MEDICATION ASSISTED RECOVERY

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Learning Objectives

- Name three medications approved by FDA for the treatment of alcohol dependence
- Understand the “kindling” phenomenon
- Name two medications approved by FDA for the treatment of opiate dependence

Nature of Addiction

- **Loss of Control**
- **Harmful Consequences**
- **Continued Use Despite Consequences**

“That is not one of the seven habits of highly effective people.”

Medications Today: Addictions

Alcohol:	**Disulfiram (Antabuse)** **Naltrexone (ReVia, Trexan, Vivitrol)** **Acamprosate (Campral)** **Ondansetron**	**Deterrence** **Reward Blocker** **?? NMDA, GABA** **5-HT3 Serotonin**
Opiates:	**Naloxone (Narcan)** **Naltrexone (ReVia, Trexan)** **Methadone** **Buprenorphine (Suboxone, Subutex)**	**Overdose Rx** **Receptor Blocker** **Replacement** **Replacement**
Stimulants:	**(None to Date)**	
Nicotine:	**Nicotine Replacement** **(gum, patches, lozenge, spray, inhaler)** **Bupropion (Wellbutrin, Zyban)**	**Replacement** **??**

Alcohol: Ancient Knowledge

- Aristotle:
  - **“Drunken women bring forth children like themselves”**
- Plutarch:
  - **“One drunkard begets another.”**

Alcohol: Egyptians

- **Hathor**
  - **Goddess of Love, Music, and Beauty…also a goddess of wine (and beer), was both a goddess of love and a goddess of destruction**

Spectrum of Alcohol Use

- Moderate (low risk) drinking
- Hazardous (at risk) drinking

  - level of consumption or pattern, that if persists likely to result in harm
- Harmful drinking (alcohol abuse)

  - adverse physical, psychiatric, social or legal effects
- Alcohol dependence

Terminology For Alcohol Use Behaviors

Term	Description	
Moderate Drinking	men:	≤ 2 drinks/day
	women:	≤ 1 drink/day
	over 65:	≤ 1 drink/day
At Risk Drinking	men:	> 14 drinks/week
		> 4 drinks /occasion
	women:	> 7 drinks/week
		> 3 drinks/occasion

Alcohol Abuse: DSM IV*
(Harmful Drinking)

1. Failure to fulfill obligations at work, school, or home.
2. Recurrent use in hazardous situations.
3. Legal problems related to alcohol.
4. Continued use despite alcohol-related social problems.

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*American Psychiatric Association, 1994

Alcohol Dependence: DSM IV*

1. Withdrawal symptoms.
2. Use of larger amounts than intended ("tolerance").
3. Unsuccessful attempts to control use.
4. Great deal of time spent or recovering from use.
5. Important social or occupational activities reduced.
6. Use despite alcohol-related physical or psychological problems.

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*American Psychiatric Association, 1994

The Natural History of Alcoholism

- Multiple treatment attempts precede stable recovery
- Addicts die prematurely
- Alcoholics do listen to their doctors
- Outcomes and compliance are on a par with other chronic disorders (diabetes, hypertension, etc.)

Stages of Change (DiClemente)

- Precontemplation
- Contemplation
- Preparation
- Action
- Maintenance

Alcoholism is 40-60% Genetic

Genetic Inheritance I.

- Animal Breeding Studies
  - **Normal lab animals avoid alcohol, but become stably addicted to opiates and stimulants**
  - **Selective breeding has produced alcohol-preferring rats**
  - **It is possible to breed animals for “addictivity”**

Genetic Inheritance II

- Human Family Tree Studies
  - **Alcoholism runs in families “Drunkards beget drunkards”**
  - **Males have higher rates of alcoholism than females**
  - **Females may have more depression**
  - **Males show more antisocial behaviors**

Genetic Inheritance III

- Twin & Adoption Studies
  - **Identical >>Fraternal>>Sibling>>2nd Degree Relative**
  - **Child of Alcoholic raised by non-alcoholic foster parents**
    - **4X increase in alcoholism for males**
    - **9X increase if father is antisocial**
  - **Child of Non-Alcoholic parent raised by alcoholic foster parents**
    - **No increased risk**

Twelve-Step Groups

- Myths
  - **Only AA can treat alcoholics**
  - **Only a recovering individual can treat an addict**
  - **12-Step groups are intolerant of prescription medication**
  - **Groups are more effective than individuals because of confrontation**

Twelve-Step Groups

- Facts
  - **Available 7 days/week, 24 hrs/day**
  - **Work well with professionals**
  - **Primary treatment modality is fellowship (identification)**
  - **Safety and acceptance predominate over confrontation**
  - **Offer a safe environment to develop intimacy**

Myths of Addiction Treatment

- Myth of Character Weakness
- Myth of Holding One's Liquor
- Myth of Self-Medication
- Myth of Detoxification
- Myth of Single Neurotransmitter
- Myth of Magic Bullet Medication
- Myth of Brain Reversibility

Alcohol Withdrawal

- **Kindling Hypothesis**
  - **Recurring, untreated withdrawals**
  - **Glutamate-mediated excitotoxicity**
- **CIWA-Ar Withdrawal Scale**
  - **Initial loading dose of benzodiazepine**
  - **Symptom-triggered adjustments**

CIWA-Ar:

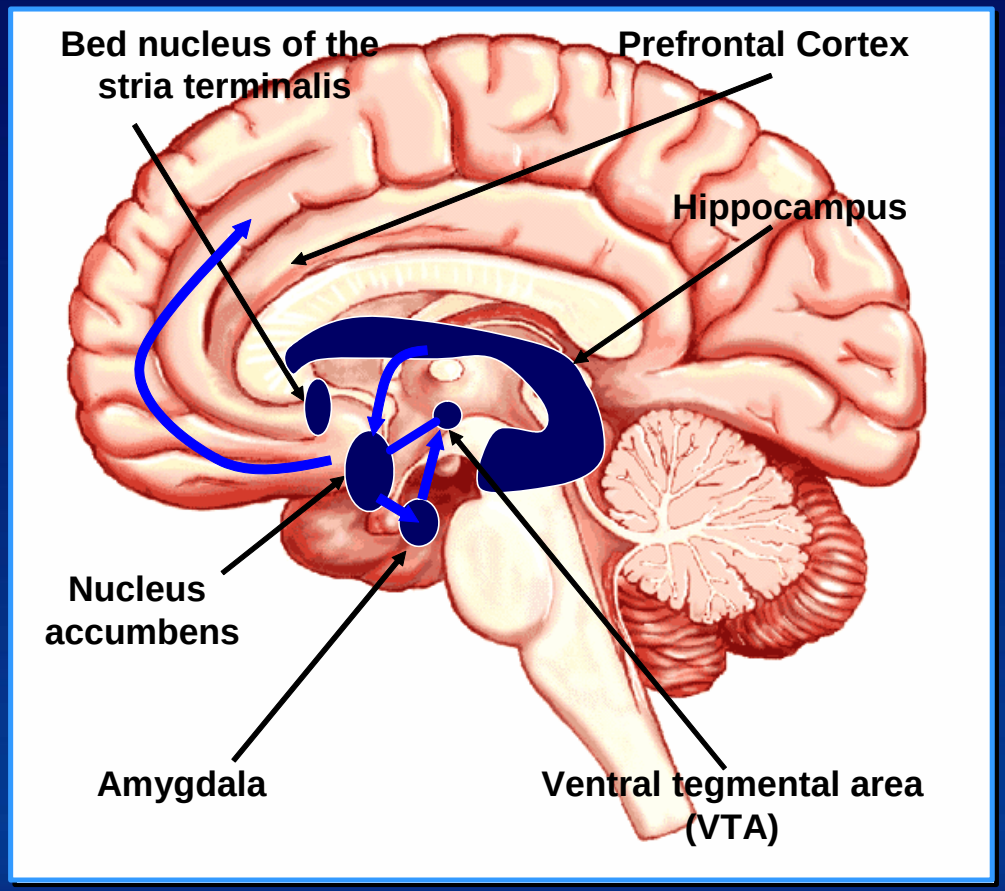
Clinical Institute Withdrawal from Alcohol Scale (Revised)

- CIWA permits “symptom-triggered” benzodiazepine management
- Front-loading of benzodiazepines decreased total dose of BZ and duration of intervention
- Multiple, untreated episodes of alcohol withdrawal may lead to kindling of seizures and perhaps of hallucinosis and delirium tremens

Possible “Kindling” Irreversible Phenomena

- Alcoholic
  - Seizures
  - ? Paranoia
  - ? Hallucinosis & DT’s
- Post-Stimulant Psychosis
  - ? Paranoia
  - ? Auditory hallucinations
- Heroin and Opiates
  - ? Lowered Pain Tolerance

Relapse and Conditioning



- Repeated alcohol use has caused "conditioning" to occur in related circuits
- Now "cues" associated with alcohol use can activate the reward and withdrawal circuit
- This can evoke anticipation of alcohol or feelings similar to withdrawal that can precipitate relapse in an abstinent patient

Source: Messing RO. In: Harrison's Principles of Internal Medicine. 2001:2557-2561.

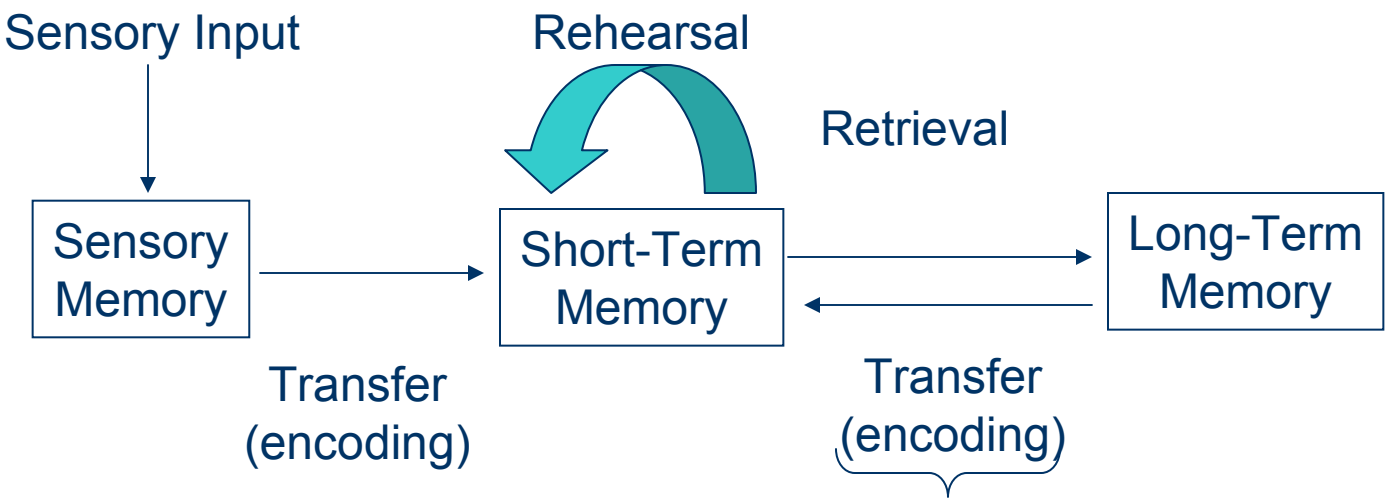
Cerebellar Degeneration

- Typically develops >10 years of heavy drinking (Charmess 1993)
- 40% of alcoholics at autopsy show cerebellar shrinkage
- May be related to thiamine deficiency

Memory & Thiamine

- Wernicke's Encephalopathy
  - Acute, life-threatening
  - Symptom Triad (not all are needed)
    - Mental Confusion
    - Cranial nerve palsies
    - Ataxia
- Wernicke-Korsakoff Syndrome
  - Chronic, anterograde amnesia
  - Alcohol amnestic disorder
- Alcoholic Dementia
  - A continuum of cognitive deficits from mild to severe
  - Impairments of visuo-spatial functioning
  - Perseveration is failed problem-solving strategies

Memory



Alcohol primarily interferes with the transfer of Information from short-term to long-term storage

Atkinson and Shiffrin (1968)

Medications: Alcohol

Disulfiram (Antabuse) Calcium Carbimide	ALDH blockers	May also have efficacy for reducing cocaine use
Naltrexone (ReVia, Vivitrol) Nalmefene	Opioid antagonists	
Acamprosate (Campral)	Glutamate stabilization	Reduction of protracted withdrawal?
Ondansetron	Serotonin-3-receptor Antagonist	May be effective in an older subset of alcoholic population
Topiramate (Topamax)	Dopamine inhibition Glutamate stabilization	Reward Reduction Reduction of protracted withdrawal?

Alcohol Relapse - Prevention

- **Disulfiram (Antabuse)**
  - **250 mg qd**
  - **Liver Function Tests, EKG**
- **Naltrexone (ReVia, Trexan, Vivitrol)**
  - **50 mg qd, half-dose for 3-4 days at start**
  - **Liver Function Tests**
  - **This med blockades ALL opiates, even morphine**
- **Acamprosate (Campral)**
  - **Recently approved in U.S.-2004**

FDA-Approved Pharmacotherapies for Alcohol Dependence

Drug Class	***Mini-Profile***
Disulfiram (antabuse®)	* Inhibits aldehyde dehydrogenase * When taken with alcohol, ↑ (acetaldehyde) leads to nausea, dizziness, headache, flushing * Decreases desire to drink * Poor tolerability profile * Black box warning, safety issues

Alcohol: Oxidative Metabolism

EtOH + NAD (nucatinumide adenasine dehydrogenase)

→ Acetaldehyde + NADH + H+

ADH

(Alcohol Dehydrogenase)

Acetaldehyde + NAD → Acetate + NADH + H+

ALDH

(Aldehyde Dehydrogenase)

Site of Action of Antabuse: Blockade of ALDH produces Increase in nauseating Acetaldehyde which is Normally cleared rapidly

FDA-Approved Pharmacotherapies for Alcohol Dependence

Drug Class	***Mini-Profile***
Naltrexone (ReVia®)	* Opioid antagonist * Binds to opioid receptors, thus blocking alcohol reward pathways * Black box warning, safety issues

FDA = US Food and Drug Administration.
Antabuse is a registered trademark of Odyssey Pharmaceuticals, Inc.
ReVia is a registered trademark of the DuPont Merck Pharmaceutical Company
Source: O'Connor PG, et al, N Engl J Med. 1998;338:592-602.

Naltrexone Studies

NTX Study	Additional Therapy	Slowed Response	Drinking Reduction	Craving Reduction
Older Studies				
Volpicelli et al. 1992	Intensive multimodality	+	+	+
O'Malley et al, 1992	Supportive/Coping Skills	+	+	
Volpicelli et al, 1997	Relapse prevention Treatment completions	+	+	
Anton et al, 1999	Cognitive-behavioral	+	+	+
Report Studies				
Chick et al, 2000	Compliant patients only		+	+
Morris et al, 2001		+	+	
Guardia et al, 2002		+	+	
Krystal et al, 2001	TSF Twelve Step Facilitation			

Endogenous Opioids

- Endogenous opiates contribute to the rewarding properties of alcohol
- Opiate antagonists reduce alcohol consumption
- Alcoholics may have reduced B-endorphin in CSF, plasma, and altered sensitivity to alcohol challenge

VIVITROL Summary of Efficacy

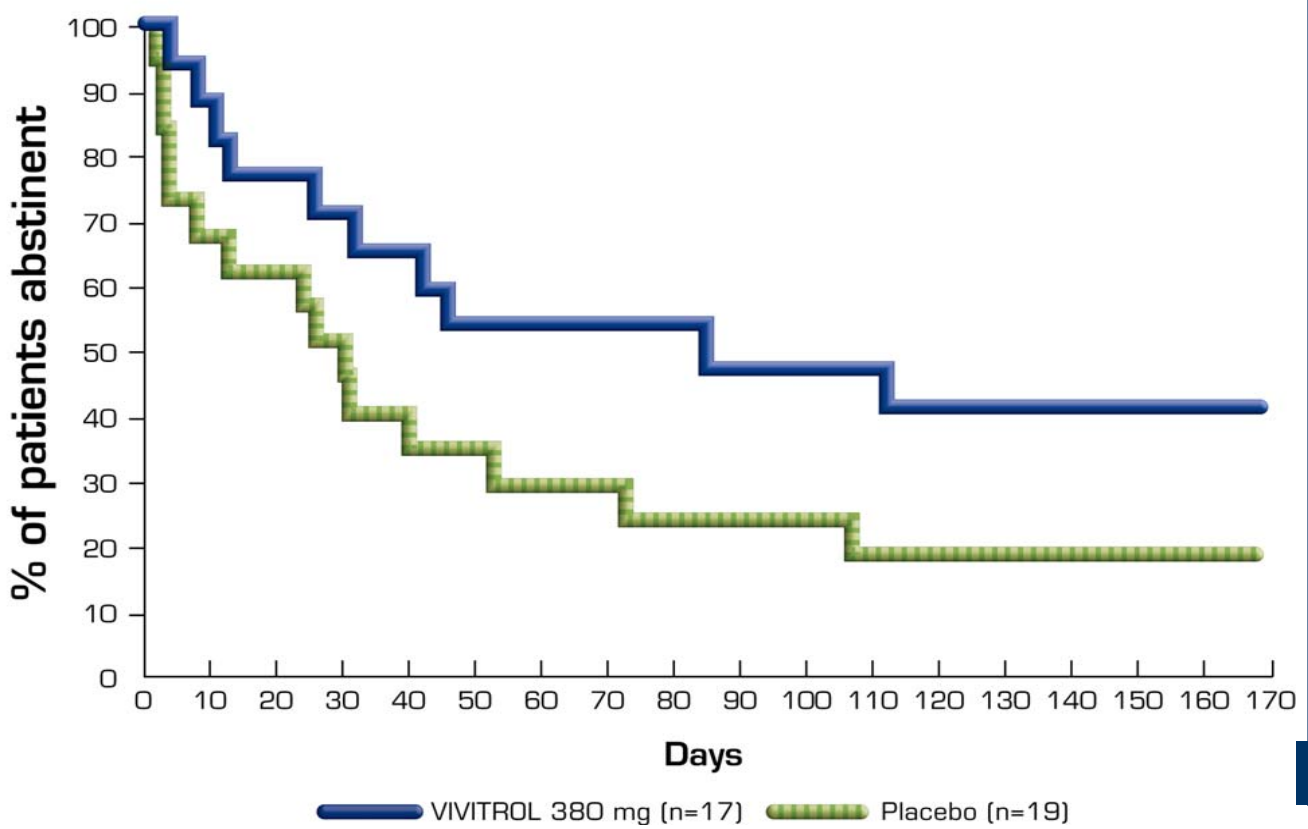
- Subjects treated with VIVITROL 380 mg*
  - Had a greater reduction in the number of heavy drinking days than those treated with placebo

- Patients receiving VIVITROL 380 mg who were abstinent for a week prior to treatment initiation*
  - Were more likely to maintain complete abstinence throughout the 6-month study
  - Had a greater reduction in the number of any drinking days
  - Had a greater reduction in their number of heavy drinking days

*All patients treated with psychosocial support

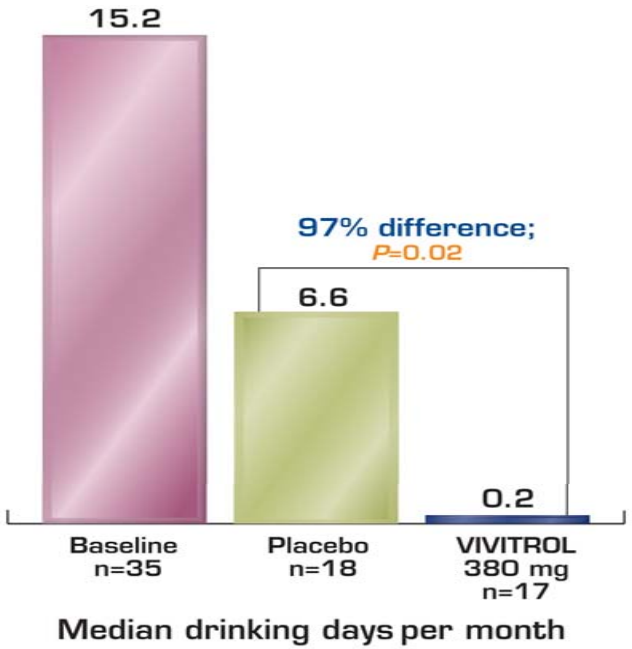
VIVITROL full Prescribing Information. Alkermes, Inc.

VIVITROL Prolonged Abstinence



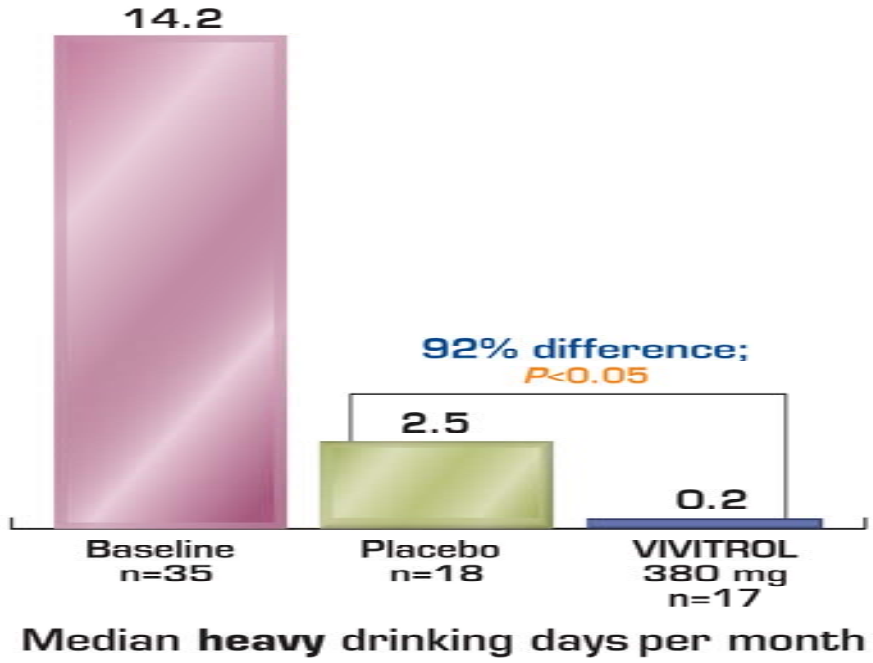
Patients abstinent for 7 days prior to treatment initiation
Data on file. Alkermes, Inc.

VIVITROL Significantly Reduced Drinking Days



Patients abstinent for 7 days prior to treatment initiation
Data on file. Alkermes, Inc.

VIVITROL Significantly Reduced Heavy Drinking Days



Patients abstinent for 7 days prior to treatment initiation
Data on file. Alkermes, Inc.

Most Common Adverse Events

	VIVITROL (%)	Placebo (%)
Nausea*	29	11
Vomiting	12	6
Headache	21	18
Fatigue	20	12
Dizziness	13	4
Injection site reaction**	65	50

*** Nausea was generally mild in intensity, lasted 2 to 3 days, and was less common with subsequent injections.**

Discontinuation rate due to nausea was 2%

**** Discontinuation rate due to injection site reactions was 3%**

VIVITROL full Prescribing Information. Alkermes, Inc.

Pain Management

- Patients should be advised to carry a card to alert medical personnel to the fact that they are taking VIVITROL
- In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged
  - A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred

- In an emergency situation in patients receiving VIVITROL, a suggested plan for pain management is
  - Regional analgesia,
  - Conscious sedation with a benzodiazepine and non-opioid analgesics, or
  - General anesthesia

VIVITROL full Prescribing Information. Alkermes, Inc.

Dosage and Administration

- VIVITROL 380 mg is given as an intramuscular (IM) gluteal injection every 4 weeks or once a month
- VIVITROL should be administered by a healthcare professional, alternating buttocks each month, using only the components provided
- VIVITROL must NOT be administered intravenously

VIVITROL full Prescribing Information. Alkermes, Inc.

Acamprosate in Europe

- In 14 of 15 European clinical trials with more than 3,000 patients, acamprosate increased abstinence rates by about 50%
- Recently approved for use in the U.S.

Effects of Alcohol on Neural Circuits

Glutamate System

Administration of Alcohol

Acute Alcohol Effect

- **Inhibits NMDA receptors**
- **Effect: ↓ anxiety, ↑ sedation**

Chronic Alcohol Use

Alcohol Free

CNS Equilibrium

Adaptation

- **↑ # and/or function of NMDA receptors on neurons**
- **Balances acute alcohol effect**
- **Effect: tolerance, dependence**

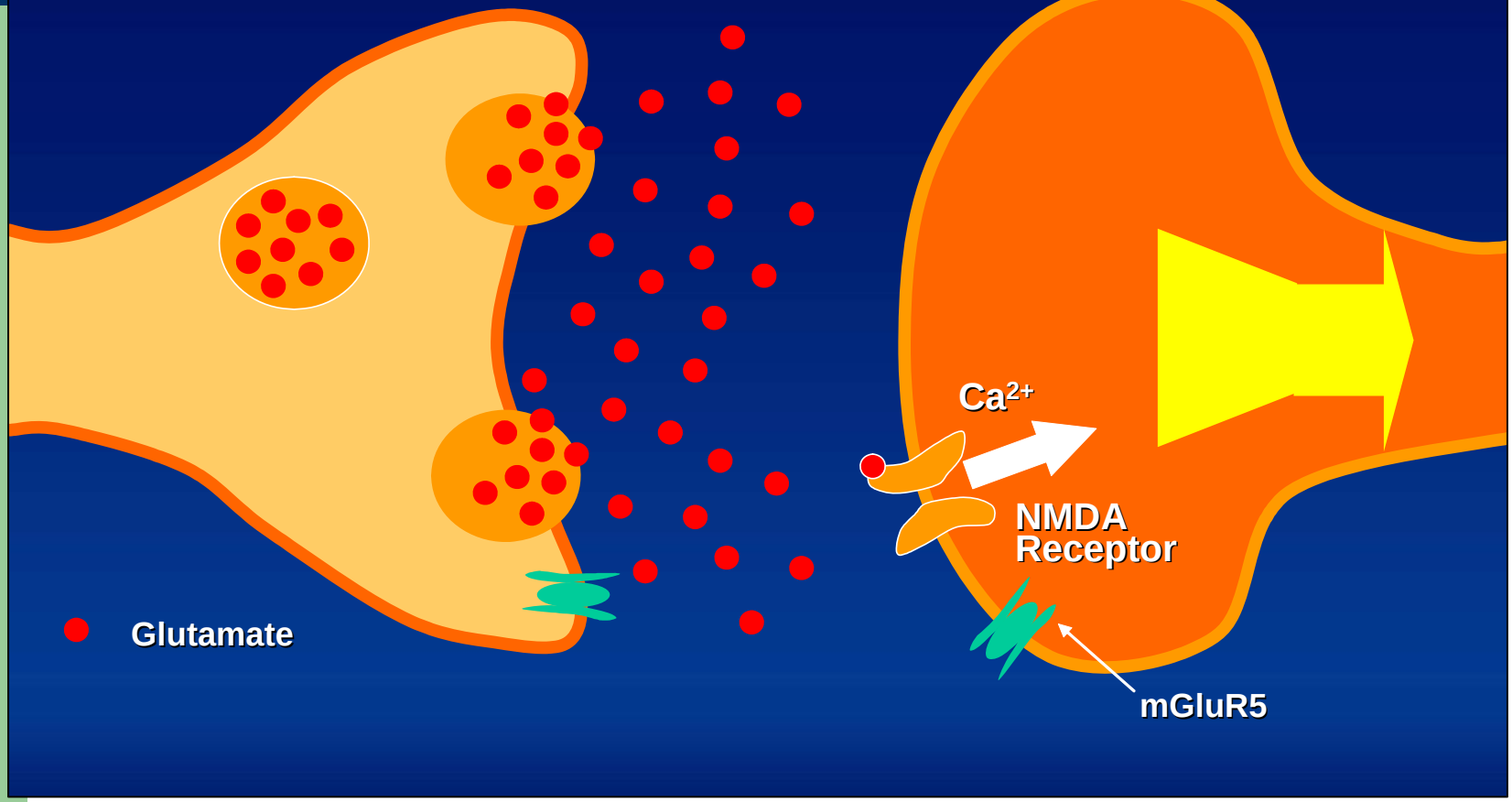
Withdrawal

- **Increased glutamatergic activity**
- **Effect: - *Acute:* dysphoria, hallucinations**
  - *Post-acute:* sleep/mood disturbances

Removal of Alcohol

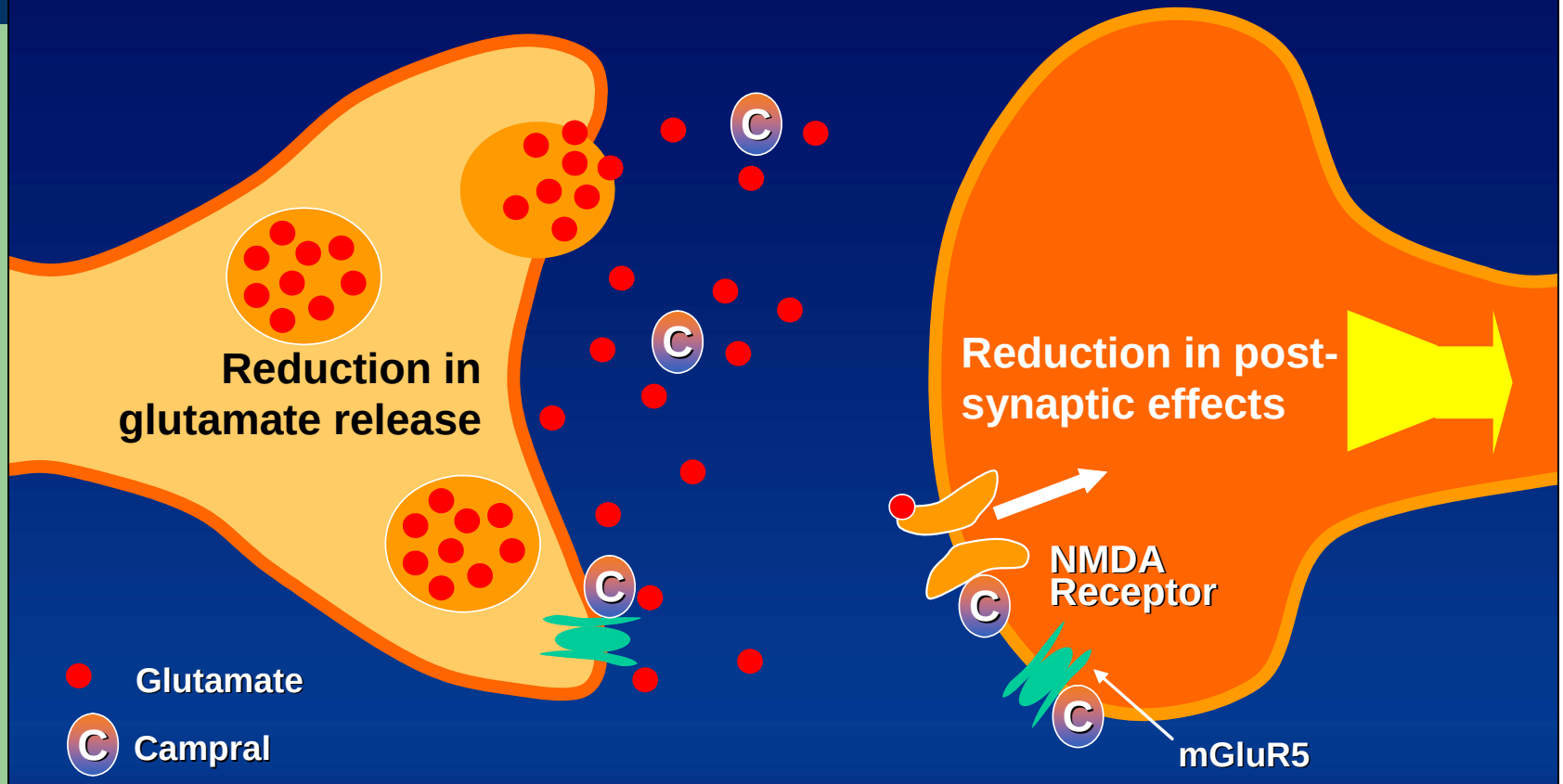
Source: Littleton J. *Alcohol Health Res World*. 1998;22:13-24.

Pathophysiology of Potential Relapse



Balancing Pathophysiology

Campral®



Summary: Acamprosate Clinical Trial Data

- Primary and other efficacy outcomes separated acamprosate-treated patients statistically from placebo
  - Complete abstinence
  - Percentage of days abstinent
  - Time to first drink
- In all 3 pivotal studies, psychosocial support was given to patients
- Acamprosate was safe and well tolerated
- No addiction potential

Summary of Acamprosate

- Acamprosate efficacy (complete abstinence, percentage of days abstinent, and time to first drink) was superior to placebo in combination with psychosocial support
- Acamprosate is a safe and well-tolerated therapy
  - Discontinuation rates due to adverse events were similar to placebo (8% for acamprosate-treated patients vs 6% for placebo)
  - Safe for use in combination with commonly used medications in the patient population
- Unique mechanism of action is thought to restore normal neurotransmitter balance
- Acamprosate has been used by over 1.5 million patients worldwide

Therapy With Campral® (acamprosate calcium)

*Appropriate Patients For Treatment**

- **Committed to the goal of abstinence**
- **Agree to participate in counseling (psychosocial support)**
- **Willing to be compliant with treatment**

*meet *DSM-IV* criteria for alcohol dependence

Buprenorphine and Office-Based Treatment of Opioid Dependence

Opioid Dependence (DSM-IV) (3 or more within one year)

- Tolerance
- Withdrawal
- Larger amounts/longer period than intended
- Inability to/persistent desire to cut down or control
- Increased amount of time spent in activities necessary to obtain opioids
- Social, occupational and recreational activities given up or reduced
- Opioid use is continued despite adverse consequences

ASAM & AAPM & APS Consensus Statement

- “Addiction is a primary, chronic, neurologic 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 cravings.

What Addiction Isn't: Physical Dependence

- Pharmacologic effect characteristic of opioids
- Withdrawal or abstinence syndrome manifest on abrupt discontinuation of medication or administration of antagonist
- Assumed to be present with regular opioid use for days-to-weeks
- Becomes a problem if:
  - Opioids not tapered when pain resolves
  - Opioids are inappropriately withheld

What Addiction Isn't: Tolerance

- Pharmacologic effect characteristic of opioids
- Need to increase dose to achieve the same effect or diminished effect from same dose
- Tolerance to various opioid effects occurs at differential rates
- Tolerance to non-analgesic effects often beneficial to patients (sedation, respiratory depression)
- Analgesic tolerance is rarely the dominant factor in the need for opioid
- Patients requiring dose escalation most often have a change in pain stimulus (disease progression, infection, etc.)

(Foley, 1991)

Addiction

- Compulsive Use
- Loss of control
- Continued use despite adverse consequences

“Pseudo-Addiction”

- Pattern of drug seeking behavior of pain patients receiving inadequate pain management that can be mistaken for addiction
  - Cravings and aberrant behavior
  - Concerns about availability
  - “Clock-watching”
  - Unsanctioned dose escalation
- Resolves with reestablishing analgesia

Weissman, DE, Haddox, JD. Opioid pseudo addiction-an latrogenic syndrome. Pain 1989, 36-363.

What is the Risk of Addiction and Aberrant Behavior?

- Boston collaborative Drug Surveillance Project: Porter and Jick, 1980. *NEJM.*
  - 4 cases of addiction in 11,882 patients with no prior history of abuse who received opioids during inpatient hospitalization.

- Dunbar and Katz, 1996, *JPSM*.
  - 20 patients with **both** chronic: pain and substance abuse problems on chronic opioid therapy
  - Nine out of 20 abused medication
  - Of the 11 who did not abuse the medications, all were active in recovery programs with good family support

Spectrum of Risk of Addiction or Aberrant Behavior

~ 45%

<1 %

HIGH
Long-term Exposure to Opioids in Addicts,
Dunbar and Kafz

LOW
Short-term Exposure to Opioids in Non-addicts
Porter and Jick

Where is your patient ?

Differential Diagnosis of Aberrant Drug-Taking Attitudes and Behavior

- Addiction
- Pseudo-addiction (inadequate analgesia)
- Other psychiatric diagnosis
  - Encephalopathy
  - Borderline personality disorder
  - Depression
  - Anxiety
- Criminal Intent

(Passik & Portenoy 1996)

Defining the Problems

- Difficulties in assessing the risk of aberrant behavior and addiction.
- Misunderstandings about what addiction is and the shortcomings of present definitions when applied to the clinical pain management situation.
- The absence of well-articulated management strategies for patients with different substance abuse-related problems and aberrant behavior.

Aberrant Drug-taking Behaviors: The Model

- **Probably more predictive**
  - Selling prescription drugs
  - Prescription forgery
  - Stealing or borrowing another patient's drugs
  - Injecting oral formulation
  - Obtaining prescription drugs from non-medical sources
  - Concurrent abuse of related illicit drugs
  - Multiple unsanctioned dose escalations
  - Recurrent prescription losses
- **Probably less predictive**
  - Aggressive complaining about need for higher doses
  - Drug hoarding during periods of reduced symptoms
  - Requesting specific drugs
  - Acquisition of similar drugs
  - Unsanctioned dose escalation 1-2 times
  - Unapproved use of the drug to treat another symptom
  - Reporting psychic effects not intended by the clinician

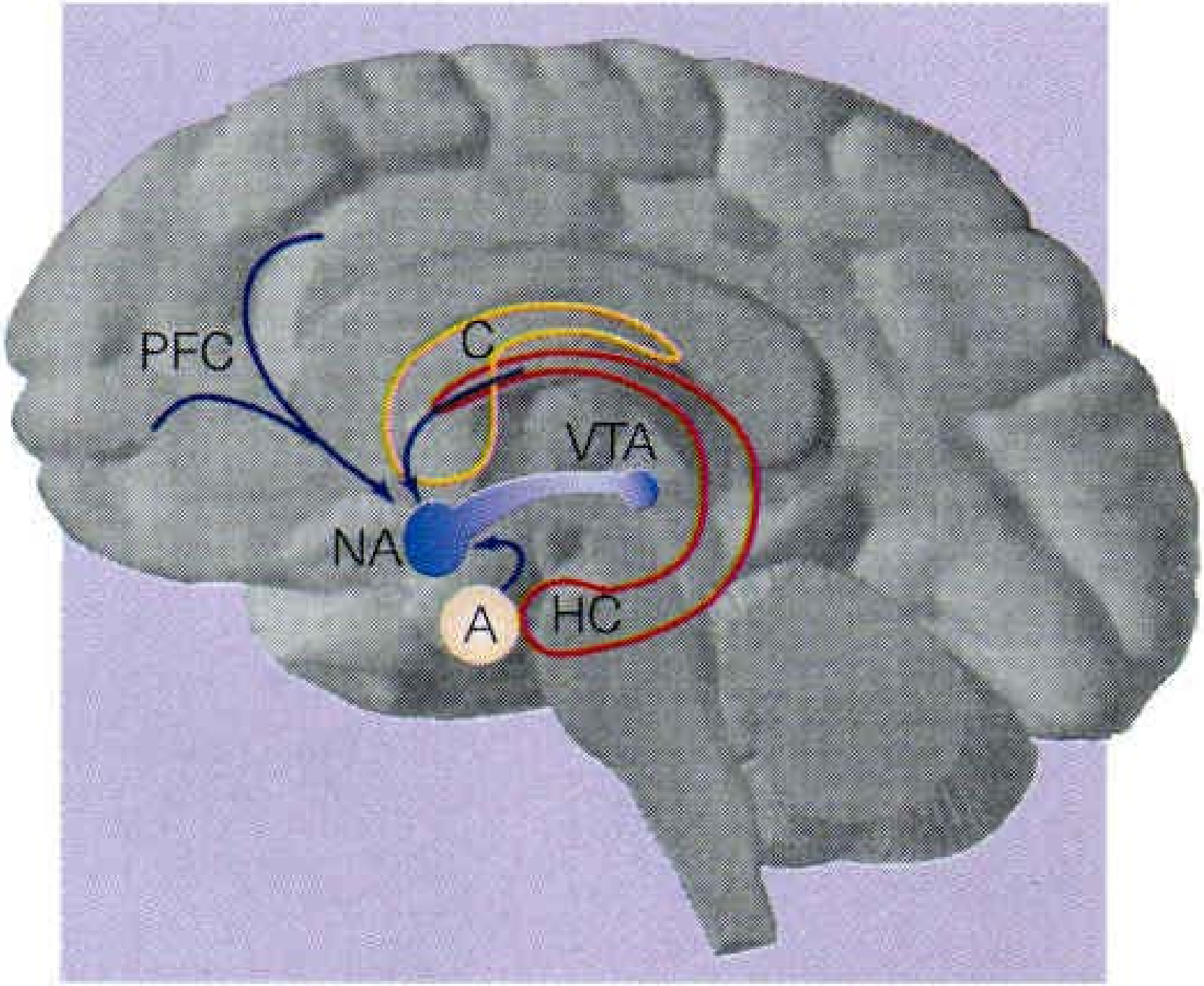
Passik and Portency, 1998

Opioid Dependence

- Opioid dependence is a chronic, progressive, relapsing medical condition
- Profound neurobiologic changes accompany the transition from opioid use to opioid addiction
- Pharmacologic treatments are effective in normalizing the neurobiologic status, decreasing illicit opioid use, medical and social complications

Changes in Neurobiology

- Repeated exposure to short acting opioids leads to neuronal adaptations
  - Mesolimbic dopaminergic system
    - adaptations in G protein-coupled receptors
    - up regulation of CAMP second messenger pathway
- Changes
  - Mediate tolerance, withdrawal, craving, self-administration
  - Insight into the chronic and relapsing nature of opioid dependence
  - Basis of specific pharmacotherapies to stabilize neuronal circuits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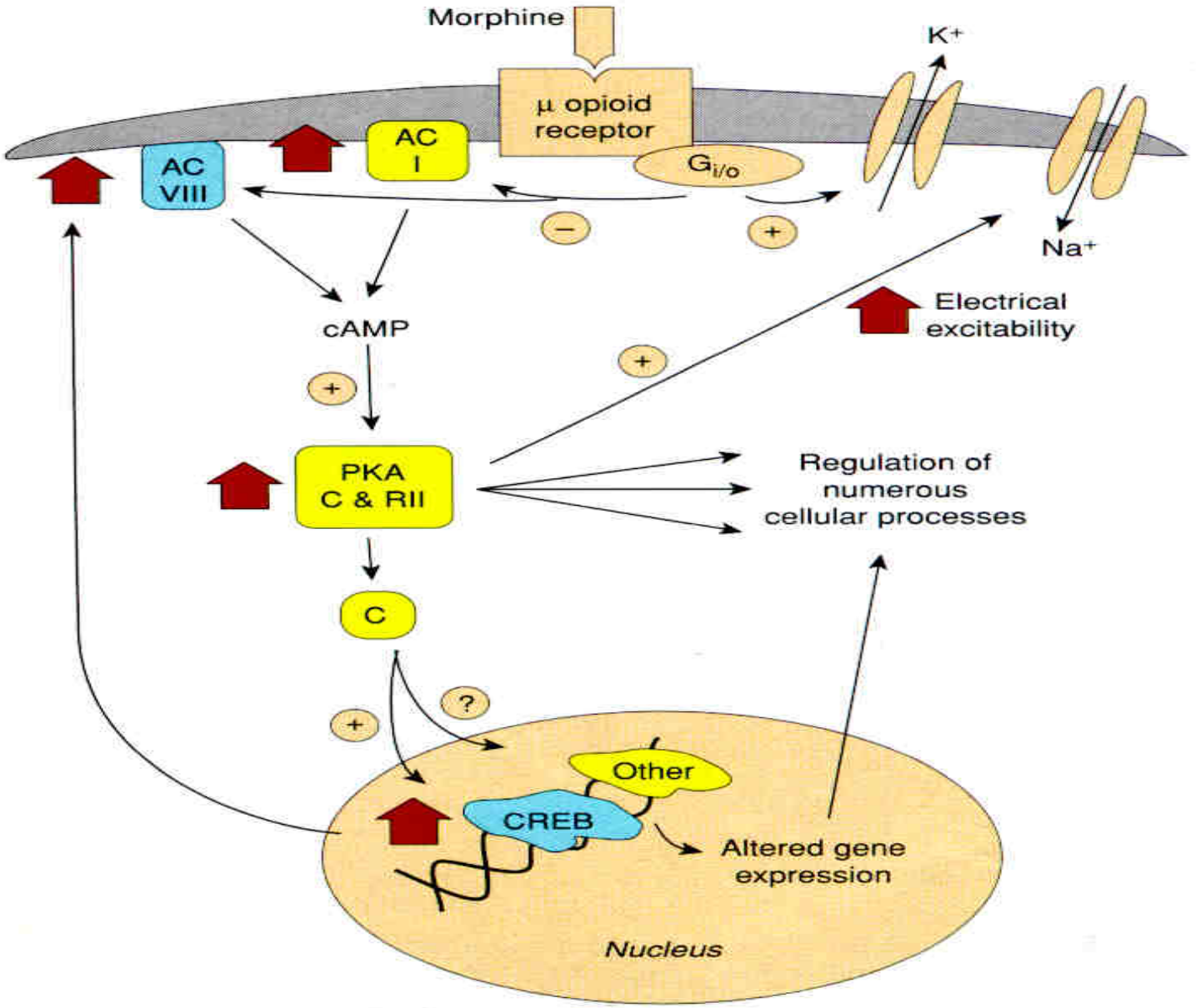

Morphine
μ opioid receptor
K+
Na+
AC VIII
AC I
Gi/o
cAMP
Electrical excitability
PKA C & RII
Regulation of numerous cellular processes
C
?
Other
CREB
Altered gene expression
Nucleus

Opioid Agonist Treatment Rationale

- Cross-tolerance
  - prevent withdrawal
  - relieve craving for opioids
- Narcotic blockade
  - block or attenuate euphoric effect of exogenous opioids

Buprenorphine: Why is it needed?

- Federal law prohibits physicians from prescribing methadone (or other DEA Schedule II medications) for detoxification from opiate addiction EXCEPT in a federally licensed opiate treatment program (OTP) (this includes methadone maintenance).

Buprenorphine: What is it?

- Buprenorphine joined methadone, LAAM, and Naltrexone as the fourth medication for treating opiate addiction

Legislation: DATA 2000

- Permits qualified physicians to obtain a waiver to treat opioid addiction with Schedule III, IV, and V opioid medications (or combinations of such medications)
  - Medications must be approved by the FDA for that indication
  - Medications may be prescribed or dispensed

Legislation: DATA 2000

- Medications Approved by FDA 10/8/02 for use in the treatment of Opioid Addiction are:
  - Subutex® CIII 2mg, 8mg sublingual tablet
    - Buprenorphine
  - Suboxone® CIII 2/.5mg, 8/2mg sublingual tablet
    - Buprenorphine and Naloxone (4:1 ratio)
- No other opioid agonist or partial agonist medications have been approved
- Methadone is Schedule II
- Buprenorphine is Schedule III

Pharmacology: Full Opioid Agonists

- Occupy the receptor and activate that receptor
- Increasing doses of the drug produce increasing receptor-specific effects until a maximum effect achieved
- Most abused opioids are full agonists
- Examples: heroin, hydrocodone, methadone, morphine

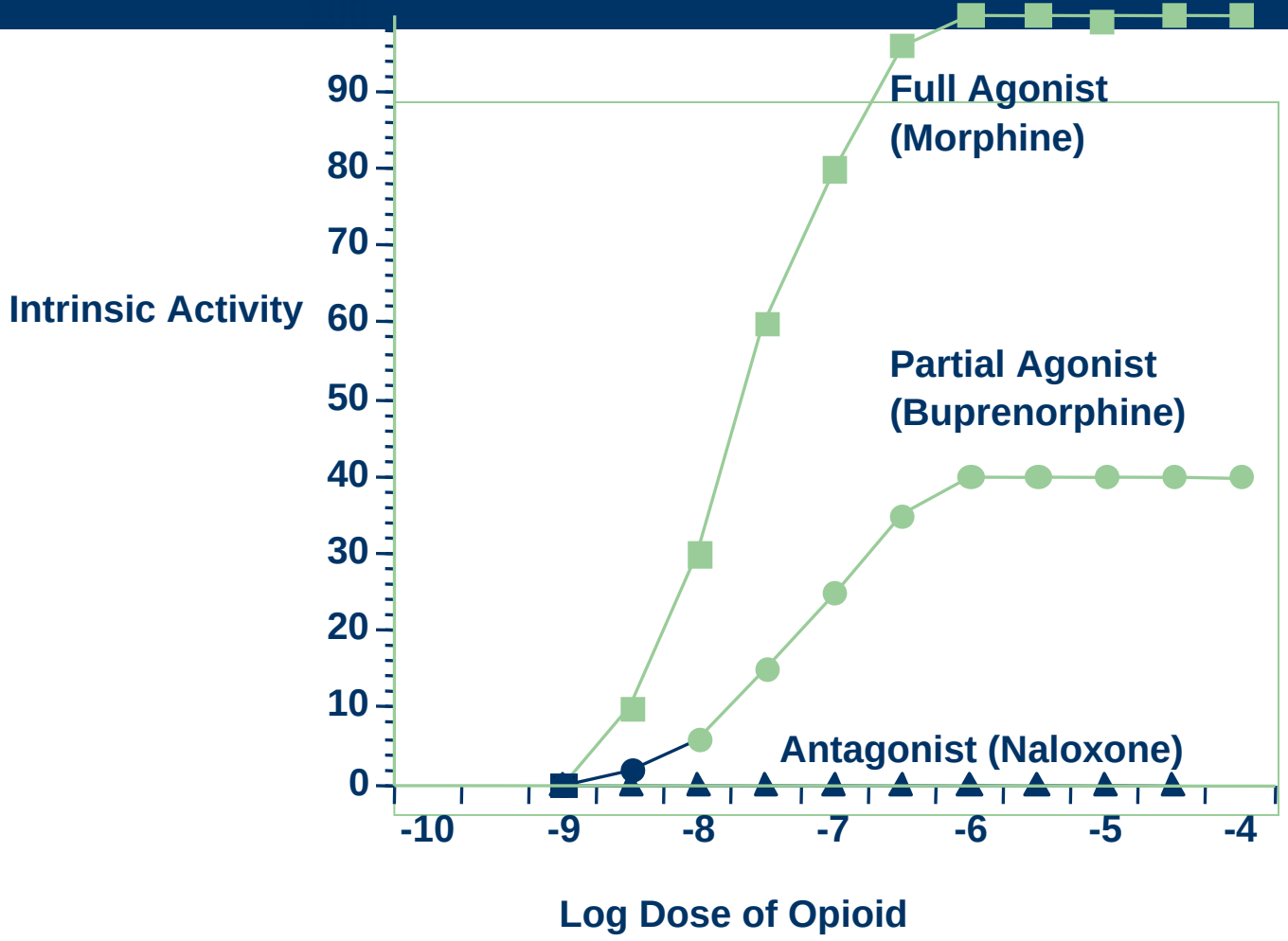
Pharmacology: Partial Opioid Agonists

- Bind to and activate receptor
- Increasing dose does not produce as great an effect as does increasing the dose of a full agonist (less of a maximal effect is possible)
- “Ceiling effect” on respiratory depression
- Example: buprenorphine

Pharmacology: Opioid Antagonists

- Bind to receptors but don’t activate the receptor
- Block the receptor from activation by full and partial agonists
- Examples: Naloxone, Naltrexone

Intrinsic Activity: Full Agonist (Morphine), Partial Agonist (Buprenorphine), Antagonist (Naloxone)



Withdrawal Signs and Symptoms

- Dysphoric mood
- Sweating
- Piloerection
- Diarrhea
- Yawning
- Mild fever
- Insomnia
- Craving
- Distress/irritability
- Nausea or vomiting
- Muscle aches/cramps
- Lacrimation
- Rhinorrhea
- Pupillary dilitation

Duration of Action

- Onset of action: 30 – 60 minutes (after S/L administration)
- Peak effects: 1 – 4 hours
- Half-life ~24 to 36 hours (receptor levels vs serum levels)

Buprenorphine/Naloxone Combination (Suboxone®)

- Addition of naloxone to buprenorphine to decrease abuse potential of tablets
- If taken as medically directed (dissolve under tongue), predominant buprenorphine effect
- If opioid dependent person dissolves tablet and injects, predominant naloxone effect (and precipitated withdrawal)

Safety Overview

- Highly safe medication (acute and chronic dosing)
- Primary side effects: like other mu agonist opioids (e.g., nausea, constipation), but may be less severe
- No evidence of significant disruption in cognitive or psychomotor performance with buprenorphine maintenance
- No evidence of organ damage with chronic dosing

Safety

- Low risk of clinically significant problems
- No reports of respiratory depression in clinical trials comparing buprenorphine to methadone
- Pre-clinical studies suggest high doses of buprenorphine should not produce respiratory depression or other significant problems
- Overdose of buprenorphine combined with other drugs may cause problems (reviewed below)

Safety

- Reports of deaths when buprenorphine injected along with non-medical doses of benzodiazepines
  - Reported from France, where buprenorphine-only tablets available: appears patients dissolve and inject tablets
- Probably possible for this to occur with other sedatives as well

Objectives of Maintenance Treatment

- To normalize and stabilize brain function
- To improve psychosocial functioning
- To reduce mortality from overdose and infection
- To reduce opioid and other illicit drug use
- To reduce transmission of HIV, HCV, HBV

Maintenance Treatment

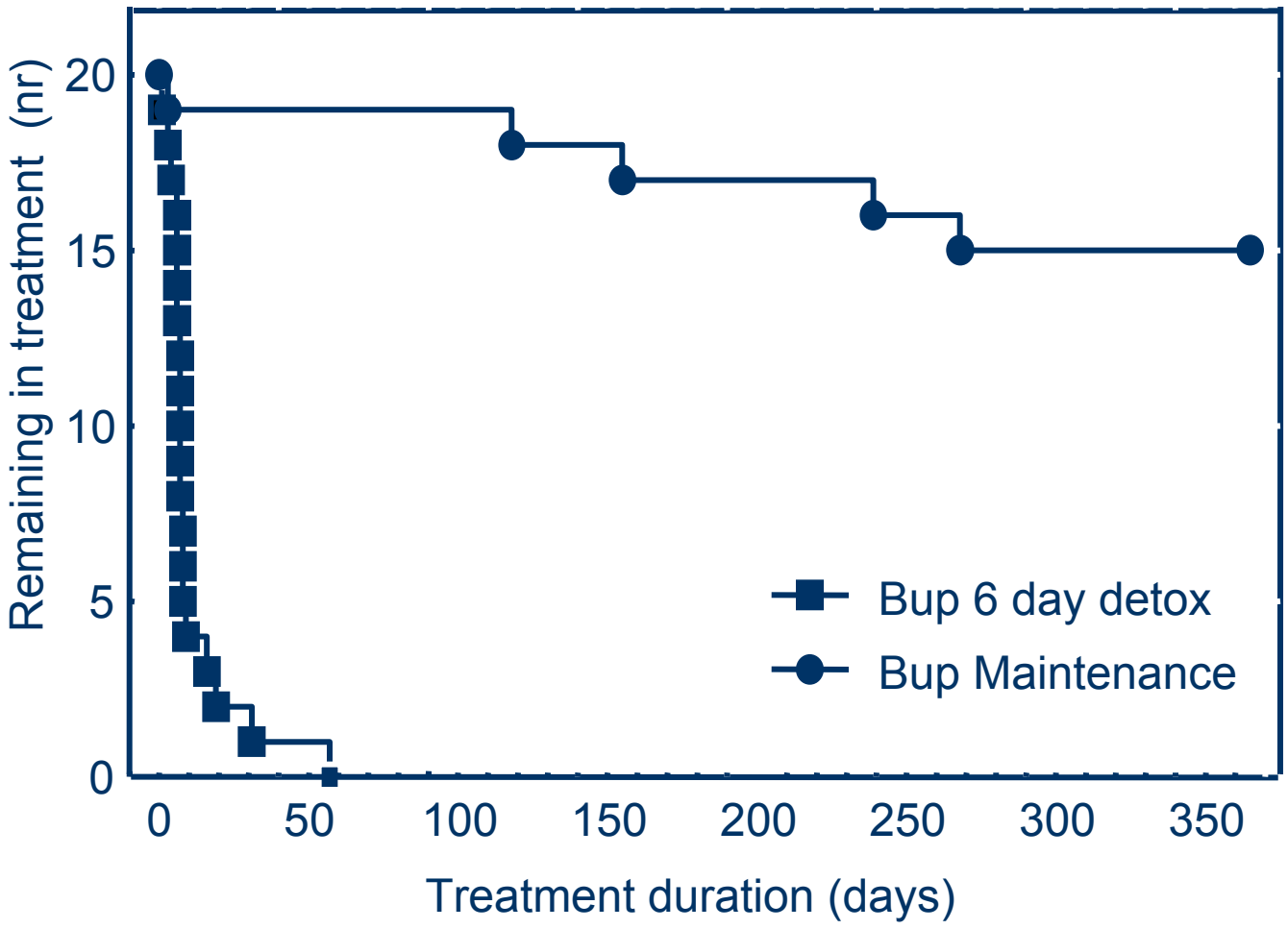
- Majority of patients respond to 4-24 mg daily
- No maximum or minimum duration of treatment
- Provides opportunity for health care providers to address all aspects of needed care (e.g. psychosocial, medical, etc.)
- Variability between patients (e.g., absorption, metabolism,elimination) requires individualized dosing
- No maximum recommended dose
  - Use of illicit opioids and treatment retention improves with increasing dose (Ling, *Addiction* 1998)
- Recommend once daily dosing, two tablets at a time

Medical Withdrawal (Detox)

- Minimal rebound withdrawal following short courses of buprenorphine
- Minimal symptomatic medication needed
- Post-Medical Withdrawal (Detox) linkages
  - Medical Withdrawal is only the first step
  - Opioid Agonist Maintenance treatment
  - Antagonist treatment
  - Psycho-social interventions

Detoxification vs. Maintenance

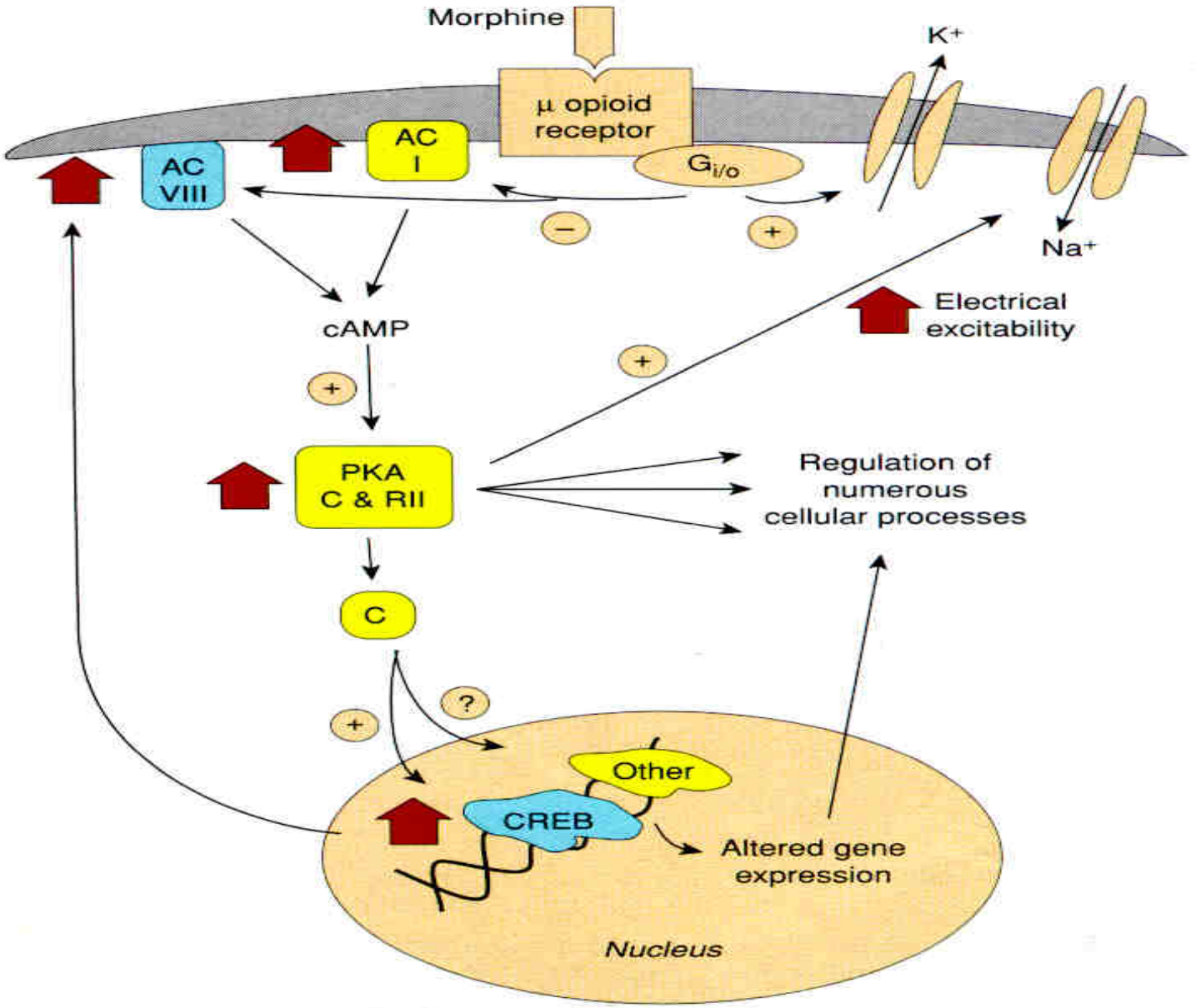
All Patients: Group CBT Relapse Prevention, Weekly Individual Counseling, Three times Weekly Urine Screens



Buprenorphine RCT
A tragic appendix: Mortality
Heilig, Lancet 2003

	Detox	Buprenorphine	Cox regression
Dead	4/20 (20%)	0/20 (0%)	χ^2=5.9; p=0.015

In Summary


Morphine
μ opioid receptor
K+
Na+
AC VIII
AC I
Gi/o
cAMP
Electrical excitability
PKA C & RII
Regulation of numerous cellular processes
C
?
Other
CREB
Altered gene expression
Nucleus

THANK YOU.