

# The Truth About Opioid Pain Management:

## Addiction, Physical Dependence and Patient Evaluation

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Chronic Pain Specialist  
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# DISCLOSURE STATEMENT INFORMATION

## ◆ Howard A. Heit MD, FACP, FASAM

- Purdue Pharma
  - Visiting Faculty Program, 1997 – Present
  - Consultant, 1998 – Present
- Cephalon
  - Visiting Faculty Program, 2003 – Present
  - Consultant, 2003 – Present
- Ligand and Organon
  - Visiting Faculty Program, 2004 – Present
  - Consultant, 2004 – Présent

Pain is the most common complaint for which individuals seek medical attention!

Foley, K.,  
Dismantling the Barriers: Providing Palliative and Pain Care.  
JAMA 2000:115

## ◆ Chronic Pain

- Pain that has outlived its usefulness

## ◆ Acute Pain

- An adaptive, beneficial response necessary for the preservation of tissue integrity.

Oaklander AK. The pathology of pain.  
Neuroscientist. 1999;5(5):302-10.

# Barrier to Pain Management: Knowledge of Common Definitions in Pain and Addiction Medicine

# Addiction

- ◆ **Addiction** is a primary, **Chronic**, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired **Control** over drug use, **Compulsive** use, **Continued** use despite harm, and **craving (5 C's)**.

Consensus Document  
The American Academy of Pain Medicine  
The American Pain Society  
The American Society of Addiction Medicine  
2001

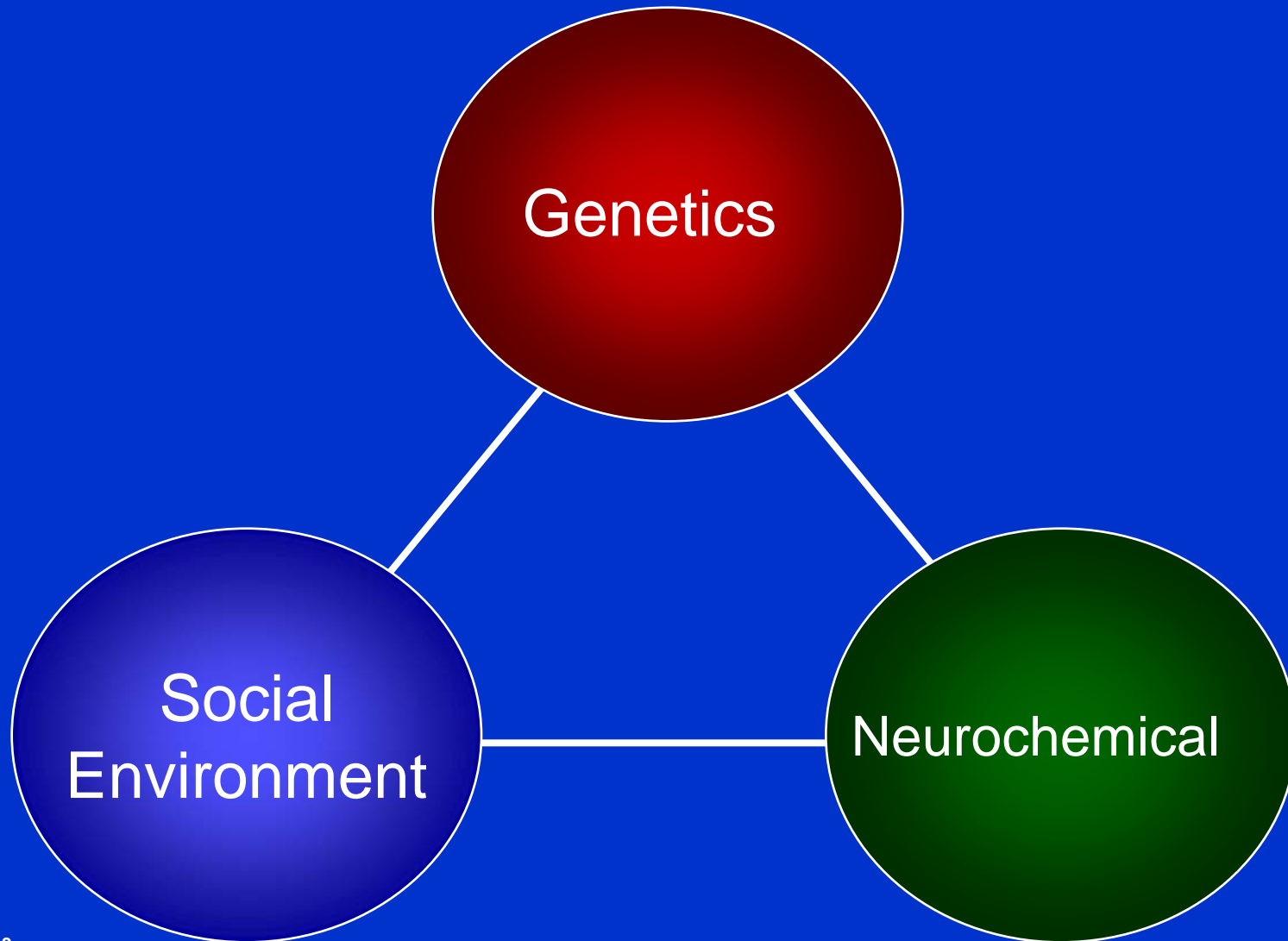
# Physical Dependence

- ◆ **Physical dependence** is a state of adaptation that is manifested by a drug-class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Consensus Document  
The American Academy of Pain Medicine  
The American Pain Society  
The American Society of Addiction Medicine  
2001

Physical dependence and addiction can coincide, but physical dependence does not equal addiction in all cases. Physical dependence is a **neuro-pharmacological phenomenon** while addiction is both a **neuro-pharmacological and behavior phenomenon**.

# Triangle of the Disease of Addiction



# Tolerance

- ◆ **Tolerance** is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
  - **Key:** All other conditions being constant
    - BAD: Disease or syndrome is progressing
    - GOOD: Functional activity is increasing

Consensus Document  
The American Academy of Pain Medicine  
The American Pain Society  
The American Society of Addiction Medicine  
2001

# Pseudotolerance

- ◆ Need to increase opioid dose that is not due to tolerance but due to other factors
  - Disease progression - **Yes**
  - New disease - **Yes**
  - Increased physical activity - **Yes**
  - Lack of compliance - **No**
  - Change in medication - **Maybe**
  - Drug interaction - **Maybe**
  - Addiction - **No**
  - Deviant behavior - **No**

Pappagallo, M  
J Pharm Care Pain Symptom Control  
1998;6:95-98

# Use of Methadone for Pain [cont'd]

## Dosing considerations

### ◆ Induction

### ◆ Cytochrome P- 450 Enzyme Activity

- Larger doses may be required if taking
  - Dilantin®
  - Tegretol®
  - Rifampin
  - Hypoglycemic agents (including insulin)
  - Phenobarbital
  - Nevirapine
  - Ritonavir

# Use of Methadone for Pain [cont'd]

## Dosing considerations

- ◆ Inhibition
- ◆ Cytochrome P- 450 Enzyme Activity
  - Smaller doses may required if taking
    - Cimetidine
    - Ketoconazole
    - Fluconazole
    - Erythromycin
    - Fluvoxamine
    - Paroxetine
    - Ritonavir
    - Grapefruit juice

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Pappagallo, M  
J Pharm Care Pain Symptom Control  
1998;6:95-98

# Pseudoaddiction

- ◆ The patient who seeks additional medications appropriately or inappropriately secondary to significant undertreatment of the pain syndrome. When the pain is treated in the proper manner, all inappropriate behavior ceases.

Weissman DE, Haddox JD.

Pain, 1989; 36: 363-66

# Addiction versus Pseudoaddiction in Pain Management

## ◆ Addiction

### ➤ Prospectively

- Patient's behavior and complying with the treatment agreement becomes *aberrant* despite "Rational Pharmacotherapy."

## ◆ Pseudoaddiction

### ➤ Retrorespectively

- Patient's behavior and complying with the treatment agreement *normalizes* with "Rational Pharmacotherapy."

Gourlay D, Heit HA et al.  
*Pain Med.* 2005;6(2):107-112.

# History of AA

- ◆ *AA/NA compatible with treatment of all medical and mental disorders\**
- ◆ Should be considered essential in treatment of addictive disorders
  - Older adults with drinking problems are more likely to use alcohol to manage their physical pain\*\*
    - 21% versus 56%

\*Chappel JN. ASAM Review Courses on 12-Step Programs.

\*\*Brennan PL, Schutte KK, Moos RH  
Addiction  
100(6):777-86

# Prevalence of Addiction in the General Population

- ◆ Approximately 10% (3% - 16%)
  - Relapse rate with long-term opioid use is unknown

Portenoy RK, Savage SR. *J Pain Symptom Manage.* 1997;14:S27-35.

# Opioid Treatment for Pain and Addiction

- ◆ Addiction to opioids in the context of pain treatment has been reported to be **rare** in those with no history of addictive disorders\*
- ◆ **What is “iatrogenic addiction”?**

\*Portenoy, R.K., Savage, S.R.  
*Journal of Pain and Symptom Management.*  
Vol. 14 No. 3 (Suppl.) Sept. 1997

# Choice of Opioids for the Treatment of Acute, Chronic or Acute Pain Superimposed on Chronic Pain

- ◆ Long acting opioids/CR/MR/SR opioids
- ◆ IR opioids
- ◆ RO opioids

# Pharmacokinetics of Drugs

## ◆ Drug

- Absorption
- Distribution
- Binding (or distribution) in tissue
- Biotransformation
- Excretion

## ◆ “What the body does to the drug”

Principle of Addiction Medicine  
Second Edition  
1998;99-102

# Pharmacodynamics of Drugs

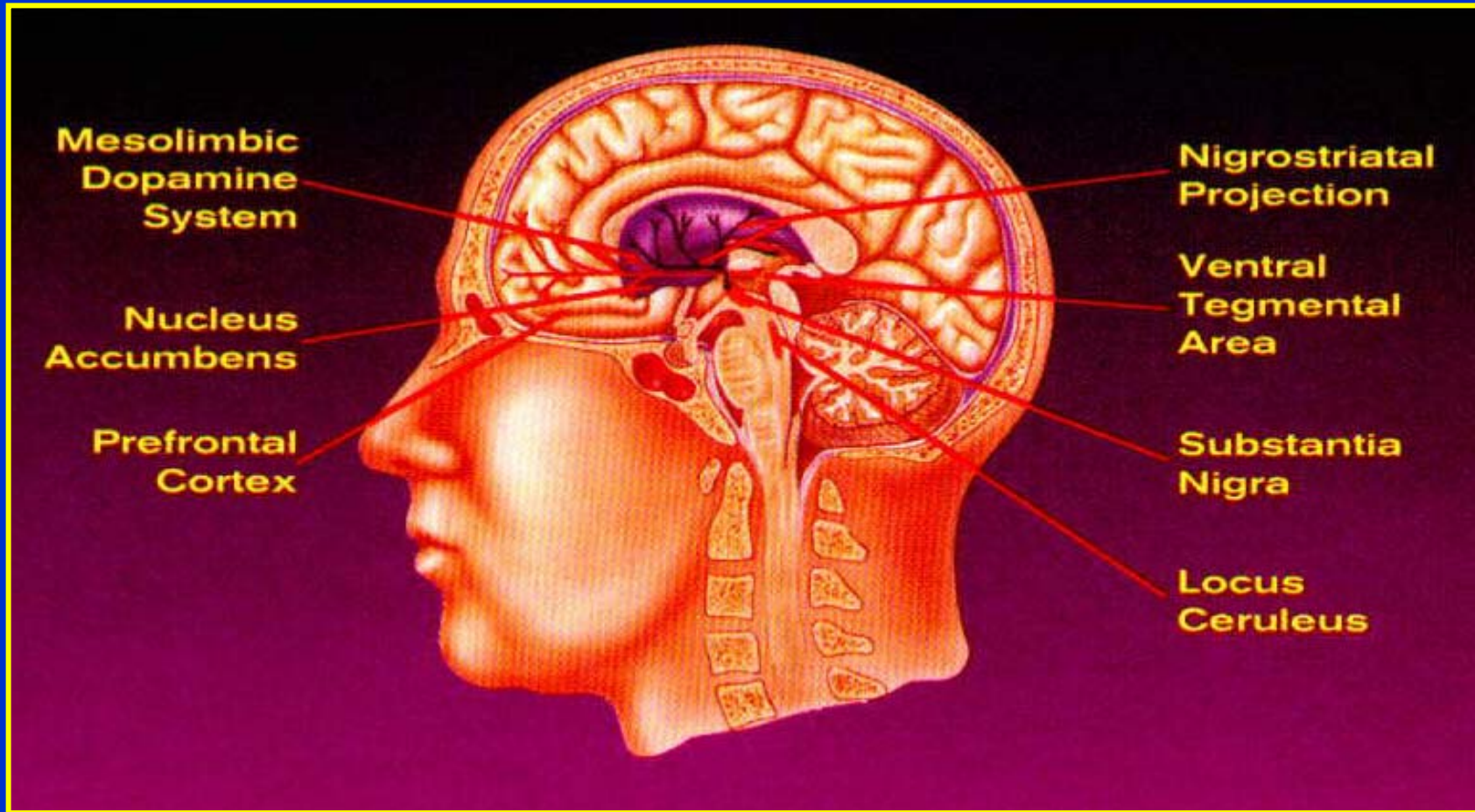
## ◆ Drug

➤ Mechanism by which drugs produce their effect

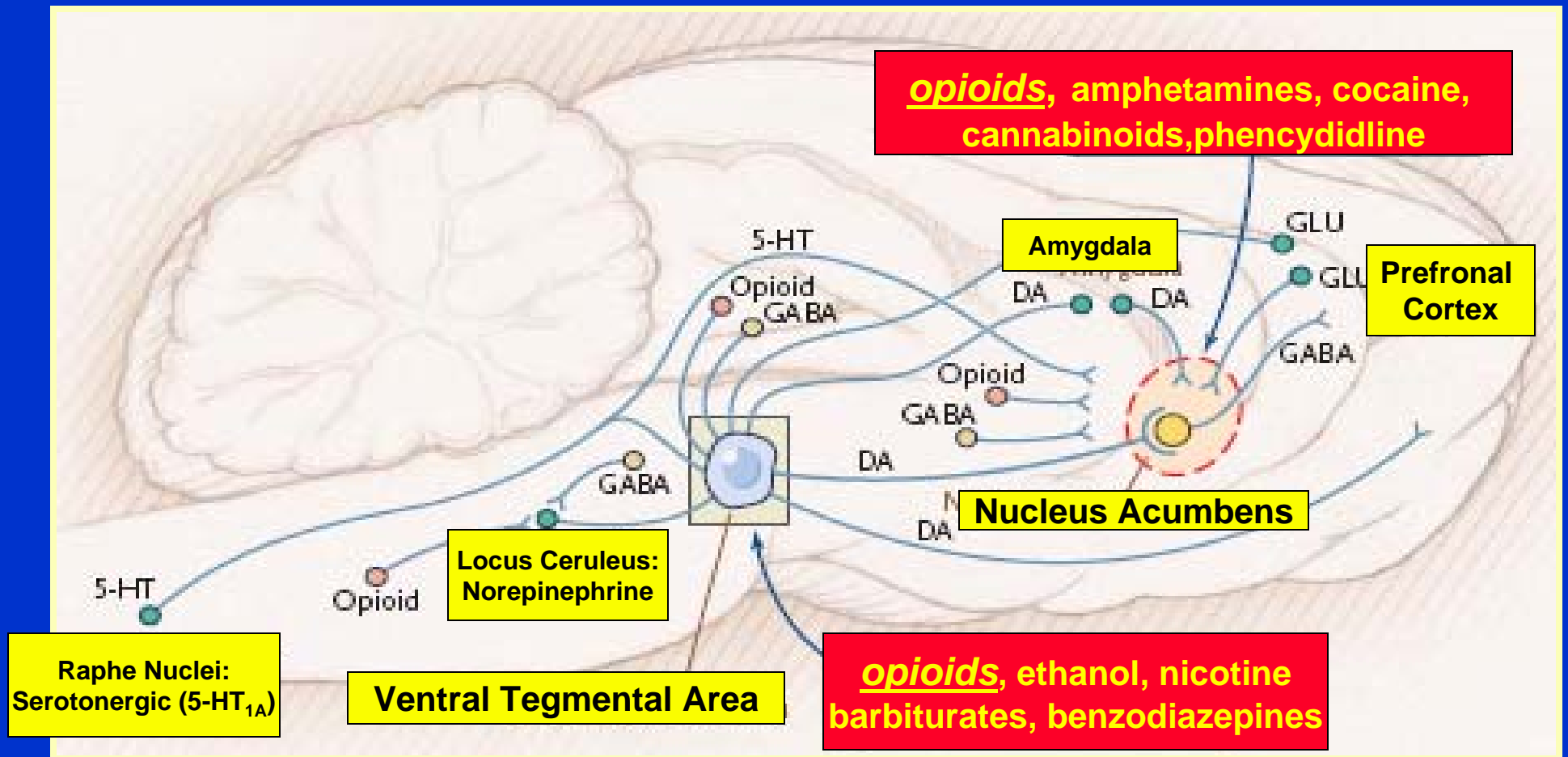
◆ “What the drug does to the body”

Principle of Addiction Medicine  
Second Edition  
1998;99-102

# Common Reward Pathway: Mesocorticolimbic Dopamine System



# Common Reward Pathway: Mesocorticolimbic Dopamine System



5-HT = serotonin; GABA = gamma-aminobutyric acid;  
NE = norepinephrine; DA = dopamine; GLU = glutamine.

# Properties of Medications Going Through the Common Reward Pathway

- ◆ Pharmacokinetic and pharmacodynamic properties
  - “Faster speed of dopamine elevation”
  - “Faster diminution of dopamine elevation”
    - Positive reinforcement
    - *In genetically susceptible individuals*
  - “Slower speed of dopamine elevation”
  - “Slower diminution of dopamine elevation”
    - Lack of positive reinforcement

Volkow ND, Ding Y-S, et al.

Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain.

Archives of General Psychiatry 52:456-463, 1995.

Wise RA, Newton P, et al.

Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats.

Psychopharmacology 120:10-20, 1995.

# Mesolimbic Dopamine System and Drug Misuse

## ◆ Circuit # 1

### ➤ LIKE

- Pleasure circuit
- Meso-accumbens dopamine system

## ◆ Circuit # 2

### ➤ WANT

- Desire and urge circuit
- Basolateral nucleus of the amygdala

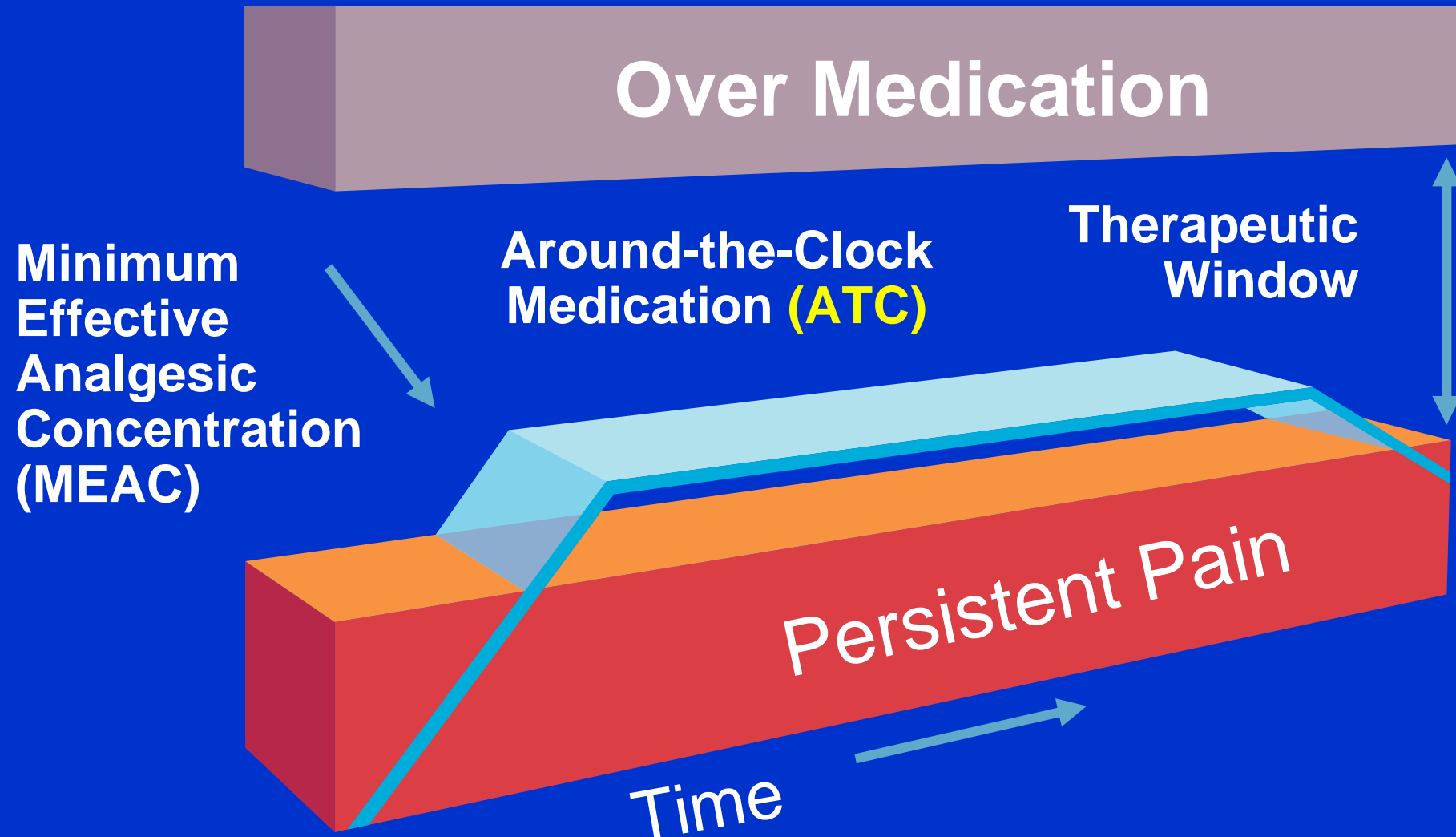
## ◆ Circuit # 3

### ➤ NEED

- Desire and demand circuit
- Physical dependence
  - » Periaqueducal gray matter of brain stem

O'Brien CP, Gardner EL  
Pharmacology & Therapeutics  
2005;108;18-58

# Oral Patient Controlled Analgesia [OPCA]



# Opioid Blood Levels in Opioid Pain Management

## ◆ Chronic pain syndromes

- Opioids adjusted to just above the blood levels that relieves pain (MEAC)
  - No euphoria
  - Achieve functional goals

The Mount Sinai Journal of Medicine  
Vol. 67: No. 5&6  
Oct./Nov. 2000  
Stimmel, B., and Kreek, M.J.

# Opioid Blood Levels in Opioid Pain Management

- ◆ There is **No** analgesic ceiling of pure mu opioids agonists
  - However, **No Ceiling** does not mean **No Limit**
  - Titrate
    - Decrease pain
    - Increase function
    - *Treat breakthrough pain*
    - *Treat acute pain superimposed chronic pain*
  - Titrate upward as clinically necessary

# Differences Between a Chronic Pain Patient and an Addicted Patient

## Pain Patient

1. Not out of control with medications
2. Medications improve quality of life
3. Will want to decrease medication if side effects are present

## Addicted Patient

1. Out of control with medications
2. Medications cause decreased quality of life
3. Medication continues or increases despite side effects

Schnoll SH, Finch J.  
*J Law Med Ethics.*  
1994;22(3):252-256.

# Differences Between a Chronic Pain Patient and an Addicted Patient

## Pain Patient

4. Concern about the physical problem
5. Follows the agreement for the use of the opioids
6. Frequently has medicines left over

## Addicted Patient

4. Unaware or in denial about any problems
5. Does not follow the agreement for use of the opioids
6. Does not have medicines left over, loses prescriptions, and always has a “story”

Schnoll SH, Finch  
*J. J Law Med Ethics.*  
1994;22(3):252-256.

One Drink: 12 oz Beer = 5 oz Wine = 1.5 oz Liquor (80 proof)

*Alcohol Alert. April 2005:65*

U.S. Dept. of Health & Human Services

NIH, NIAAA

# CAGE Questionnaire

- ◆ “Have you felt the need to **C**ut down on your drinking (or drug use)?”
- ◆ “Have people **A**nnoyed you by criticizing your drinking (or drug use)?”
- ◆ “Have you ever felt bad or **G**uilty about your drinking (or drug use)?”
- ◆ “Have you ever needed an **E**ye opener the first thing in the morning to steady your nerves or get rid of a hangover?”

Fiellin, DA, et al.  
Outpatient Management of Patients with Alcohol Problems.  
Ann of Int Med. 2000;133:815-827.

# Sensitivity and Specificity of CAGE Questionnaire

- ◆ Two out of four questions positive on CAGE questionnaire\*
  - Current diagnosis of alcohol misuse or dependency
    - Sensitivity – 77% - 94%
    - Specificity – 79% - 97%
- ◆ NIAAA and NIH recommends using the CAGE questionnaire\*\*

\*Fiellin DA, et al. *Ann Intern Med.* 2000;133(10):815-827.

\*\**Alcohol Alert.* April 2005:65

# Urine Drug Testing

## ◆ Urine drug testing

- Plays a key role in safely managing the pain patient
  - Confirmation of the agreed upon treatment plan
  - Diagnose relapse or drug misuse as early as possible
  - Advocate for the patient for third party interests

## ◆ Compliance testing

- Importance of drug identification not just 'drug-class' identification

# Urine Drug Test (cont)

- ◆ Initial testing is done with class-specific immunoassay drug panels
  - Typically do not identify individual drugs within a class
- ◆ This is followed by a technique such as gas chromatography/mass spectrometry (GC/MS)
  - To identify, or confirm the presence or absence of, a specific drug and/or its metabolites

Heit HA, Gourlay D.

*J Pain Sympt Manage.* 2004;27(3):260-267

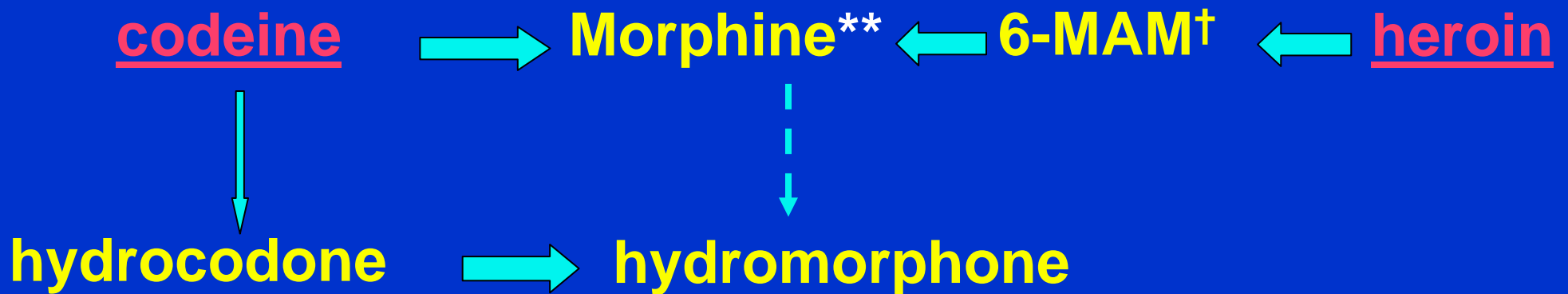
# Synthetic/Semisynthetic Opioids

- ◆ Opiate immunoassays detect morphine and codeine
  - Does *not detect* synthetic opioids
    - Methadone
    - Fentanyl
  - Does *not reliably detect* semisynthetic opioids
    - Oxycodone
  - Chromatography/mass spectrometry (GC/MS) will identify these medications

Heit HA, Gourlay D.

*J Pain Sympt Manage.* 2004;27(3):260-267.

# Metabolism\* of Opioids



\*Not comprehensive pathways, but may explain the presence of apparently unprescribed drugs

†6-MAM: 6-monoacetylmorphine; an intermediate metabolite

\*Gourlay D, Heit HA, Caplan Y.  
California Academy of Family Practice (CAFP),  
August 2004.

HEIT TEMPLATE.PPT 38

\*\*E.J. Cone, H.A. Heit, Y.H. Caplan, D. Gourlay:  
J. Anal. Toxicol.:  
Evidence of Morphine Metabolism to Hydromorphone  
in Pain Patients Chronically Treated with Morphine,  
2006;30(1):1-5.

Drug	Approximate Retention Time
Amphetamines	48 Hours
Barbiturates	Short acting (eg, secobarbital) 24 hours Long acting (eg, phenobarbital) 2-3 weeks
Benzodiazepines	3 days if therapeutic dose ingested Up to 4-6 weeks after extended dosage (ie, 1 or more years)
<b>Cocaine (metab)</b>	<b>2-4 days</b>
Ethanol	2-4 hours
Methadone	<b>Approximately 3 days</b>
<b>Opiates</b>	<b>2 days</b>
Propoxyphene	6-48 hours
Cannabinoids	Moderate smoker (4 times/week) 5 days Heavy smoker (smoking daily) 10 days Retention time for chronic smokers may be 20 - 28 days
Methaqualone	2 weeks
Phencyclidine	Approximately 8 days Up to 30 days in chronic users (mean value = 14 days)

Note: Interpretation of retention time must take into account variability of urine specimens, drug metabolism and half-life, patient's physical condition, fluid intake, and method and frequency of ingestion. These are general guidelines only.

# Conclusion

## ◆ AA Serenity Prayer

- “God, grant me the **Serenity** to accept the things I cannot change; **Courage** to change the things I can; and the **WISDOM** to know the difference.”