



# Psychopharmacology

## Part 3

Presented by Demetra Antimisiaris, PharmD, CGP, FASCP

Associate Professor

Department of Family Medicine and Geriatrics

Associate, U of L Department of Neurology

UNIVERSITY OF  
**LOUISVILLE**<sup>®</sup>  
SCHOOL OF MEDICINE

# PART 3

- Pain Medications
- Polypharmacy
- Cannabis
- Hallucinogens
- Steroids

# OPIOID PAIN MEDICATIONS

- Two pathways originating in lower brain stem modulate transmission of pain.
  - Physical component
  - Descending NE and 5HT which activate endorphin neurons. (antidepressants can effect too)
- Affective component and emotional response to pain.
  - Chronic pain treatment focuses on behavioral modification, CBT, biofeedback
- Judicious opioid use is important

# OPIOID PAIN MEDICATIONS

## Controlled Substances Guidelines

The following should be documented in every chart when chronic controlled substances are being prescribed.

Guidelines per Kentucky Medical Board of Licensure

1. \_\_\_\_\_ Complete History and Physical to Include:  
(date completed)
  - Nature and intensity of the pain/condition
  - Current and past treatments for pain/condition
  - Underlying or coexisting disease or condition
  - Effect of the pain/condition on physical and psychological function
  - History of any substance abuse
  - Family History, esp. any 1<sup>st</sup> degree relative with chemical dependence problems
2. \_\_\_\_\_ Document 1 or more recognized medical indication(s) for the use of the  
(date completed) controlled substance
3. \_\_\_\_\_ Document through patient records or clinical trial that non-addictive  
(date completed) medication regimens have been inadequate or unacceptable for solid clinical reasons
4. \_\_\_\_\_ Kasper report initially and as needed to aid in documenting the patients  
(date completed) history of drug utilization (needs to be kept separate from chart)
5. \_\_\_\_\_ Signed Controlled Substances Contract on chart.  
(date completed) Controlled Substance Contract not applicable because :  
\_\_\_\_\_
6. \_\_\_\_\_ Documented Treatment Plan  
(date completed)
7. \_\_\_\_\_ Documented discussion of risk, benefits, and limitation of treatments  
(date completed)
8. \_\_\_\_\_ Documentation of Medication: Date, Type, Dosage, Quantity, and Refills  
(date completed)
9. \_\_\_\_\_ Document periodic review of effectiveness  
(date completed)
10. \_\_\_\_\_ Document diagnostic, therapeutic, laboratory results, and consultations or  
(date completed) evaluations

# OPIOID PAIN MEDICATIONS

## CONTROLLED SUBSTANCE AGREEMENT

### UofL Family & Geriatric Medicine

Controlled substances have the potential to be addictive and must be taken exactly as prescribed. I \_\_\_\_\_, understand that if I am prescribed a controlled substance I must adhere to the following restrictions.

PLEASE INITIAL EACH LINE

**Failure to conform to any of the below listed restrictions may result in being dismissed as a patient of the Family and Geriatric practice sites and being reported to the Louisville Metro Police Prescription Drug Squad.**

1. \_\_\_\_\_ I will not use any alcohol or illegal drugs.
2. \_\_\_\_\_ I will not take any other prescribed medications without first notifying Doctor \_\_\_\_\_.
3. \_\_\_\_\_ I will notify Doctor \_\_\_\_\_ immediately of any other physician(s) currently prescribing me a controlled substance(s) or that has been prescribed to me in the past 30 days (including Emergency Rooms and Immediate Care Centers.) Failure to do so is a **felony crime** (KRS 218a140 Obtaining or attempting to obtain drugs by fraud or deceit) and will be reported to the Louisville Metro Police Prescription Drug Squad.
4. \_\_\_\_\_ I will submit to random urine and/or serum drug screens as ordered.
5. \_\_\_\_\_ I will purchase all of my medication at \_\_\_\_\_ Pharmacy and authorize Doctor \_\_\_\_\_ to communicate with my pharmacist. There must also be a signed pain contract in the patient's chart or the patient will be brought in for a signed pain contract within 2 weeks.
7. \_\_\_\_\_ I understand that it is illegal to share this medication.
8. \_\_\_\_\_ I understand that drinking alcohol with this medication may be fatal.
9. \_\_\_\_\_ I agree to keep my medication locked in order to prevent

# OPIOID RECEPTORS

- Opioid Receptors
  - Mu Receptors
  - Kappa Receptors
  - Delta Receptors
  
- Classification
  - Pure agonists
  - Pure antagonists
  - Mixed antagonists – antagonists
  - Partial agonists

# OPIOIDS

- Effects
  - Analgesia
  - Bradycardia
  - Respiratory depression
  - Physical dependence
  - Euphoria
  - Can release histamine
  - Stimulates chemoreceptor trigger zone (nausea)
  - Suppress cough
  
- Tolerance and Dependence
  - Molecular basis is thought to involve glutaminergic mechanism
  - Activation of NMDA receptors correlates to resistance
  - Glutaminergic receptors (NMDA) may regulate mRNA of mu receptors
  - Ketamine found to prevent late onset and long lasting enhancement in pain sensitivity after initial analgesic effect dissipated.

# OPIOID EFFECTS

**TABLE 9.1** Acute effects of opioids and rebound withdrawal symptoms

<b>Acute action</b>	<b>Withdrawal sign</b>
Analgesia	Pain and irritability
Respiratory depression	Hyperventilation
Euphoria	Dysphoria and depression
Relaxation and sleep	Restlessness and insomnia
Tranquilization	Fearfulness and hostility
Decreased blood pressure	Increased blood pressure
Constipation	Diarrhea
Pupillary constriction	Pupillary dilation
Hypothermia	Hyperthermia
Drying of secretions	Lacrimation, runny nose
Reduced sex drive	Spontaneous ejaculation
Peripheral vasodilation; flushed and warm skin	Chilliness and "gooseflesh"



# OPIOIDS

Treatment of dependence:

Old theory: medically managed withdrawal to opioid free state.

Newer theory: lifelong opioid maintenance

Area of great debate.

Medical literature shows increased rate of mortality with use of opioids.

# OPIOIDS

Table 1. Abuse-Deterrent Formulations

DRUG (GENERIC)	DOSAGE	MECHANISM
<b>Aversion</b>		
Oxecta (oxycodone HCl)	5, 7.5 mg (tablets)	AVERSION technology impedes opioid extraction via dissolution of tablets using water or alcohol, which causes the tablet to form into a viscous gel, trapping the active ingredient
<b>Physical Barrier</b>		
Exalgo (hydromorphone HCl)	8, 12, 16, 32 mg (tablets)	Osmotic Extended-Release Oral Delivery System (OROS) technology uses an osmotically active bilayer core enclosed in a semipermeable tablet shell membrane that allows both a consistent 24-h delivery rate and provides a barrier to abuse
Opana ER (oxymorphone HCl)	5, 7.5, 10, 15, 20, 30, 40 mg (tablets)	INTAC is a tamper-resistant technology designed to prevent modification of the drug into a fine powder and provide resistance to dissolution via liquids, as the remnants of a broken tablet will form a viscous gel to trap the active ingredients
OxyContin (oxycodone HCl)	10, 15, 20, 30, 40, 60, 80, 160 mg (film-coated tablets)	Reformulated to form viscous hydrogel when mixed with aqueous liquid for dissolution
<b>Agonist-Antagonist Combination</b>		
Suboxone (buprenorphine/ naloxone)	2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg (sublingual film)	Combines buprenorphine, a partial opioid agonist-antagonist, and naloxone, an opioid antagonist. Buprenorphine provides analgesia while its combination with naloxone prevents IV abuse

# SUBOXONE®

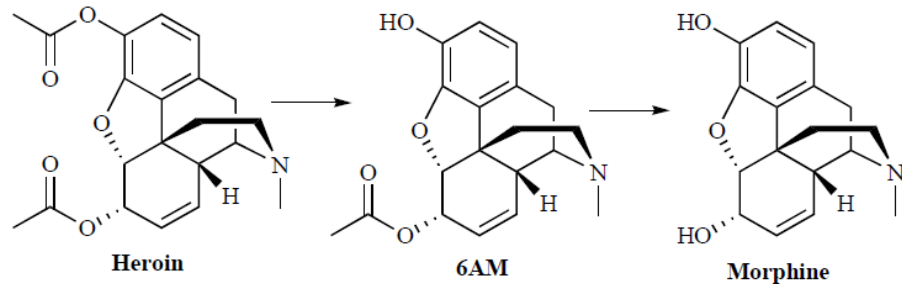
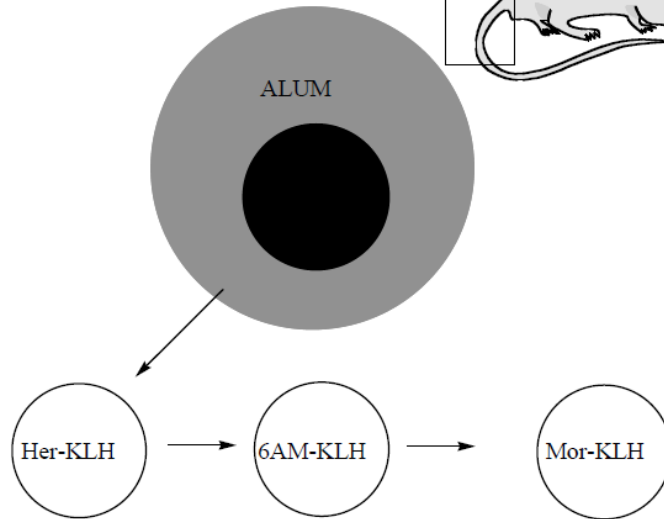
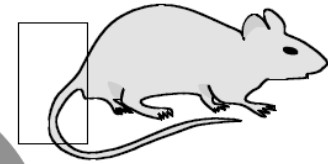
## BUPRENORPHINE/NALOXONE

M-opioid receptor agonist combined with and opioid antagonist

- 4:1
- Sublingually, naloxone exerts no clinically significant effect leaving buprenorphine to predominate.
- IV, physically dependent patients will experience withdrawal effects of naloxone.
- Buprenorphine has ceiling effects which limits addiction risk.



# OPIOIDS, COCAINE, OTHERS



+ or - BBB crossing

# NALTREXONE

M,  $\kappa$ ,  $\delta$ -Opioid receptor antagonist approved for treatment of opioid dependence.

- Hepatic (liver) toxicity
- Reversibly blocks effects of opioids.
- Low dose naltrexone:
  - Inhibiting opioid receptors cause body to increase production of endorphins or enkephalins to compensate for blocked receptors.
  - Persist after naltrexone has been eliminated from body.
  - Use in pain, fibromyalgia, fatigue thought to be due to effect on microglia which can modulate body's response to inflammation. (anti-inflammatory)
- Combination with opioids (oxycodone) w ultra low dose naltrexone to block paradoxical hyperalgesia of long-term use opioid withdrawal.
- Methylnaltrexone (Relistor<sup>®</sup>):  $\mu$ -opioid antagonist (peripherally acting) which effects constipation, itching, without effecting analgesia or precipitating withdrawals.

# METHADONE

Synthetic opioid used for maintenance therapy, blocks euphoric effects seen with opiates.

- Popularity increasing among physicians for chronic pain treatment.
- Has NMDA receptor activity and helps neuropathic pain better than many opiates. Decreased anti-nociceptive (reduced sensitivity to painful stimuli) effect of opioids.
  - (+  $\mu$  opioid receptor activity)
- Tolerance may be lesser than other opioids.
- Inexpensive.
- Q-T prolongation and sudden cardiac death risk requires EKG monitoring.

# HALLUCINOGENS, CANNABIS, AND STEROIDS

- Cannabis
  - Cannabinoid Receptor/therapeutic uses:
    - Weight loss drug (antagonist, pulled by EU after a few years)
    - Analgesia by modulating sensory input from tissue injury and reducing release of nociceptive neurotransmitters like substance P and glutamic acid.
    - Chronic pain syndrome use
  - Effects:
    - Memory impairment
    - Increased appetite
    - Impairment to focus attention and filter out irrelevant information
  - Side Effects:
    - Increased HR, BP, dry mouth, dizziness, slight nausea.
  - Tolerance and Dependence:
    - Tolerance does develop

# PSYCHEDELIC DRUGS/HALLUCINOGENS

- Anticholinergic psychedelics:
  - Scopolamine
  - Delirium
  - Drowsiness
  - Euphoria
  - Tachycardia, blurred vision, HTN, increased body temp.
- Catecholamine Like psychedelics:
  - Mescaline
  - Synthetic Amphetamine Derivatives



# PSYCHEDELIC DRUGS/HALLUCINOGENS

- Serotonin like psychedelic drugs:
  - LSD
  - DMT
  - Psilocybin and Psilocin (mushrooms)
  - Ololiuqui
  - Phencyclidine (PCP- Ketamine related)
- Toxicity
  - Psychotic states
  - Recurrent major affective disorder (or persistent)
  - “burnout” disruption of personality or chronic brain syndrome.

# STEROIDS

- Anabolic-androgenic steroids
  - Chemicals related to male hormone testosterone
- Mechanism of action
  - DHEA and androstenedione (precursor to testosterone)
  - Negative feedback on hypothalamus inhibits further stimulation of testosterone release
- Effects
  - Muscle building effects, masculinizing
  - Enhanced physical strength
  - Endurance

**TABLE 14.1 Anabolic-androgenic steroids**

Name	Route	Brand name
<b>APPROVED IN UNITED STATES</b>		
Testosterone cypionate	im	Depo-Testosterone, Virilon
Nandrolone phenpropionate	im	Durabolin
Nandrolone decanoate	im	Deca-Duraboli
Danazol	po	Danocrine
Fluoxymesterone	po	Halotestin
Methyltestosterone	po	Android, Metandren, Testred, Virilon
Oxymetholone	po	Anadrol-50
Stanozolol	po	Winstrol
<b>APPROVED OUTSIDE UNITED STATES</b>		
Testosterone enanthate	im	Delatestryl
Testosterone propionate	im	Testex, Oreton propionate
Methenolone enanthate	im	Primobolan Depot
Ethylestrenol	po	Maxibolan
Mesterolone	po	
Methandrostenolone	po	Dianabol
Methenolone	po	Primobolan
Norethandrolone	po	
Oxandrolone	po	Anavar
Oxymesterone	po	Oranabol
<b>APPROVED FOR VETERINARY USE</b>		
Bolasterone	im	Fininject 30
Boldenone undecylenate	im	Equipoise
Stanozolol	im	Winstrol
Mibolerone	po	

**STEROIDS**

# STEROIDS

- Toxicity
  - Endocrine
  - Cardiovascular
  - Liver
  - Psychological
  - Aggressive behavior
- Dependence
  - Withdrawal symptoms when removed
  - Psychological depression, fatigue, restlessness, insomnia, loss of appetite, decreased libido.

**TABLE 14.2 Effects of anabolic-androgenic steroids**

**POSITIVE EFFECTS**

- Transient increase in muscular size and strength
- Treatment of catabolic states
  - Trauma
  - Surgery

**ADVERSE EFFECTS**

**Cardiovascular**

- Increase in cardiac risk factors
  - Hypertension
  - Altered lipoprotein fractions
  - Increase in LDL/HDL ratio
  - Reported strokes/myocardial infarctions
- Hepatic effects associated with oral compounds
  - Elevated liver enzymes
  - Peliosis hepatis (greater than 6 months' use)
  - Liver tumors
    - Benign
    - Malignant (greater than 24 months' use)

**Reproductive system effects**

**In males**

- Decreased testosterone production
- Abnormal spermatogenesis
- Transient infertility
- Testicular atrophy

**In females**

- Altered menstruation

**Endocrine effects**

- Decreased thyroid function

**Immunologic effects**

- Decreased immunoglobulins IgM/IgA/IgC

**Musculoskeletal effects**

- Premature closure of bony growth centers
- Tendon degeneration
- Increased risk of tendon tears

**Cosmetic**

**In males**

- Gynecomastia
- Testicular atrophy
- Acne
- Acceleration of male pattern baldness

**In females**

- Clitoral enlargement
- Acne
- Increased facial/body hair
- Coarsening of the skin
- Male pattern baldness
- Deepened voice

**Psychologic**

- Risk of habituation
- Severe mood swings
- Aggressive tendencies
- Psychotic episodes
- Depression
- Reports of suicide

**Legislation**

- Classified as Schedule III controlled substance

**STEROIDS**

# POLYPHARMACY



# What is Polypharmacy?



- 5 or more medications taken simultaneously
- More medications used than are clinically warranted.
- A Random Uncontrolled Experiment
- Types of Polypharmacy
  - Too many drugs
  - Inappropriate choices
  - Inappropriate combinations
  - Administration errors
  - Way off label use
  - Inappropriate dosing
  - Inappropriate prescriber

# Silent Epidemic



A side effect of modern medical care

- 15 minute office visit/Hospital visit
- New drugs added annually
- Multiple specialists
- Over the counter products and supplements



## A Pill for Every Ill



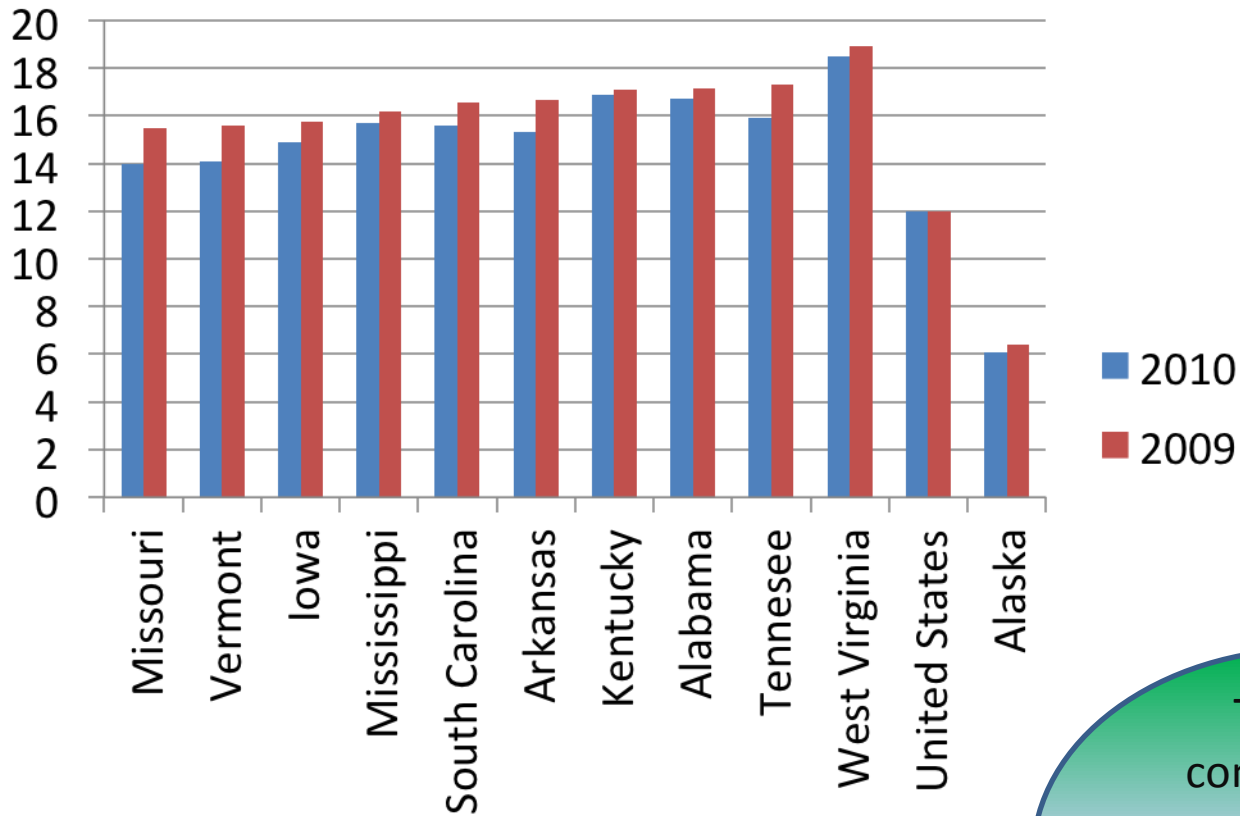
# Total drug burden is important

**Average of 2.8 drugs discontinued per patient**

**1 year mortality rate      45% in control  
   21% in study group**

**Annual referral rate to acute care      30% in control group  
   11.8% in study group**

# Scripts per capita 2010 (blue) Kaiser Foundation



The U.S. consumes 80 percent of the world's opioids and 99 percent of its hydrocodone



**"If you remember, I did mention possible side-effects."**

# Signs of Medication Related Problems: ???

- **mental status changes**

- Agitation
- Manic behavior
- Any change in affect
- confusion

- **Not eating**

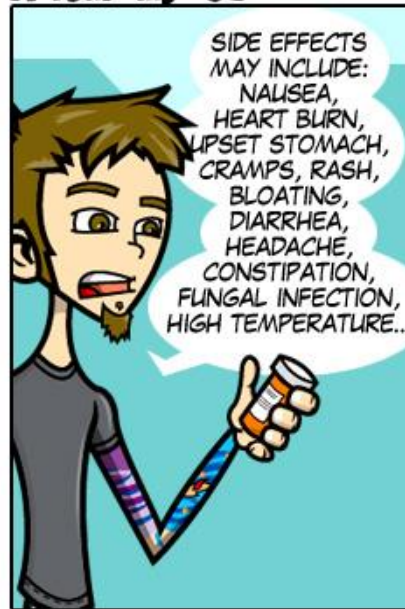
- **Not sleeping**

- **Somnolence**

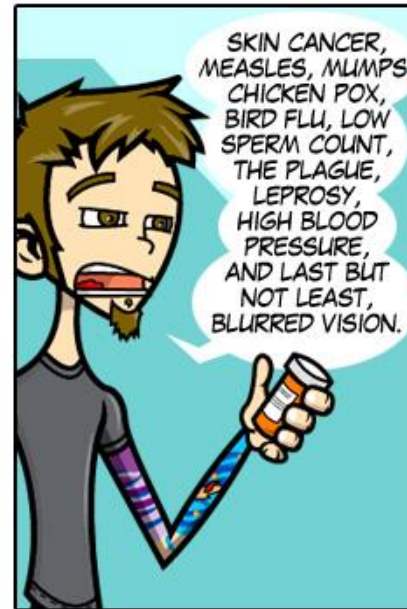
- **Falls**

- ©

## Naturally Us



www.AllNaturalMe.com



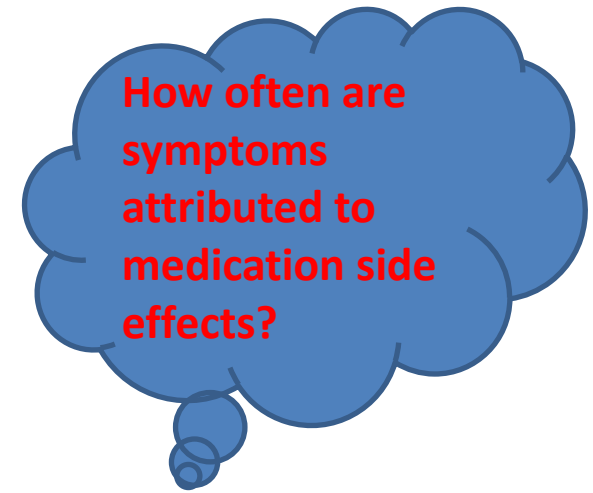
By: Sadie & THE DREG

© Copyright 2008 AllNaturalMe.com

# Akathesia and Agitation

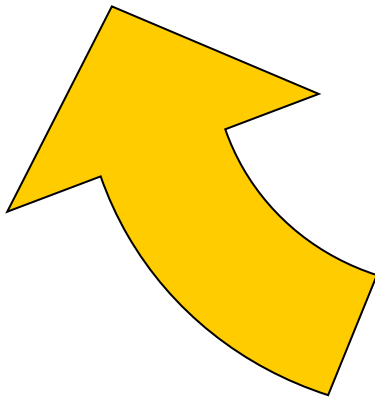


**Is it the drug  
or the  
disease?**

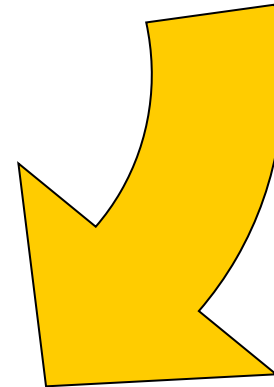


**Signs and Symptoms**  
**(multiple & nonspecific)**

**Diagnosis or  
Drug Side Effect?**



**New  
Treatment Added**



# Sheer Numbers

All substances  
are poisons,  
what  
differentiates a  
poison from a  
remedy is dose

**JC, 22 year old father of two and boyfriend**

Typical weekend binge: 40-50 pills and a quart of Jack Daniels

Several periods of staying clean

Prescribed Xanax to help his anxiety and drug withdrawal....

Toxicology report upon death: 134mg of Xanax (67 pills)





# Seems Innocent Enough

Strongly  
anticholinergic  
Lots of Tylenol

OTC



Can alter  
other  
drug  
kinetics!

Look different; but are alike



Sometimes  
anticholinergic,  
changes  
stomach pH

# Heath Ledger

1979-2008

## OTC stuff

- Doxylamine
  - NyQuil
  - Unisom
  - And who knows what else!

## Prescription stuff

- Oxycodone
- Hydrocodone
- Diazepam
- Temazepam
- Alprazolam

**Chief Complaints:**  
insomnia, anxiety,  
depression, pain and  
common cold per friends  
and family from the  
investigation

Two physicians (one in LA, one in Houston) were exonerated because “they had prescribed other medications, not the pills that killed him”

# What if?

You took hands full of random non controlled Rx and OTC pills at a pharm party?

\*Gabapentin  
+Fluoxetine  
-Digoxin  
\*Furosemide  
-Nifedipine  
\*Celecoxib



How many?  
Of which?



Your  
physiology



# What's in this bag?



Respiratory  
depression  
Sedation  
confusion

## Neurotoxic

Cardiac sudden death, inability to respond to Viagra induced bp drop, and oxycodone induced respiratory depression

**PERFECT**

Methadone X 5

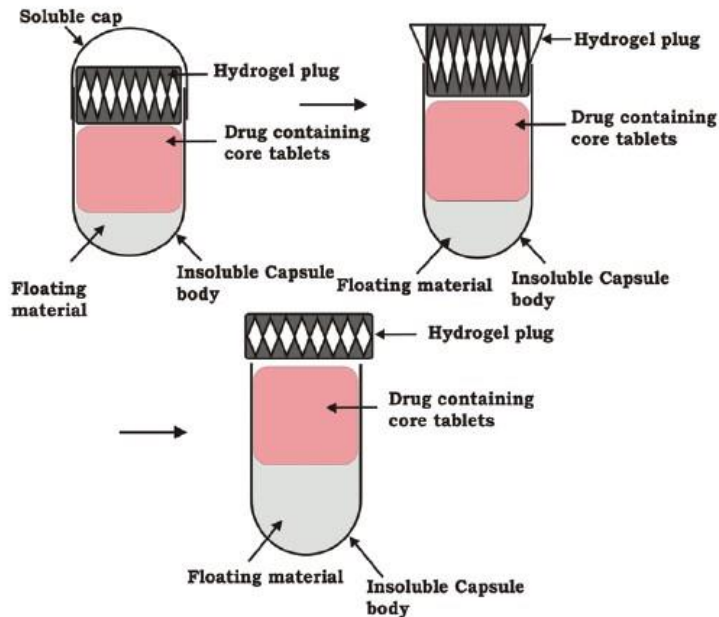
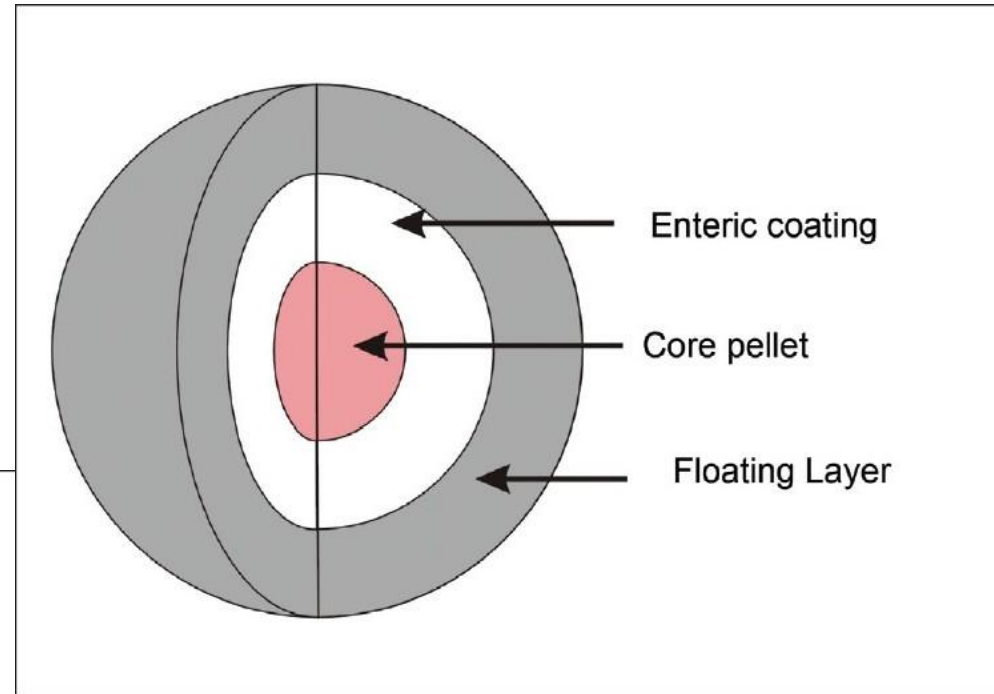
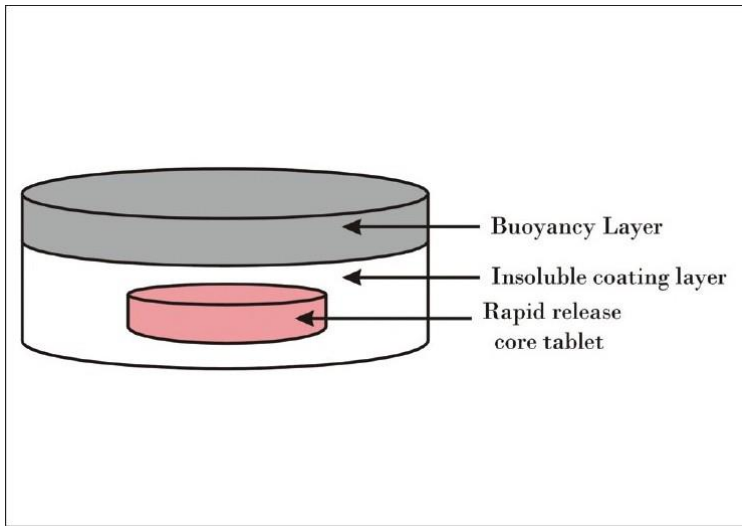
Viagra X 3

Oxycodone X 2

Drops bp, raises ht rate

Respiratory  
depression  
Sedation  
confusion

# To Crush or not To Crush?



# END OF PART 3

- Questions?
- Comments?
- Share Ideas?