10 cases with fentanyl (3%)

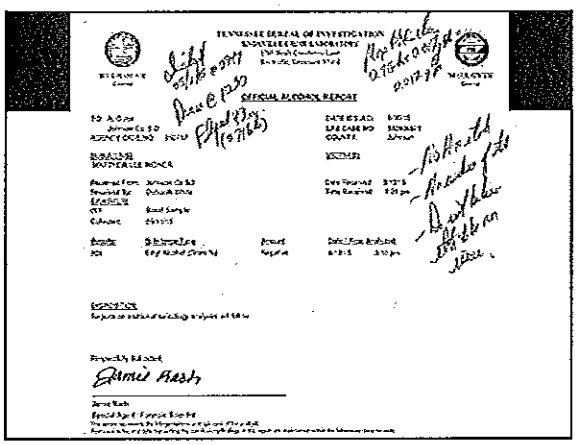
Evaluate Drug Concentrations

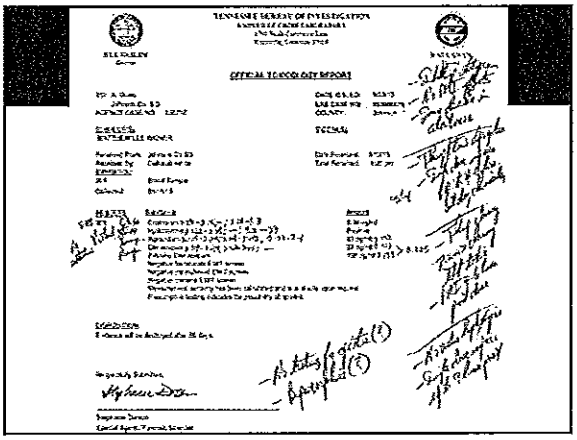
- Evaluate the types and concentrations of drugs found.
- Determine type of effects produced by the drugs present (stimulant, depressant, hallucinogen, etc.).
- Determine the extent of the effects for the concentrations found (subtherapeutic, therapeutic, toxic or lethal).
- Note potential interactions (diminutional, no effect, additive or synergistic).

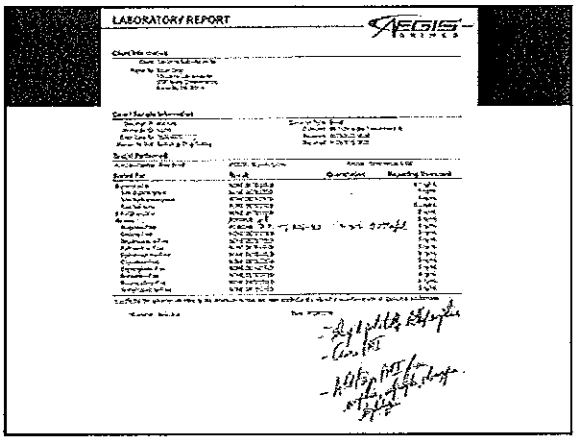
State of TN vs Matthew Widner

- This is a case of a DUI
- There were multiple drugs including an opioid.
- Second offense DUI.
- Lots of drug interactions plus the significant opioid level.



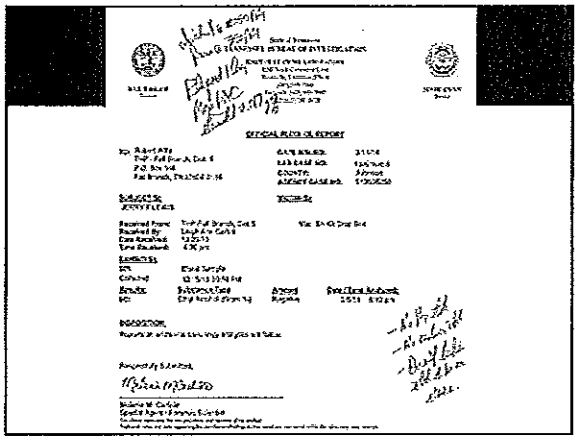


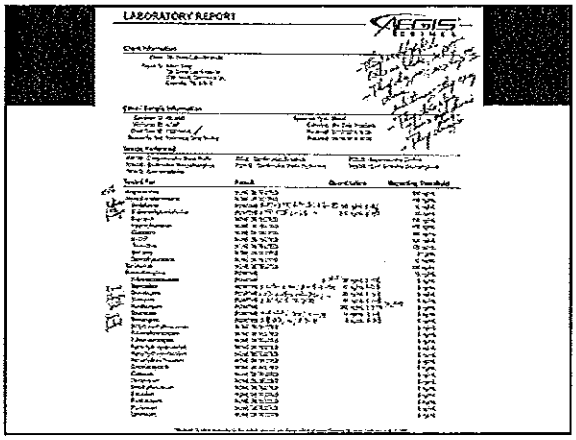


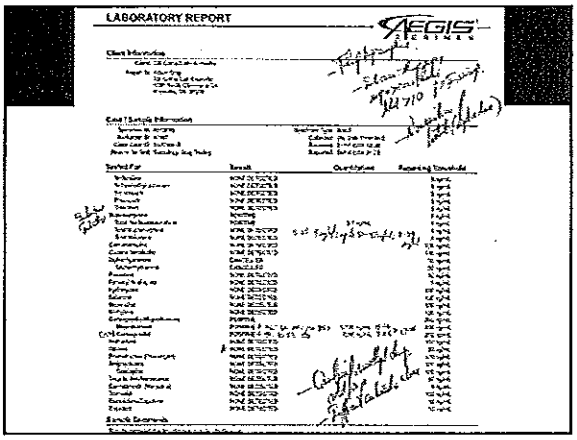


State of TN vs Jerry Lewis

- No, it was not the comedian "Jerry Lewis".
- It was Jerry Frank Lewis, 4th offense DUI.
- Stopped due to erratic driving.
- Slurred speech, slow reactions, multiple clues on SFSTs.
- Negative blood ethanol.
- Combination of multiple CNS depressants with buprenorphine.

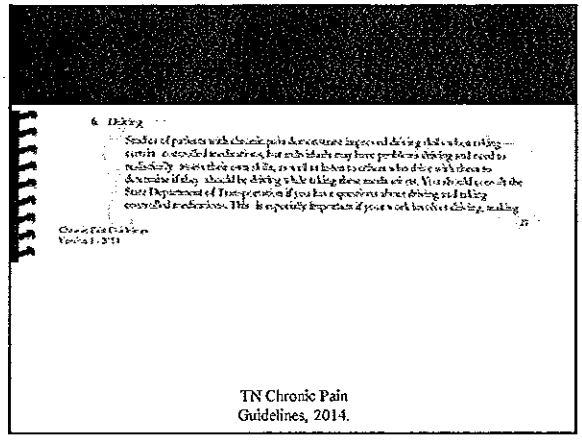






Effects of Opioids on Driving

- Opioids alone and in combination with other CNS depressants produce adverse effects on human psychomotor performance.
- This results in impaired driving.
- Regardless of the degree of tolerance a patient may develop with chronic administration of these drugs, their performance will be impaired to some degree versus their capabilities in a non-drugged state.



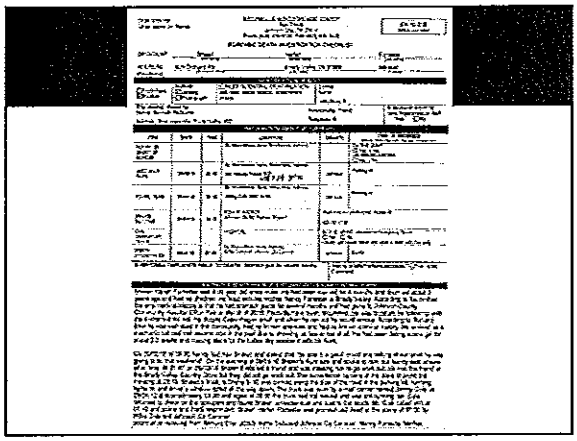
TN Chronic Pain Guidelines, 2014.

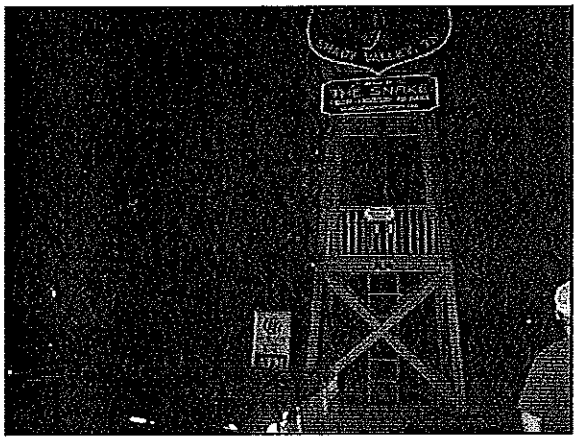
Effects of Opioids on Driving

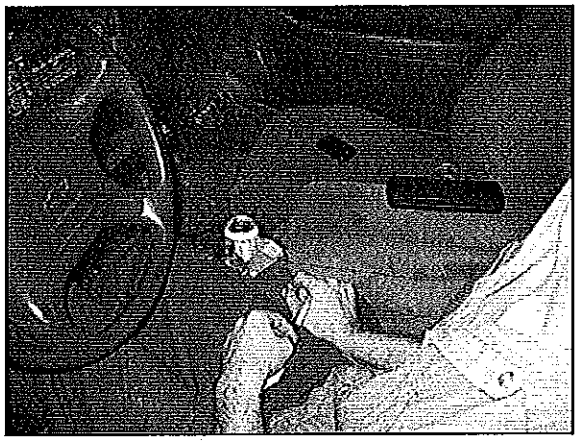
- If your pain is so severe that you cannot safely drive without treatment, there is no amount of opioid that will relieve your pain and improve your driving performance to a safe and non-drugged condition.
- Do not take opioids and drive! Even at therapeutic concentrations these drugs produce psychomotor impairment.

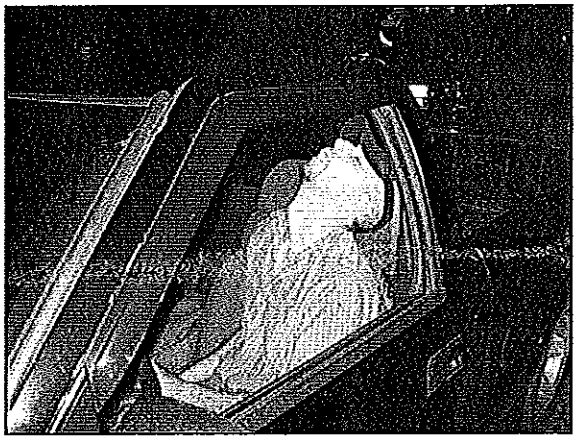
FA-10-215, A Fatal Drug Interaction

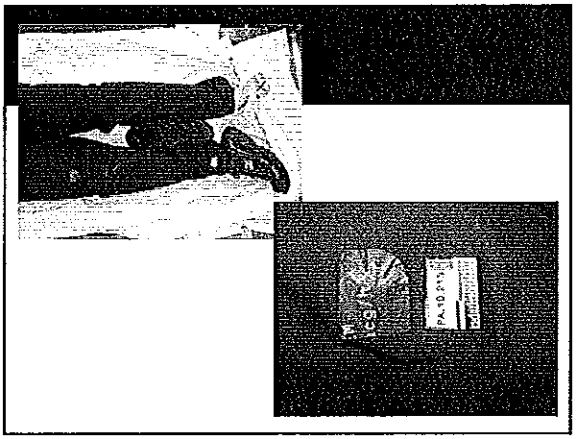
- A 29 year old white male found dead in his truck.
- Engine running.
- In a parking lot in Shady Valley, Tennessee.

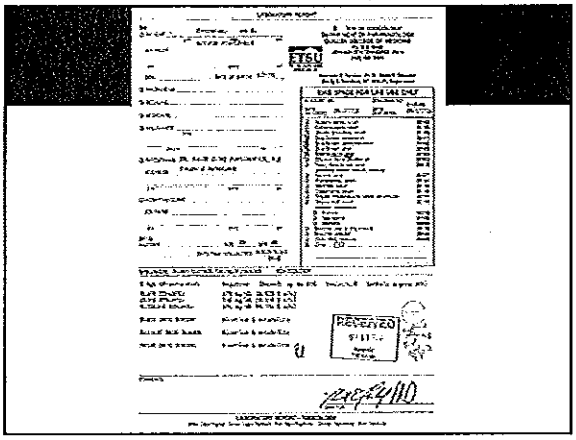


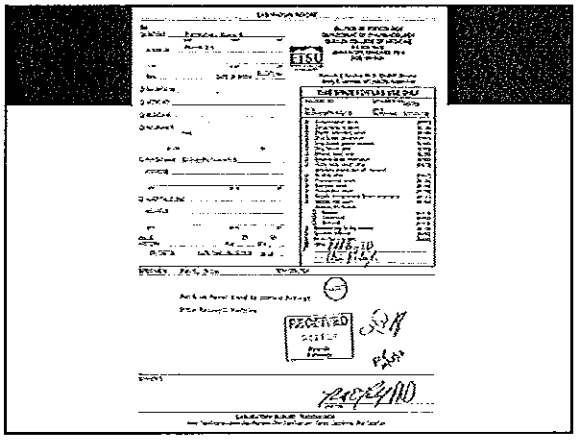


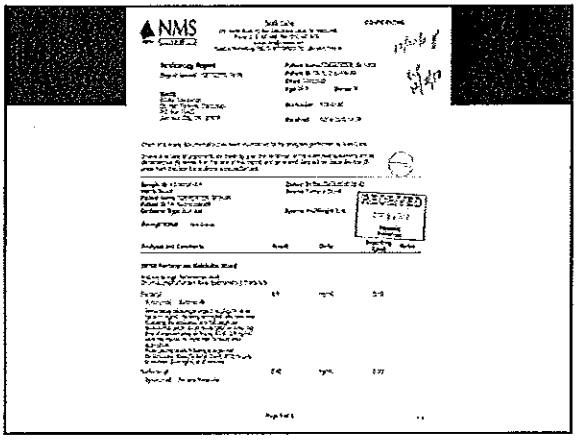


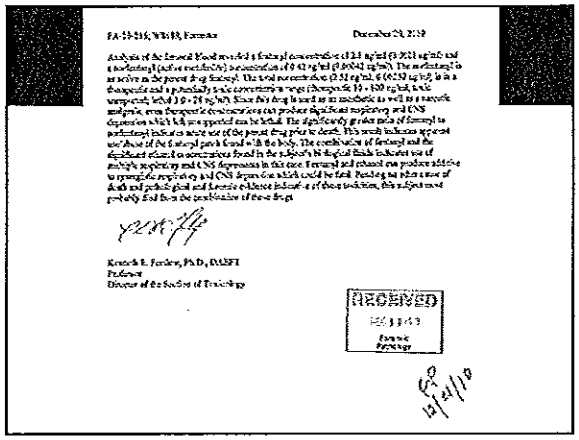


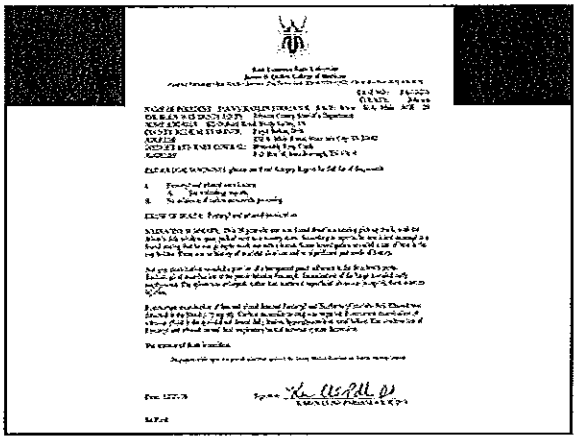


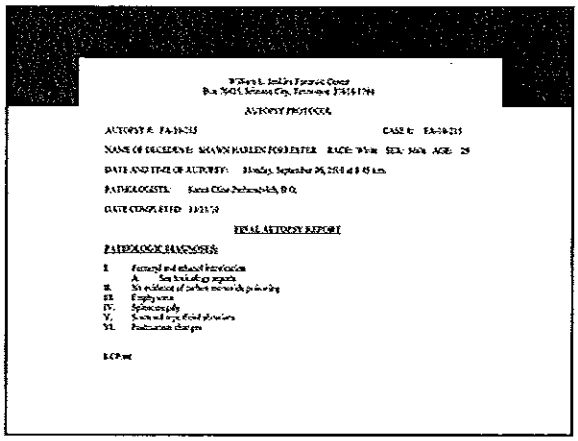












AUTOPSY PROTOCOL

FINAL AUTOPSY REPORT

PATHOLOGIC DIAGNOSES:

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