The Modern Science of Addiction

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Science Board – Food and Drug Administration
Silver Spring, Maryland
March 1, 2016

Funded primarily by NIH-NIDA (P50-05130), The Adelson Medical Research Foundation, NIH-NCRR (RUH – Dr B. Coller)

Prevalence of Drug Abuse in United States and Vulnerability to Develop Addictions

National Household Survey and Related Surveys – 2007 – 2013

Alcohol Use – ever	~ 260 million
Alcoholism	~ 16.5 million
Marijuana Use – ever	~ 104 million
Marijuana Daily Use	~ 5.7 million
Cocaine Use – ever	~ 45.6 million
Cocaine Addiction	~ 2 to 3 million
Heroin Use – ever	~ 5.7 million
Heroin Addiction	~ 1 million
Illicit Use of Opiate Medication – ever	~ 37.1 million

(i.e., 14.2% of the population 12 and over)*

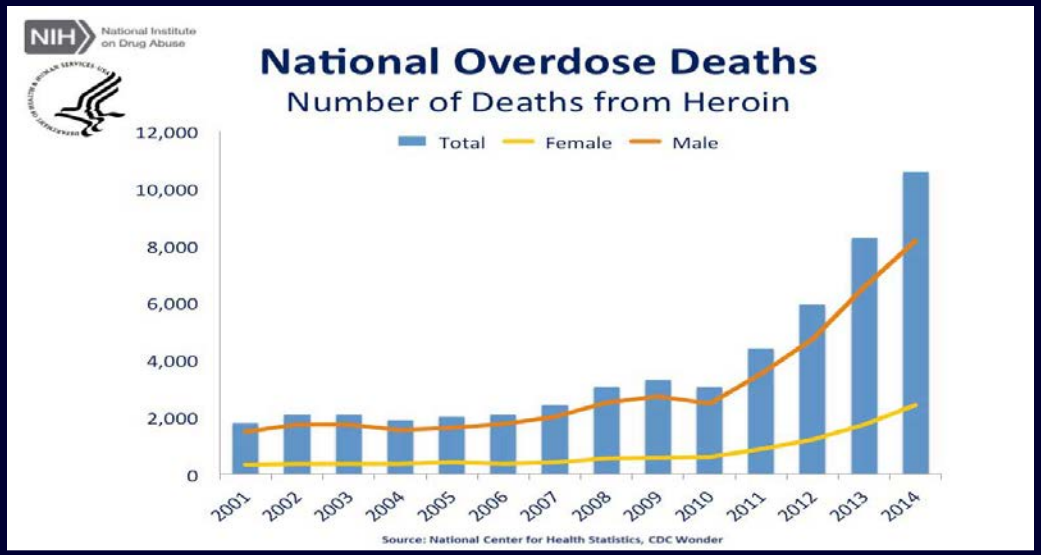
Development of Addiction After Self Exposure (meta-analyses)

Alcoholism, Cocaine, Marijuana Addictions	~ 1 in 8 to 1 in 15
Heroin Addiction	~ 1 in 3 to 1 in 5

* 2007 National Survey on Drug Use and Health

SAMHSA National Survey on Drug Use and Health, 2012; NIDA Monitoring the Future 2014; Others, 2007-2016

Number of Unintentional Drug Overdose Deaths Involving Prescription Opiates, Heroin, and Cocaine (United States, 1999-2007) and Rate of Heroin Overdose Deaths (2002-13)

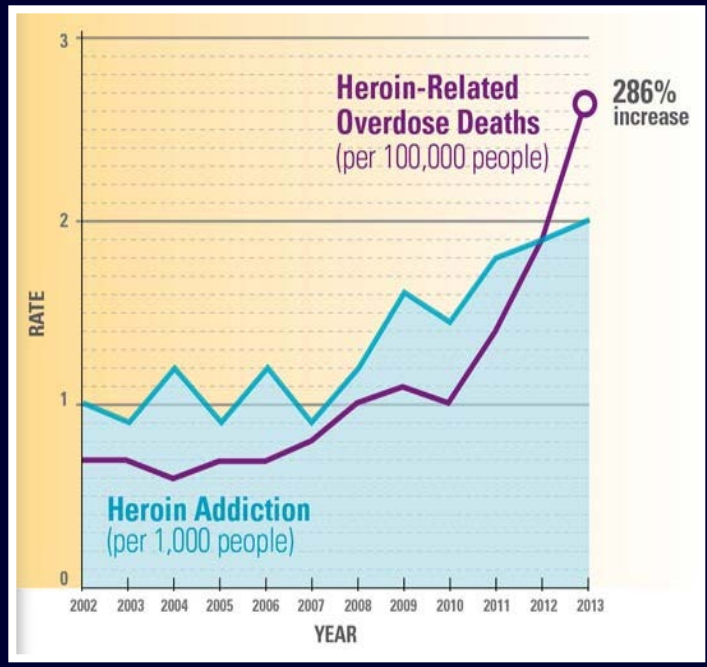


More than 3 people die every hour in the United States from illicit opiate overdose (2014). (T Frieden, Center for Disease Control and Prevention, 2015)

1.9 people die every day from heroin overdoses in New York City. (NYC Dept of Health – 2013)

47,000 persons (15 per 100,000) in the United States died of overdose deaths in 2014.

23.5 million persons aged 12 and older needed treatment for an illicit drug or alcohol abuse problem. Only 2.6 million received treatment at a specialized facility. (SAMHSA 2009)



National Vital Statistics System; MMWR 61:1, 2012; CDC Vitalsigns (online), July 7, 2015

Responding to the Heroin Epidemic

PREVENT
People From Starting Heroin

Reduce prescription opioid painkiller abuse.
Improve opioid painkiller prescribing practices and identify high-risk individuals early.

REDUCE
Heroin Addiction

Ensure access to Medication-Assisted Treatment (MAT).
Treat people addicted to heroin or prescription opioid painkillers with MAT which combines the use of medications (methadone, buprenorphine, or naltrexone) with counseling and behavioral therapies.

REVERSE
Heroin Overdose

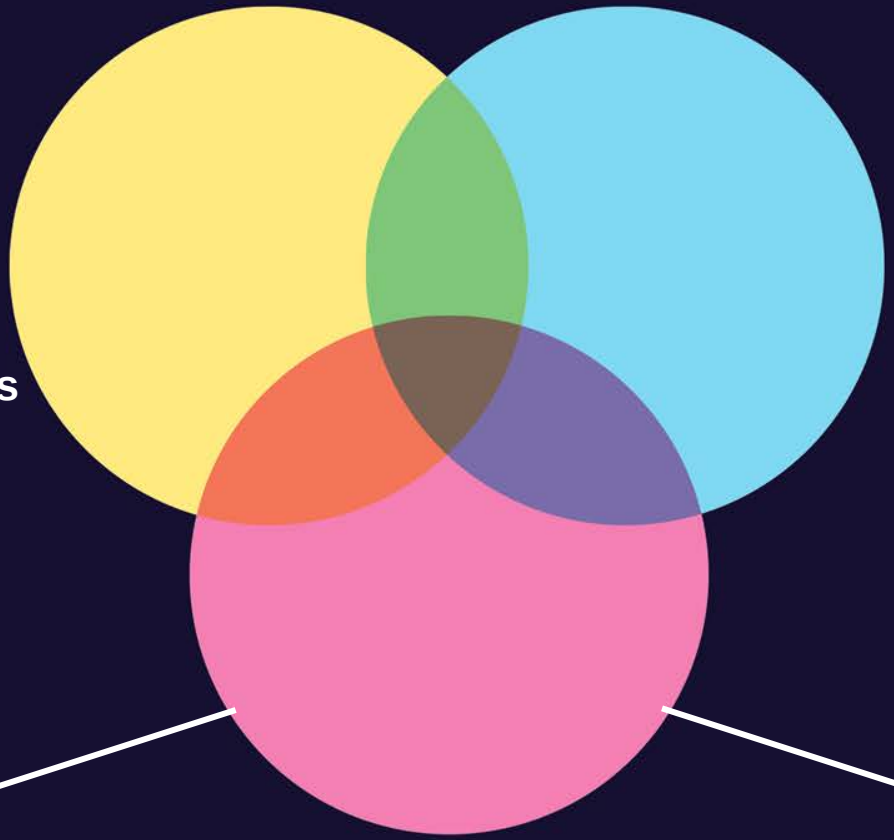
Expand the use of naloxone.
Use naloxone, a life-saving drug that can reverse the effects of an opioid overdose when administered in time.

SOURCE: CDC Vitalsigns, July 2015

CDC Vitalsigns (online), July 7, 2015

Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)



Genetic (40-80%)
- DNA
- SNPs
- other polymorphisms

Environmental (very high)
- prenatal
- postnatal
- epigenetics
- peer pressure
- cues
- comorbidity (psychiatric)
- stress-responsivity

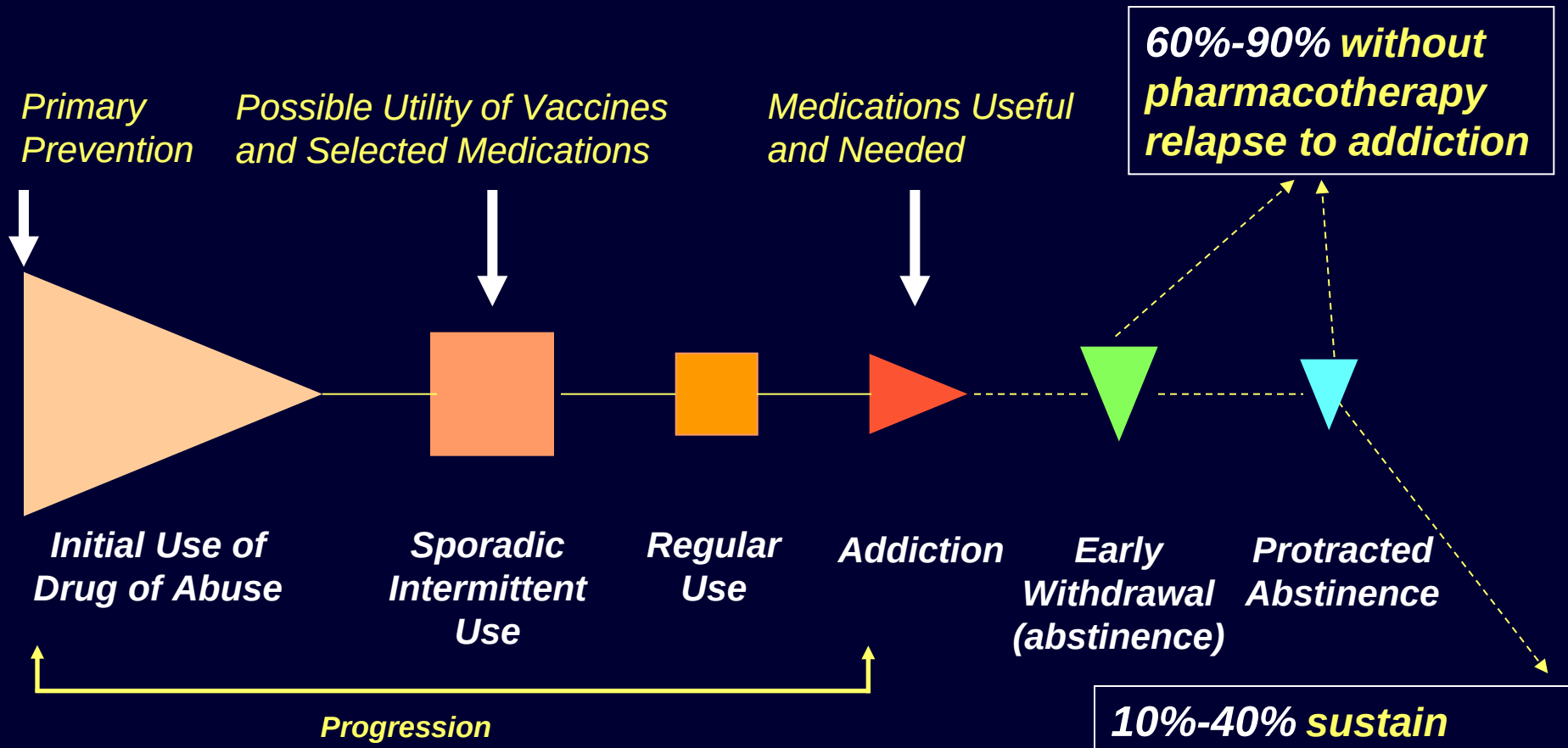
- mRNA levels
- peptides
- proteomics

Drug-Induced Effects (very high)

- neurochemistry
- synaptogenesis
- neuroneogenesis
- behaviors

Kreek et al., 2000; 2005; 2016

Natural History of Drug and Alcohol Abuse and Addictions



ADDICTION: ***Compulsive drug seeking behavior and drug self-administration, without regard to negative consequences to self or others (adapted from WHO).***

Adapted from Kreek et al., Nature Reviews Drug Discovery, 1:710, 2002; 2016

50th Anniversary of First Research Paper on Developing Methadone Maintenance Treatment

HYPOTHESIS: Heroin (opiate) addiction is a disease – a "metabolic disease" – of the brain with resultant behaviors of "drug hunger" and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.

Vincent P. Dole, Jr., MD; Marie Nyswander, MD; and Mary Jeanne Kreek, MD

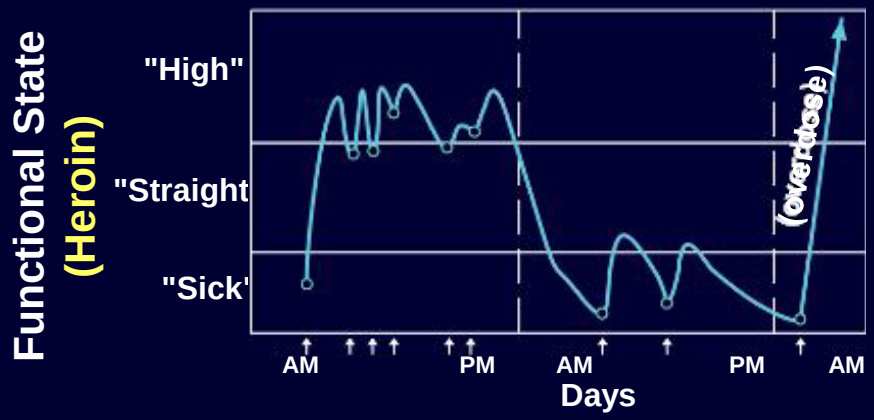
1964: Initial clinical research on development of treatment using methadone maintenance pharmacotherapy and on elucidating mechanisms of efficacy performed at The Rockefeller Hospital of The Rockefeller Institute for Medical Research:

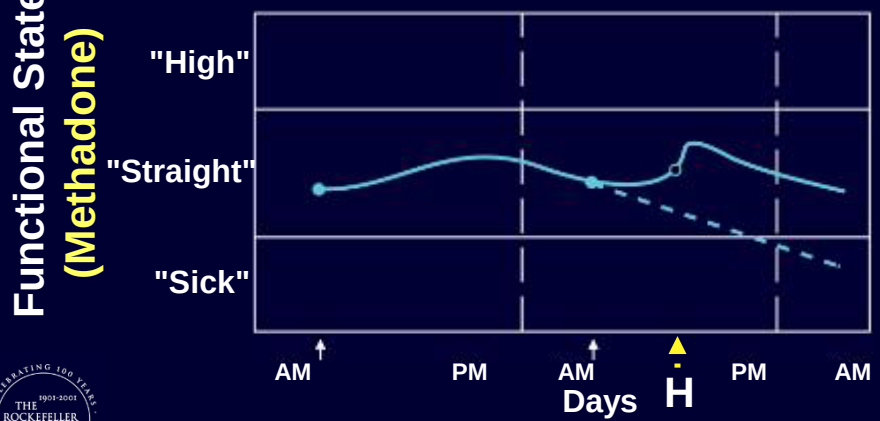
First research paper describing methadone maintenance treatment research

Dole, V.P., Nyswander, M.E. and Kreek, M.J.: Narcotic blockade: a medical technique for stopping heroin use by addicts. Transactions of the Association of American Physicians (May 1966), 79:122-136, 1966. *(including discussion)*

Dole, V.P., Nyswander, M.E. and Kreek, M.J.: Narcotic blockade. Arch. Intern. Med., 118:304-309, 1966.

Impact of Short-Acting Heroin versus Long-Acting Methadone Administered on a Chronic Basis in Humans – 1964 through 1978 Studies: Opioid Agonist Pharmacokinetics – Heroin Versus Methadone





Systemic Bioavailability After Oral Administration	Apparent Plasma Terminal Half-life ($t_{1/2}$ Beta)	Major Route of Biotrans-formation
Limited (<30%)	3min (30min for active 6 acetyl morphine metabolite; 4 6h for morphine and active morphine 6 glucuronide metabolite)	Successive deacetylation and morphine glucuronidation
Essentially Complete (>70%)	24h (48h for active [R](l) enantiomer)	N demethylation

Dole, Nyswander and Kreek, 1966; Kreek et al., 1973; 1976; 1977; 1979; 1982; Inturrisi et al, 1973; 1984

Goals and Rationale for Specific Pharmacotherapy for an Addiction

1. Prevent withdrawal symptoms
2. Reduce drug craving
3. Normalize any physiological functions disrupted by drug use
4. Target treatment agent to specific site of action, receptor, or physiological system affected or deranged by drug of abuse

Characteristics of an Effective Pharmacotherapeutic Agent for Treatment of an Addictive Disease

1. Orally effective
2. Slow onset of action
3. Long duration of action
4. Slow offset of action

Kreek, 1978; 1991; 1992; 2001

Methadone Maintenance Treatment for Opiate (Heroin) Addiction – 2016

Number of patients currently in treatment: **~ 1.3 million worldwide**

- **USA: ~ 330,000**
- **Europe: ~ 600,000**
- **Rest of world: ~400,000**

Efficacy in "good" methadone treatment programs using adequate doses (80 to 150mg/d):

Voluntary retention in treatment (1 year or more)	50 – 80%
Continuing use of illicit heroin	5 – 20%

Actions of methadone treatment:

- **Prevents withdrawal symptoms and "drug hunger"**
- **Blocks euphoric effects of short-acting narcotics**
- **Allows normalization of disrupted physiology**

Mechanism of action: **Long-acting medication (24h half-life for racemate in humans) provides steady levels of opioid at specific receptor sites.**

- **methadone found to be a full mu opioid receptor agonist which internalizes like endorphins (beta-endorphin and enkephalins)**
- **methadone also has modest NMDA receptor complex antagonism**

Kreek, 1972; 1973; 2016

Status of Methadone, Buprenorphine, and Extended Release Naltrexone Treatments in the United States – 2013 (SAMHSA, 2015)

Methadone Maintenance Treatment	
Facilities	1,282
Patients	330,308
Buprenorphine Maintenance Treatment	
Facilities	3,113
Patients	48,148
Extended Release Naltrexone Treatment	
Facilities	1,718
Patients	3,781

Source: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. National Survey of Substance Abuse Treatment Services (N SSATS), 2003 2014
Communication from: Cathie E. Alderks, PhD, Federal Project Officer, Behavioral Health Services Information System, Center for Behavioral Health Statistics and Quality, SAMHSA, 2015

Limited Targeted Pharmacotherapies Available for Specific Addictive Diseases

I. Opiate Addiction (Heroin and Illicit Use of Opiates)

a. **METHADONE** (50-80%)**
b. **BUPRENORPHINE (+ NALOXONE)** (40-50%)*
[c. **NALTREXONE / SUSTAINED RELEASE NALTREXONE** (<15%)*]

II. Alcoholism

a. **NALTREXONE** (30-40%)*
b. **NALMEFENE** (approved in Europe only, 2012)
c. **ACAMPROSATE** (low in USA)

III. Nicotine Addiction (Primarily Tobacco Smoking)

a. **NICOTINE – DIVERSE DELIVERY SYSTEMS** (?)
b. **BUPROPRION** (?)
c. **VARENICLINE** (?)

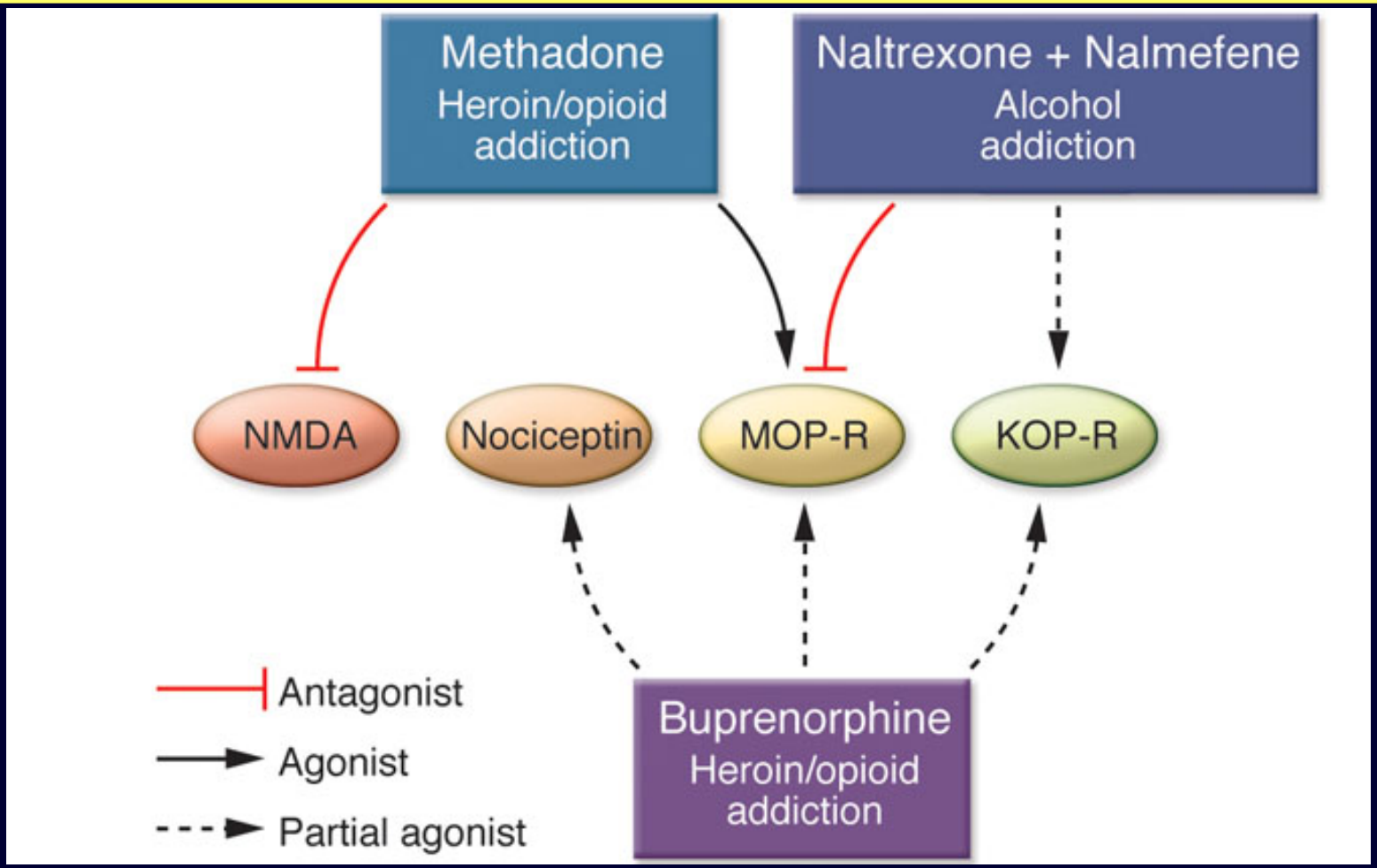
IV. Cocaine, Amphetamines and Other Stimulants

NONE

***(%)** is % of unselected persons with specific addictions who can be retained voluntarily in treatment for 3 months (*) or 12 months (**), with success in eliminating specific drug use.*

Kreek, 2016

Targets of Currently Approved Treatments for Addictive Disorders



Kreek et al, Journal of Clinical Investigation, 12: 3387, 2012

Development of an Addiction: Neurobiology

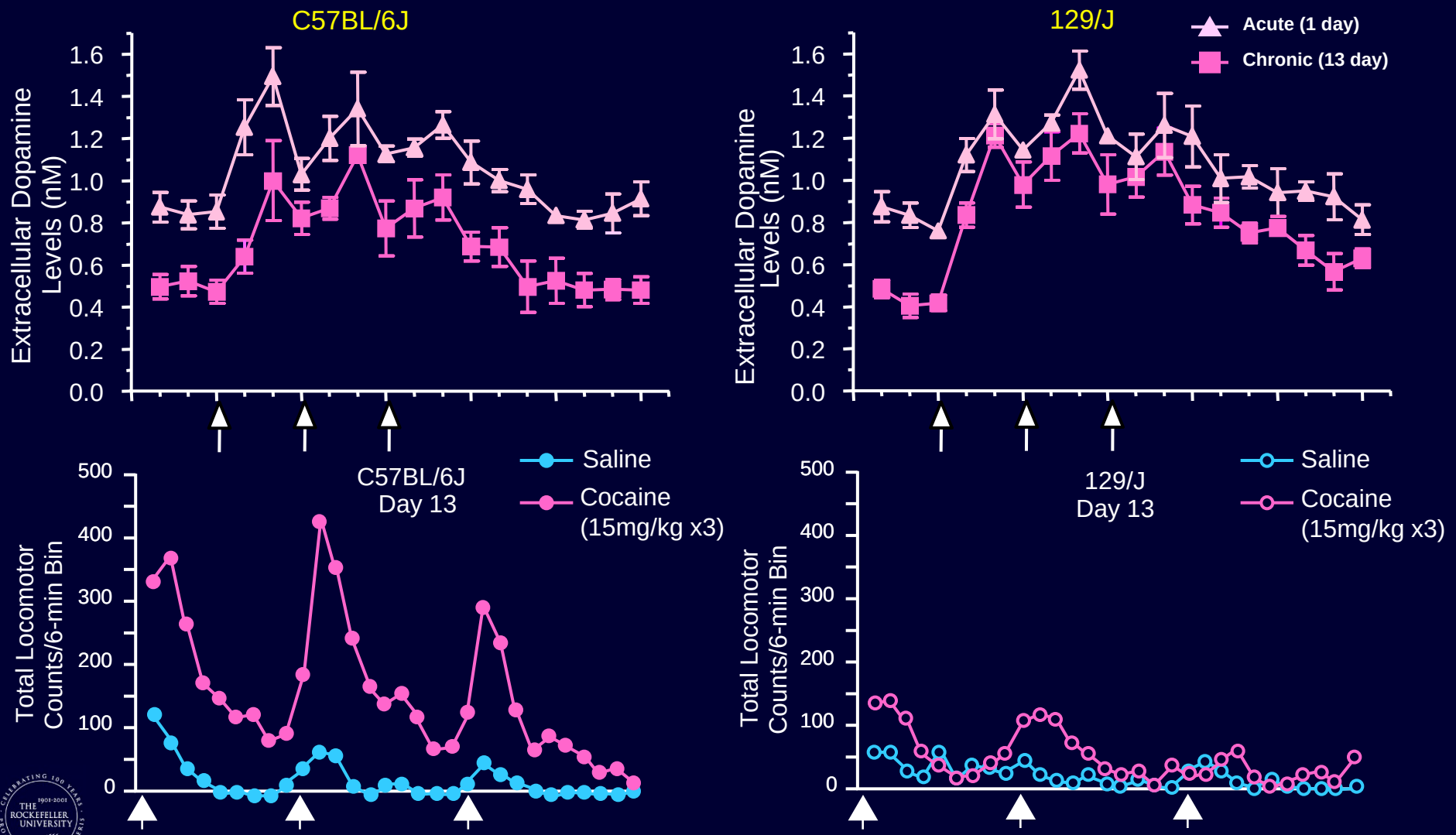
- Drugs alter normal brain networks and chemicals
- "Rewarding" or "pleasurable" effects of drugs (the so-called "reinforcing effects") involve:
  - Dopamine
  - Endorphins (acting at Mu Opioid Receptors)
- "Countermodulatory" response to reward involves:
  - Dynorphins (acting at Kappa Opioid Receptors)

Bidirectional-Translational Research: Novel and Conventional Animal Models to Mimic Human Patterns of Abuse

- **"Binge" Pattern Cocaine Parenteral Administration Model:**
  Constant or Ascending Dose
  (mimics most common pattern of human use in addiction)
- **Intermittent Heroin (Morphine) Parenteral Administration Model:**
  Constant or Ascending Dose
  (mimics most common pattern of human use in addiction)
- **"Binge" Pattern Oral Ethanol Administration Model:**
  (mimics common pattern of human excessive use)
- **Intravenous Pump Methadone Administration Model:**
  (converts short-acting pharmacokinetic properties of opioid agonist in rodent to long-acting human pharmacokinetic profile)
- **Intravenous Self-Administration (Mouse) Without or With High-Dose (also, extended access 4 h)**
- **Extended Access (10 or 18 hours) Intravenous Self-Administration (Rat) with Individual Selection of Dose Escalation**

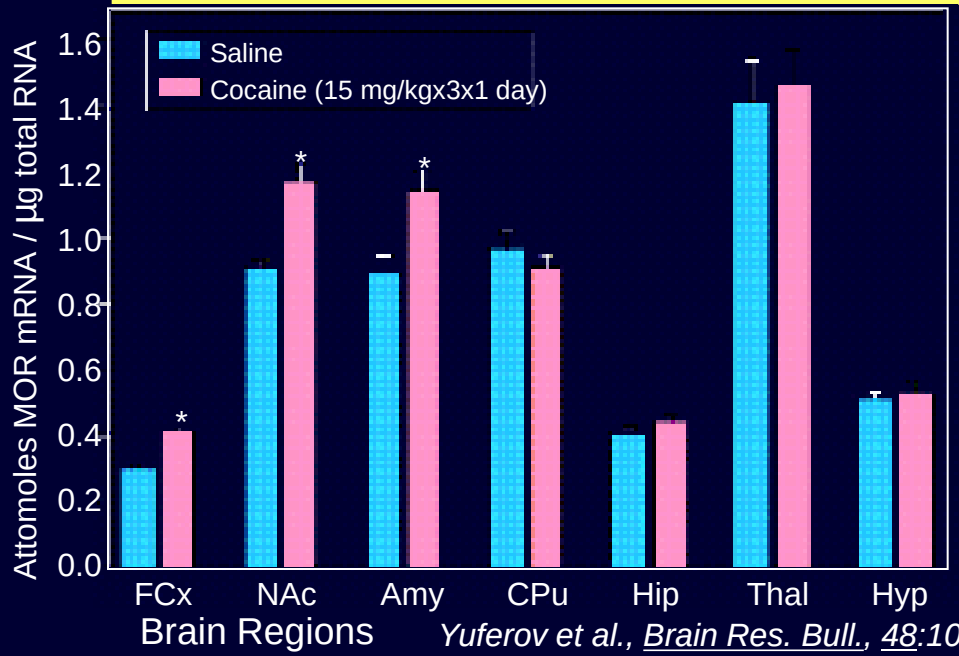
Kreek et al., 1987; 1992; 2001; 2005; 2015

REWARD – DOPAMINE: Attenuated Basal and Cocaine-Induced Increases in Extracellular Dopamine Levels in Nucleus Accumbens After Chronic "Binge" Pattern Cocaine (Microdialysis); Also Locomotor Activity Study in C57BL/6J and 129/J Mice

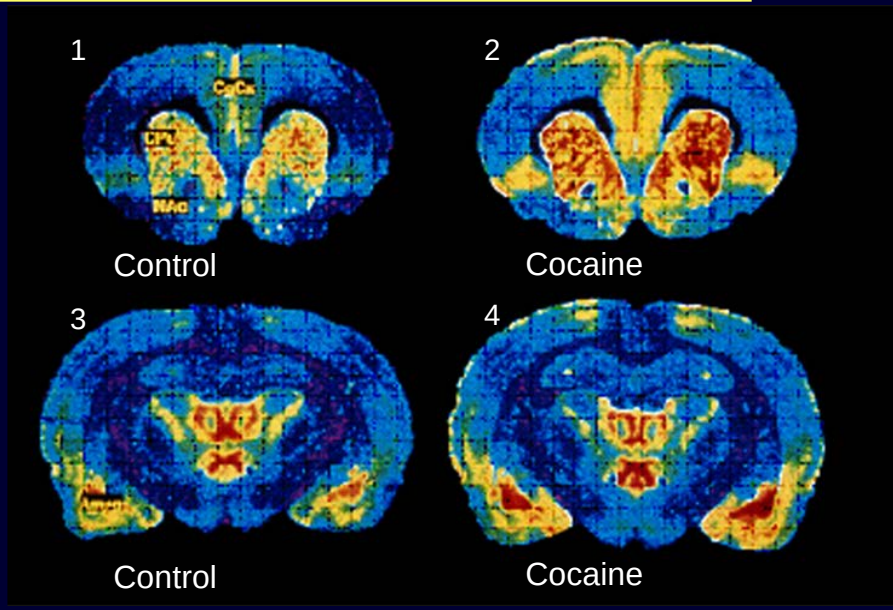


Zhang et al., Synapse, 50:191, 2003 2003; Schlussman et al., Pharmacol. Biochem. Behav., 75:123, 2003

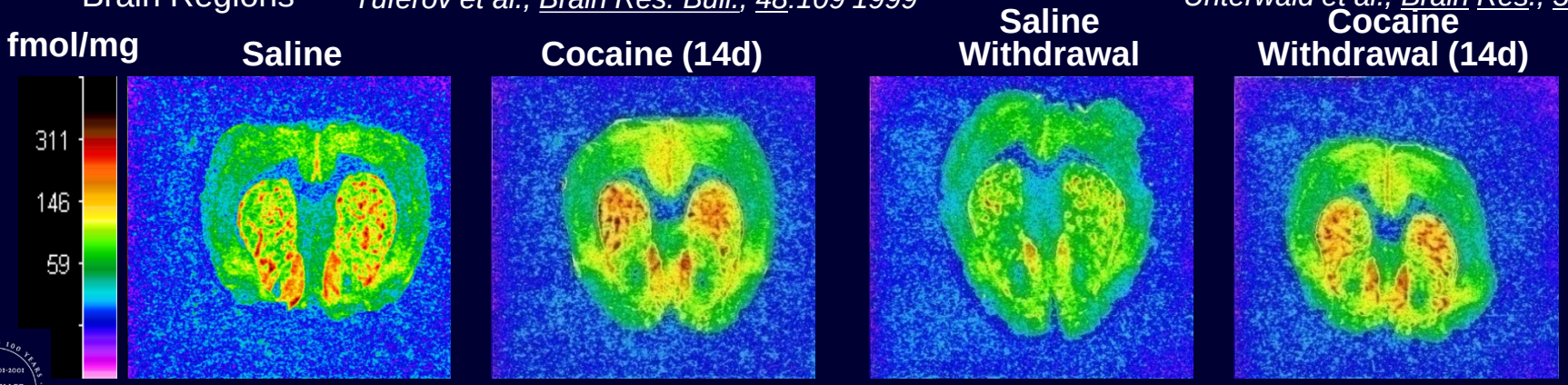
REWARD — MU OPIOID RECEPTOR-ENDORPHIN SYSTEM: Chronic Cocaine in Rat Increases Mu Opioid Receptor Gene Expression Density, But With No Increase in Mu Endorphins: A Persistent Effect After Withdrawal



Yuferov et al., Brain Res. Bull., 48:109 1999



Unterwald et al., Brain Res., 584:314 1



Bailey et al., Brain Res. Mol. Brain Res. 137:258 2005

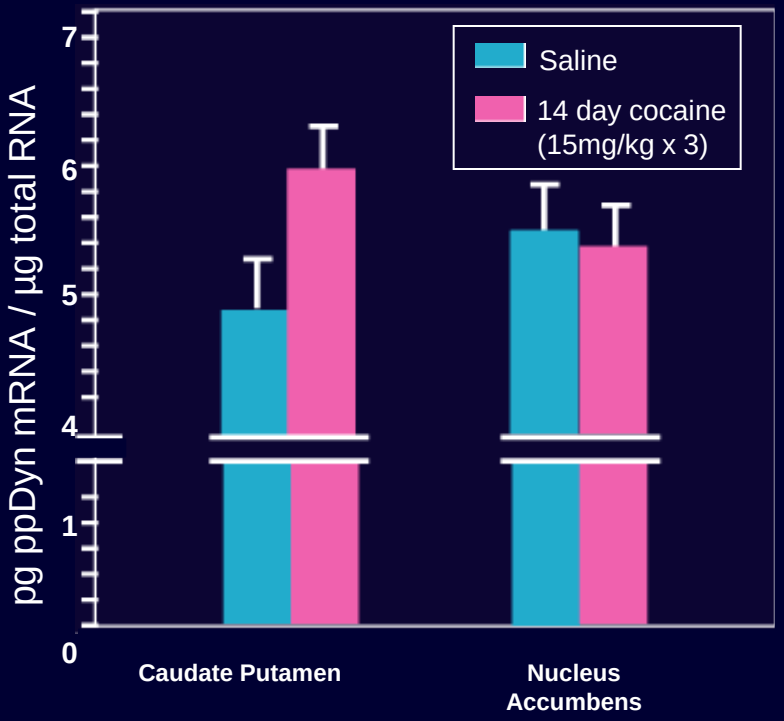
REWARD — MU OPIOID RECEPTOR-ENDORPHIN SYSTEM:
Mu Opioid Receptor Knock-Out Mice

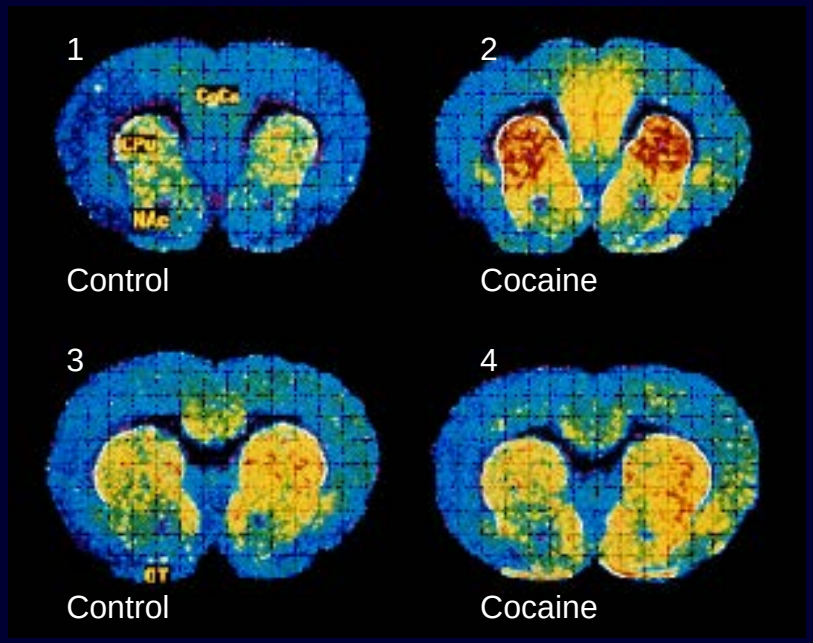
- No morphine or other mu agonist analgesia
- No heroin or morphine self-administration
- No heroin or morphine induced conditioned place preference
- Attenuated self-administration of cocaine
- Attenuated self-administration of alcohol

[Different knock-out constructs and multiple research groups, including Kieffer, Uhl, Yu, Pintar, Loh, with, e.g., Maldonado, Pasternak, Hoellt, Roberts]

Reviewed in Kreek et al., Nature Reviews Drug Discovery, 1:710-726, 2002; 2010

COUNTERMODULATION – KAPPA OPIOID RECEPTOR-DYNORPHIN SYSTEM: Cocaine Increases Kappa Opioid Receptor Density in Rat, But Kappa Opioid Receptor Directed "Dynorphins" Also Increase

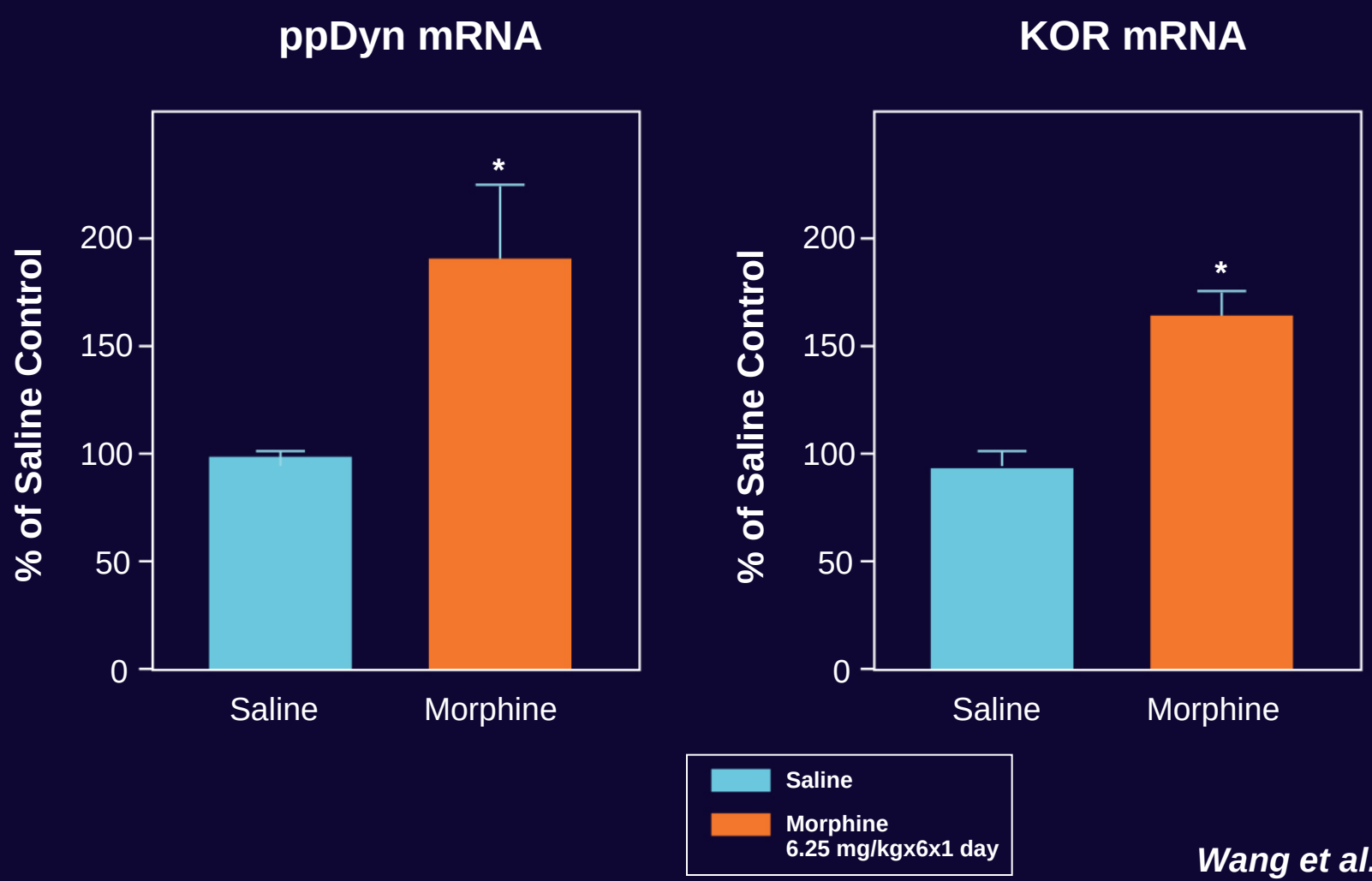




Dynorphin Acting at the Kappa Opioid Receptor Lowers Dopamine Levels and Prevents Surge After Cocaine

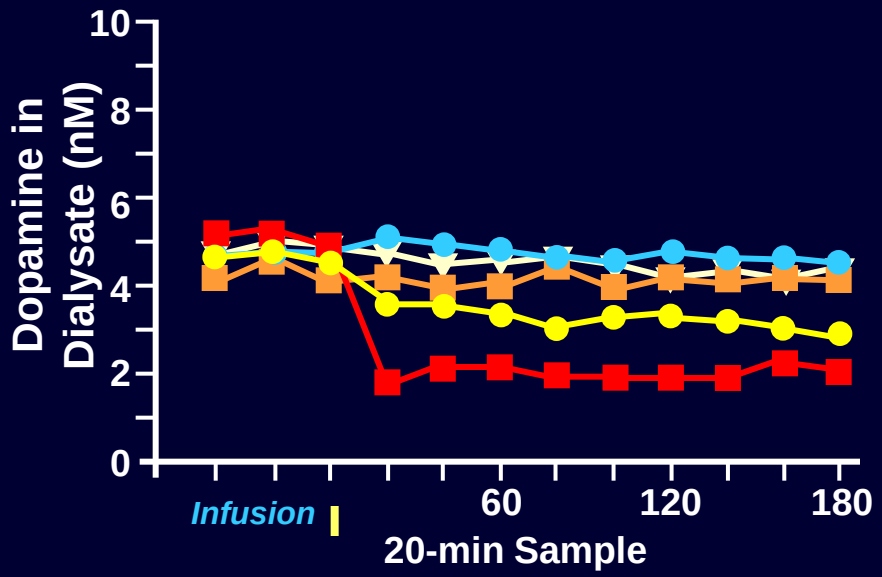
Spangler, Ho, Zhou, Maggos, Yuferov, and Kreek , Mol. Brain Res., 38:71, 1996;
Unterwald, Rubenfeld, and Kreek , NeuroReport, 5:1613, 1994

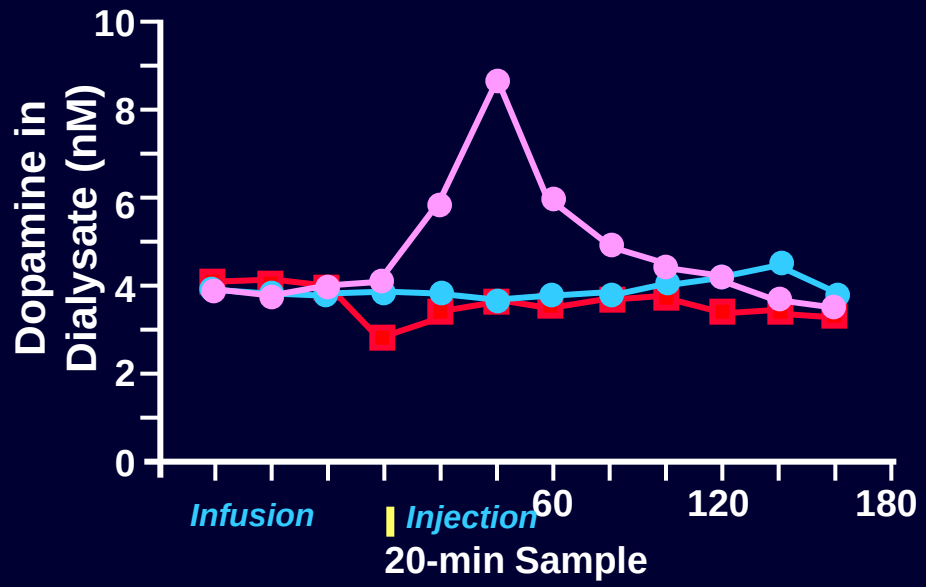
Acute Intermittent Morphine Increases Preprodynorphin and Kappa Opioid Receptor mRNA Levels in the Rat Brain



Wang et al., 1999

Natural Dynorphin $A_{1\text{-}17}$ Lowers Basal and Cocaine Induced Dopamine Levels in Mouse Striatum





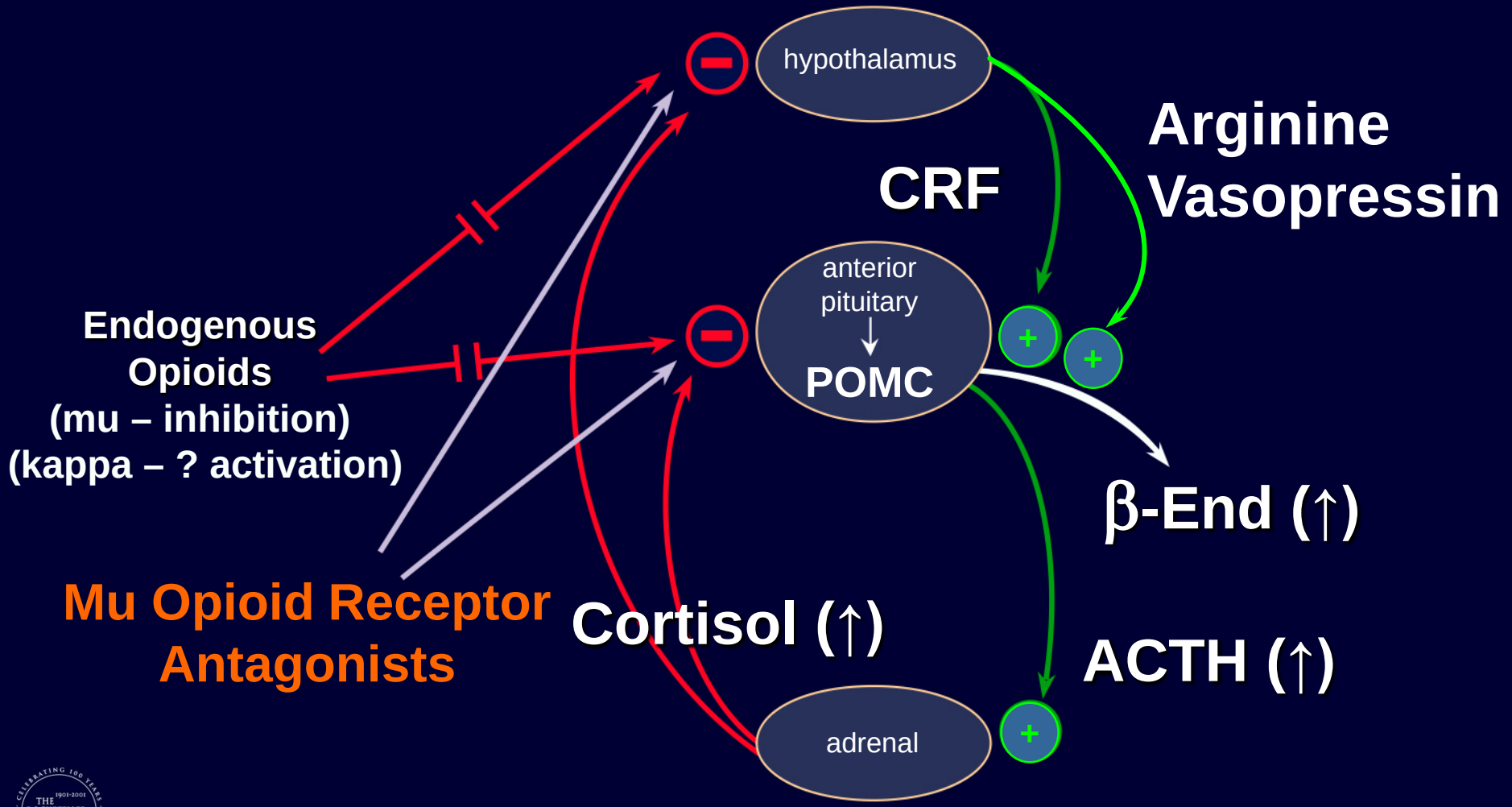
Zhang, Butelman, Schlussman, Ho, and Kreek, Psychopharmacology, 172:422, 2004

Potential Biological Target Identified for Novel Pharmacotherapies (KOPr-Dynorphin System)

- **Need: Compounds selective for this target KOPr (agonist, biased agonist, partial agonist, and antagonist).**
- **Major Clinical Concern with High Efficacy Kappa Agonist: Dysphoria; psychotomimesis**
- **Actual Concern of Research Clinician: None. Tolerance develops to psychotomimetic effects. One recent study showed little to no problems in persons with long term addictions.**
- **Potential Use in Treatments: Cocaine addiction; alcoholism; opiate addiction with concomitant cocaine or alcohol addiction**

Kreek 2016

STRESS RESPONSIVITY – Dissecting the Hypothalamic-Pituitary-Adrenal Axis in Humans: Selective Opioid Antagonist Testing



Kreek, 1984; 1998; 2006; 2014

Heroin, Cocaine, and Alcohol Profoundly Alter Stress Responsive Hypothalamic-Pituitary-Adrenal (HPA) Axis: Normalization during methadone treatment

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g., heroin addiction)

} Suppression of HPA Axis (decrease levels of HPA hormones)

- Opiate withdrawal effects *
- Opioid antagonist effects
- Cocaine effects *
- Alcohol effects

} Activation of HPA Axis (increase levels of HPA Hormones)

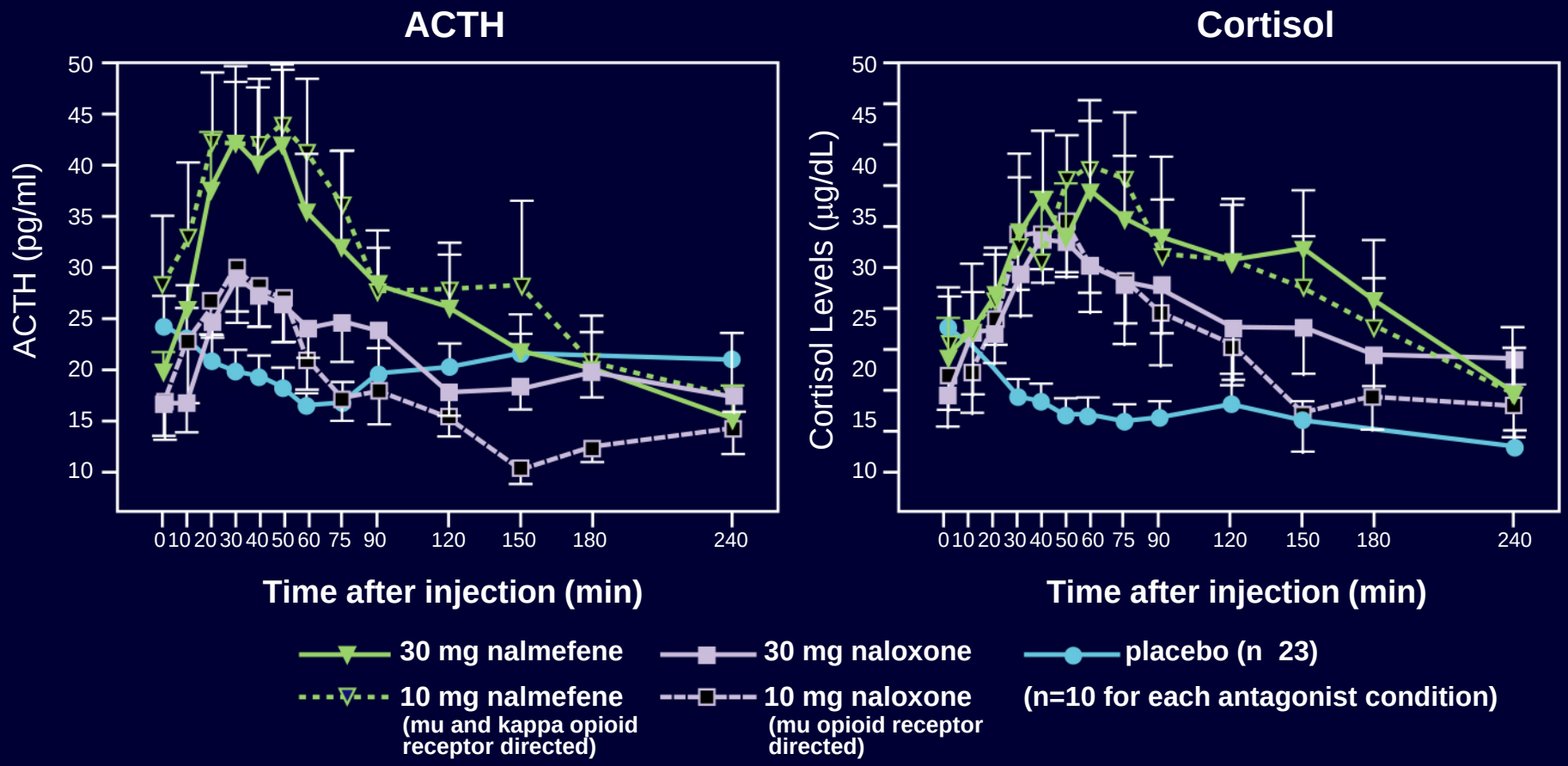
- Chronic effects of long-acting opiate (e.g. methadone in maintenance treatment)

Normalization of HPA Axis

* Our challenge studies have shown that a relative and functional "endorphin deficiency" develops.

Kreek, 1972; 1973; 1987; 1992 … 2008

Nalmefene (mu/kappa Directed) Causes Greater HPA Axis Activation Than Naloxone (mu Directed) in Normal Human Volunteers (n=23)



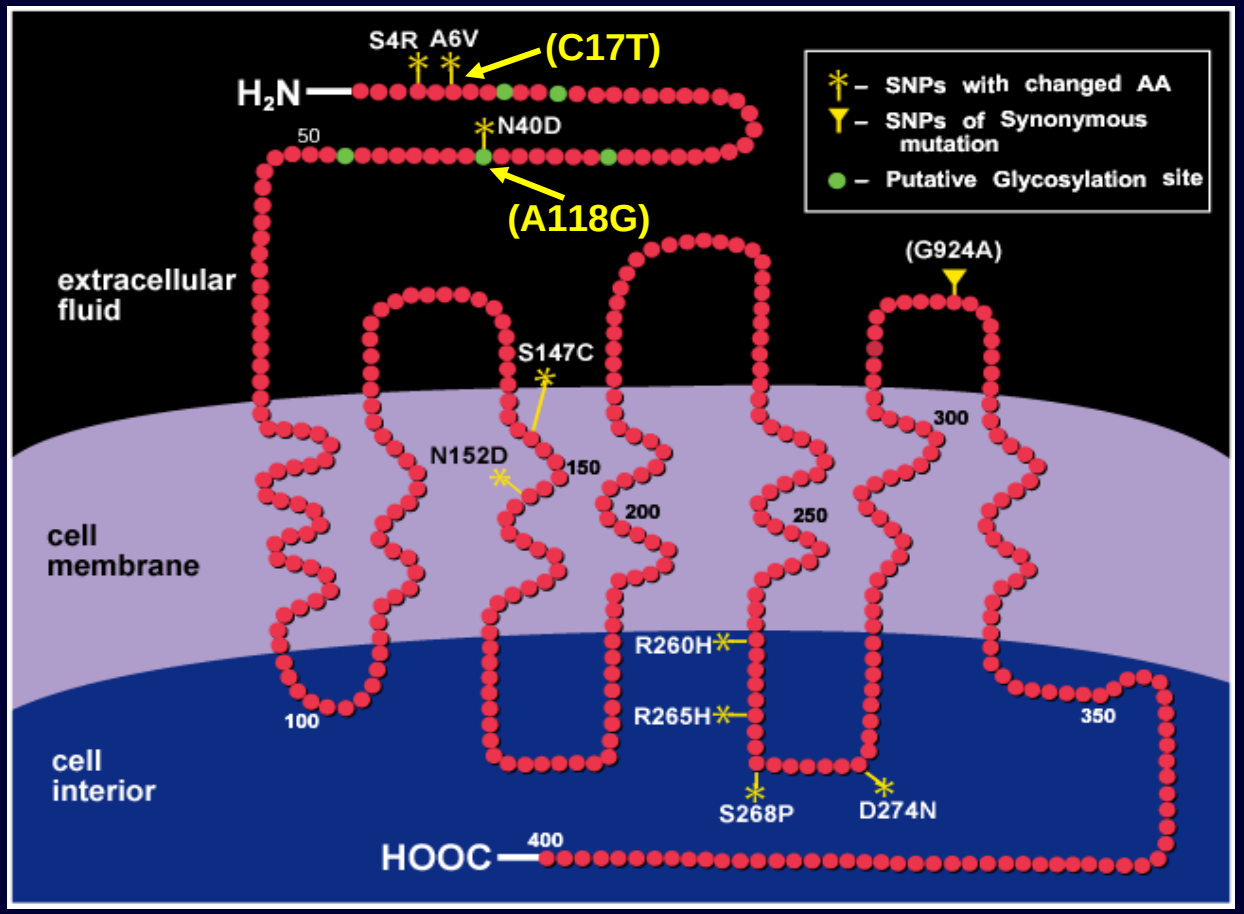
Schluger, Ho, Borg, Porter, Maniar, Gunduz, Perret, King, and Kreek, Alcohol. Clin. Exp. Res., 22,1430, 1998

Genetic Variants of the Human Mu Opioid Receptor: Single Nucleotide Polymorphisms in the Coding Region Including the Functional A118G (N40D) Variant

HYPOTHESIS

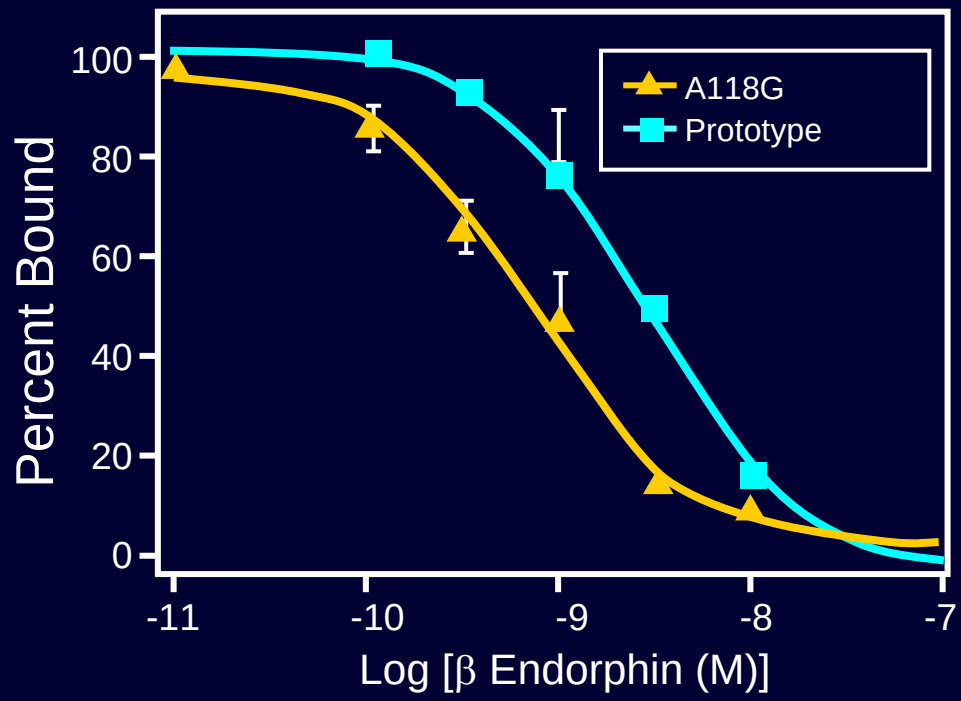
Gene variants:

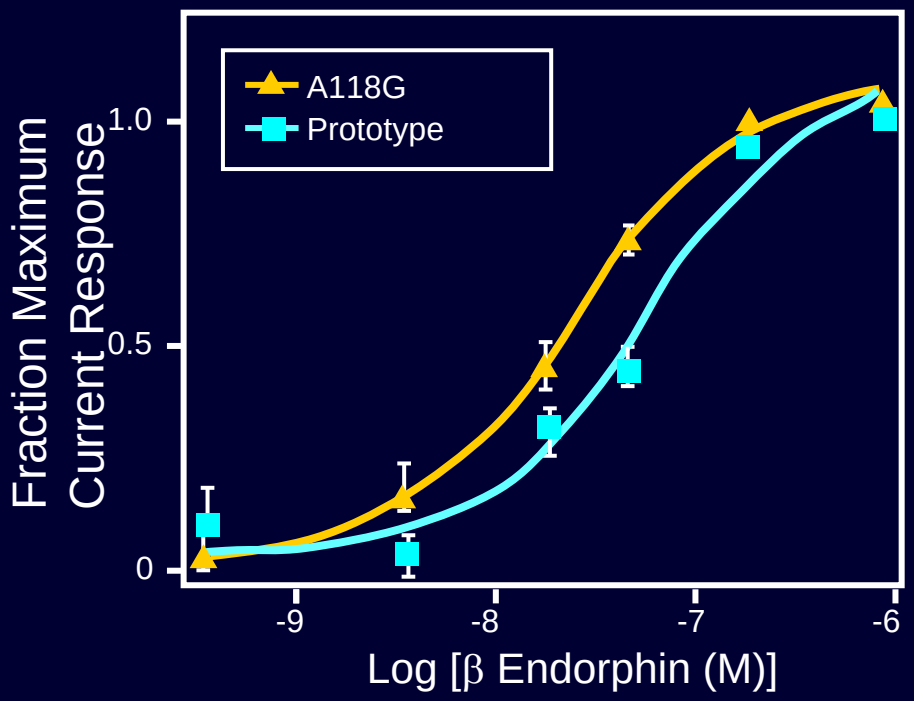
- **Alter physiology "PHYSIOGENETICS"**
- **Alter response to medications "PHARMACOGENETICS"**
- **Are associated with specific addictions**



Bond, LaForge… Kreek, Yu, PNAS, 95:9608, 1998; Kreek, Yuferov and LaForge, 2000

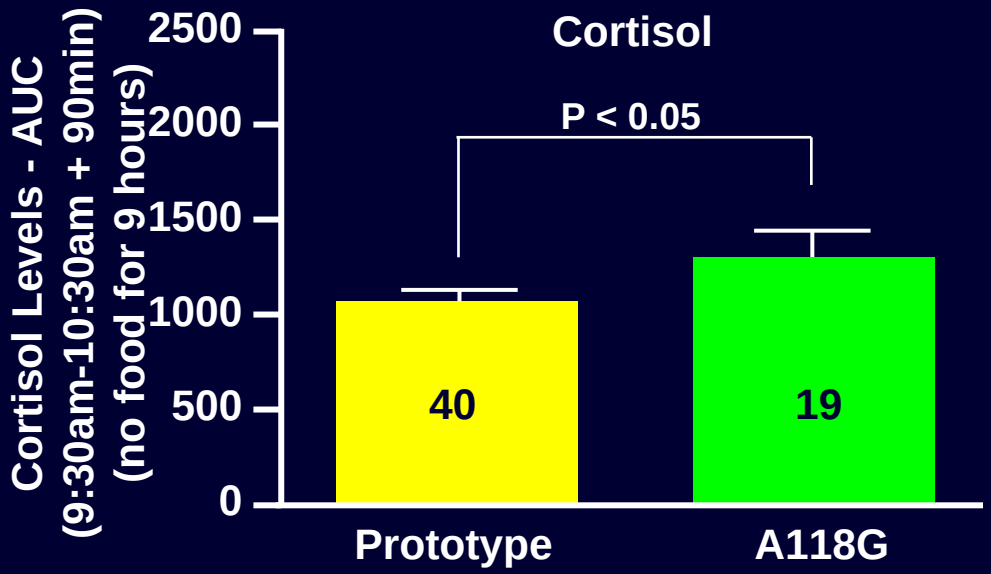
FUNCTIONAL MOP-r (A118G) VARIANT – Binding and Coupling to G Protein-Activated, Inwardly Rectifying K^+(GIRK) Channels by Beta-Endorphin at the Prototype A118A and A118G Variant of the Mu Opioid Receptor

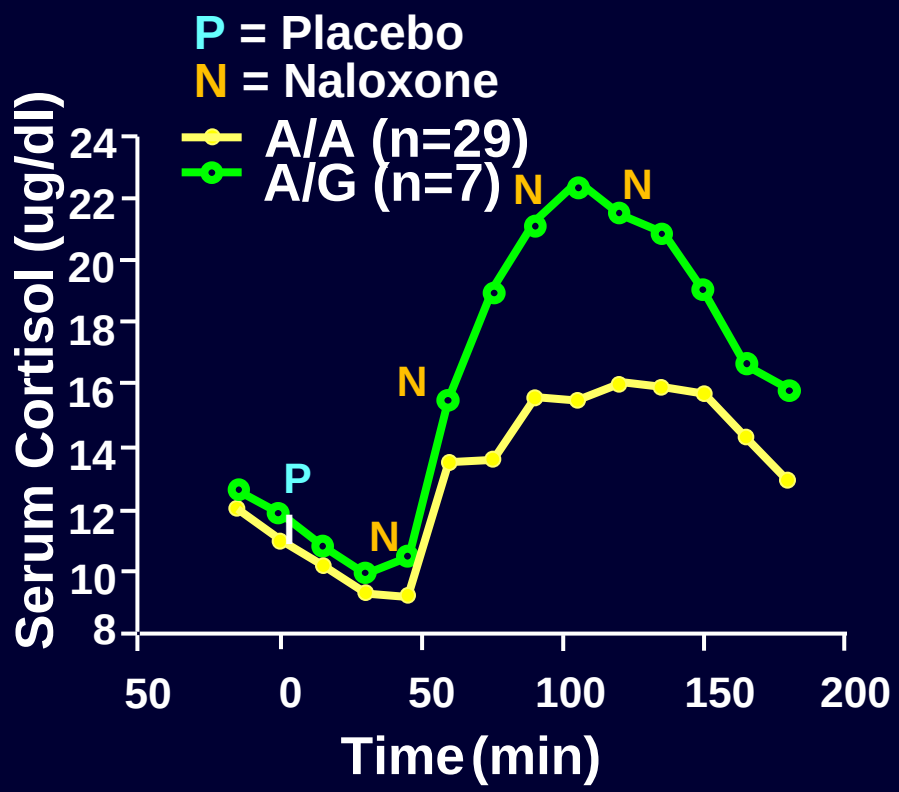




Bond, LaForge… Kreek, Yu, PNAS, 95:9608, *1998; Kreek, Yuferov and LaForge, 2000*

FUNCTIONAL MOP-r (A118G) VARIANT – "Physiogenetics" Related to A118G Variant of Human Mu Opioid Receptor Gene – Altered Stress Responsivity in Healthy Control Volunteers

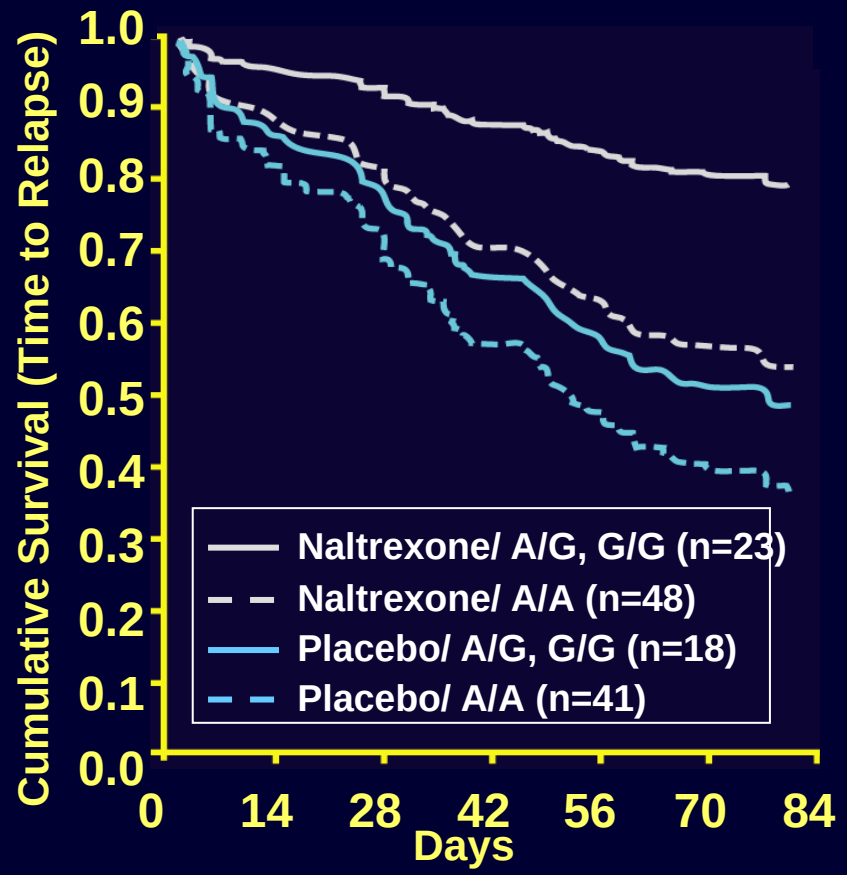


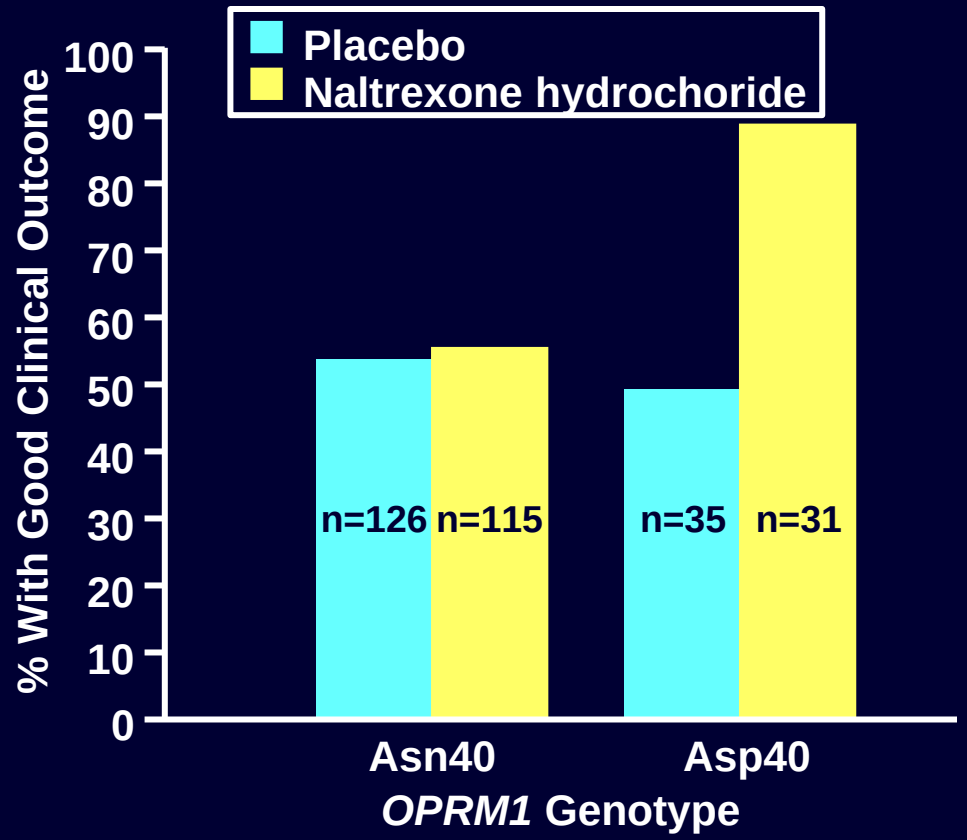


Bart et al. Neuropsychopharmacology, 31:2313-2317, 2006

Wand et al., Neuropsychopharmacol, 26:106, 2002
Chong…Wand, Neuropsychopharmacology, 31:204, 2006

FUNCTIONAL MOP-r (A118G) VARIANT –"Pharmacogenetics" Related to A118G Variant of Human Mu Opioid Receptor Gene, Which Alters Stress Responsivity: Positive Predictor of Response to Naltrexone Treatment of Alcoholics





Oslin et al., Neuropsychopharmacology, 28: 1546, 2003;
Anton… Goldman et al., Arch Gen Pscyh, 65:135, 2008

Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction and also Alcoholism in Central Sweden

	Opiate Dependent (n=139)	Control (n=170)
G/G; A/G	41	23
A/A	98	147
118G Allele Frequency	0.155	0.074

Thus, in the entire study group in this central Swedish population:
Attributable Risk due to genotypes with a G allele: 18%
(with confidence interval ranges from 8.0 to 28.0%)

Bart G , Heilig M, LaForge KS… Ott J, Kreek MJ, et al., Molecular Psychiatry, 9:547-549, 2004

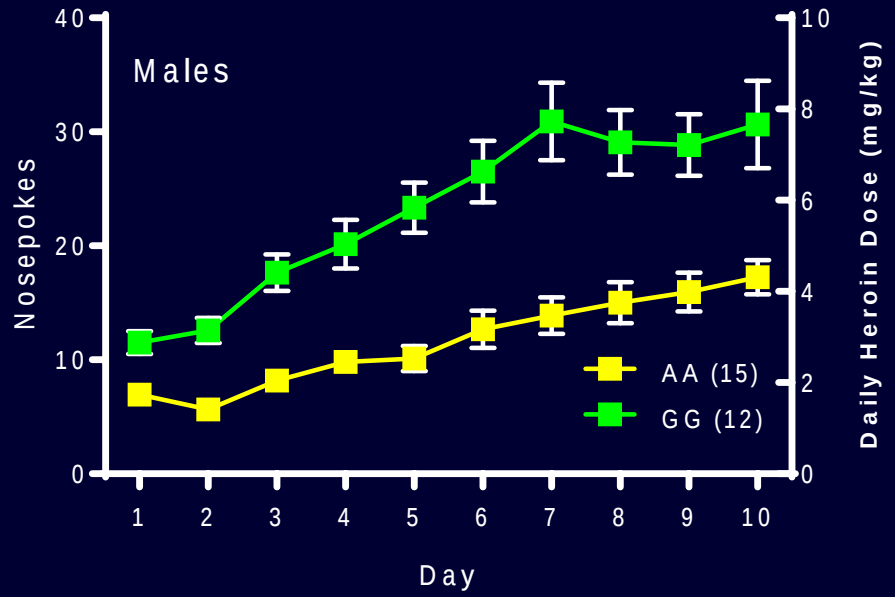
	Alcohol Dependent (n=389)	Control (n=170)
G/G; A/G	90	23
A/A	299	147
118G Allele Frequency *	0.125	0.074

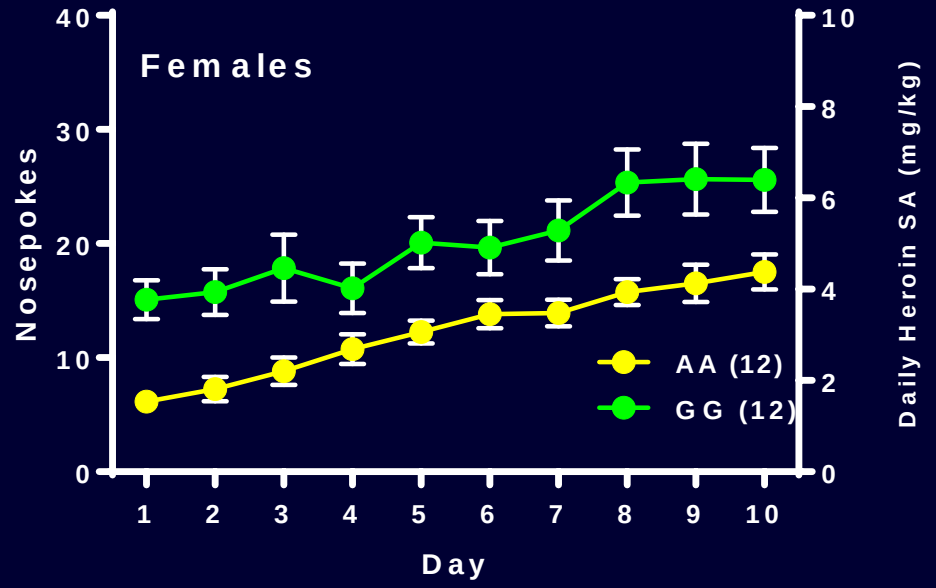
** Overall 118G Allele Frequency = 0.109*

Thus, in the entire study group in this central Swedish population:
Attributable Risk due to genotypes with a G allele: 11.1%
(with confidence interval ranges from 3.6 to 18.0%)

Bart G , Kreek MJ, LaForge KS… Ott J, Heilig M, Neuropsychopharmacology, 30:417, 2005

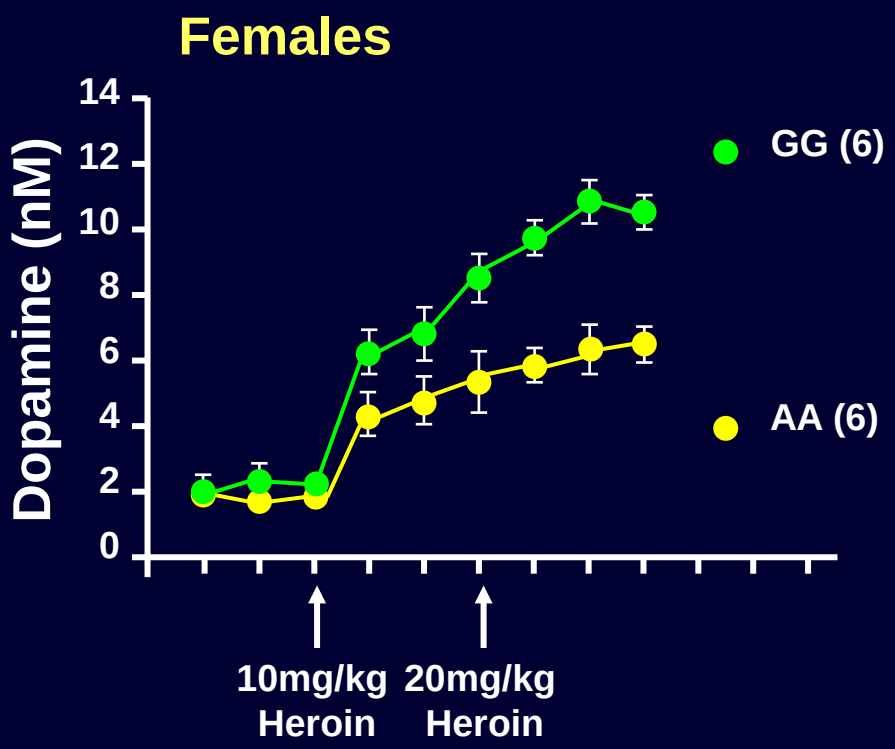
Heroin Self-Administration (10 d; 4h/d) in Male and Female Wild-Type (A/A) and Genetically Modified A112G (G/G) Mice: A Model of the Human A118G Mu Opioid Receptor Functional Variant

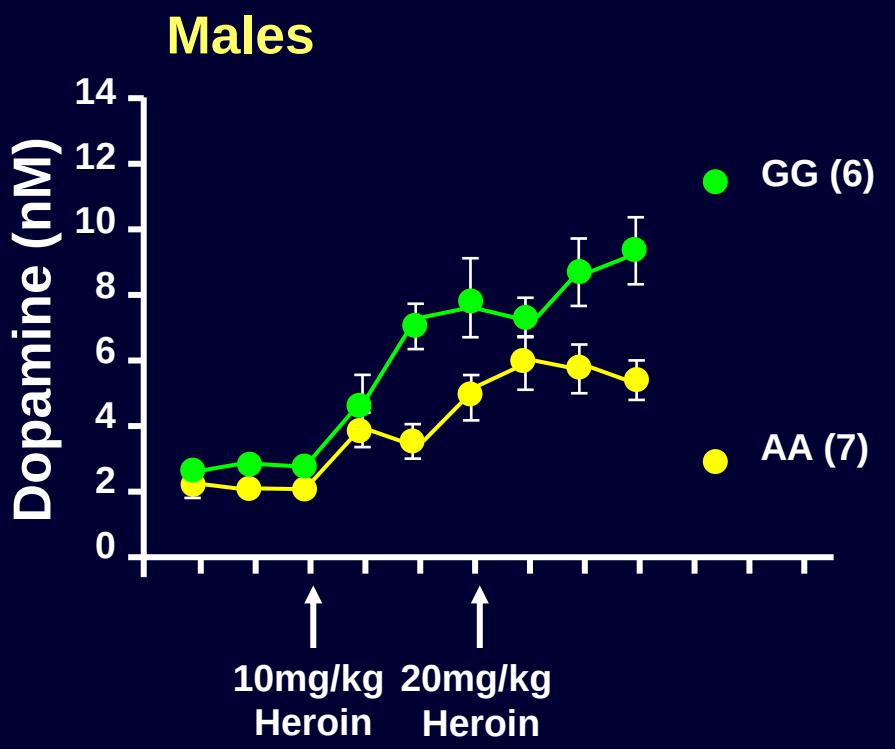




Zhang et al., Neuropsychopharmacology, 40:1091, 2015

Microdialysis in Striatum of Prototype A112A versus Genetically Modified G112G Mice: Absolute Dopamine Levels of Three Baseline Samples and Levels of Dopamine after Heroin Injections



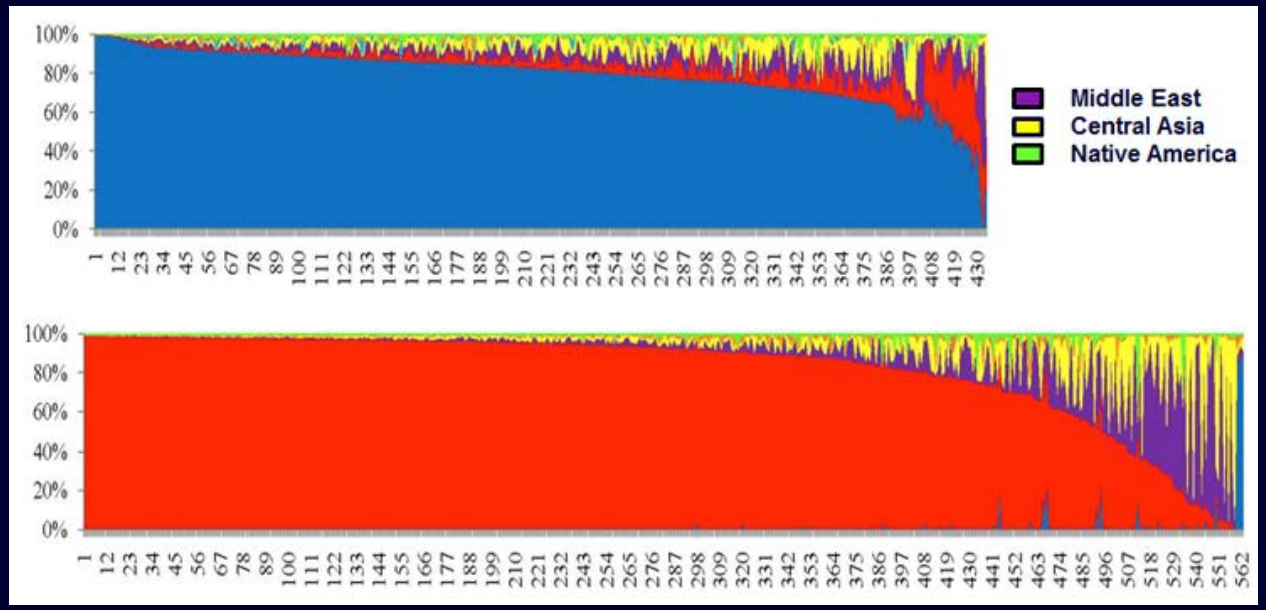


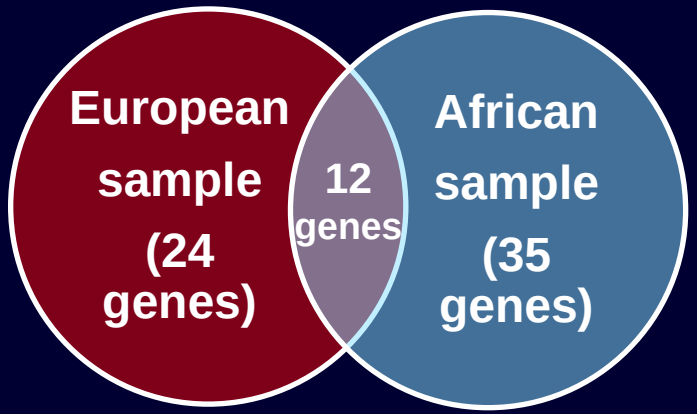
Zhang et al., Neuropsychopharmacology, in press, 2015

AIMS Markers and Gene Variants Associated with Long-Term Severe Opioid Addiction

African Descent

European Descent





Shared SNPs:
DRD2: **rs1076563**
rs2587546

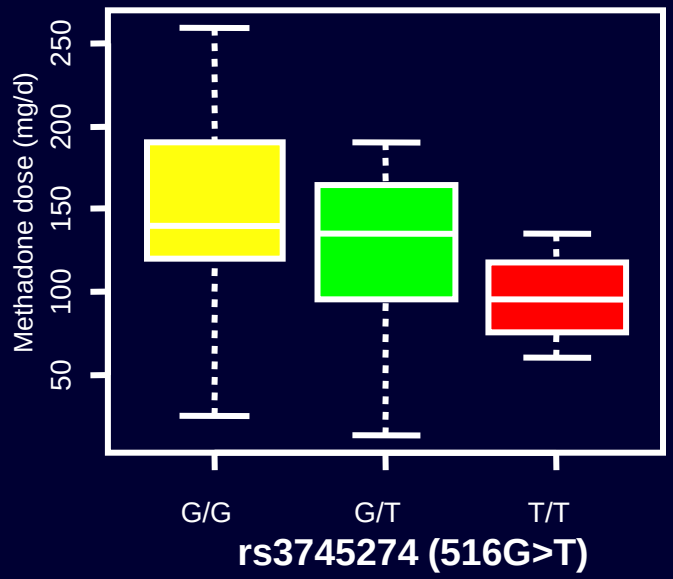
Kreek 2016, after Levran 2015

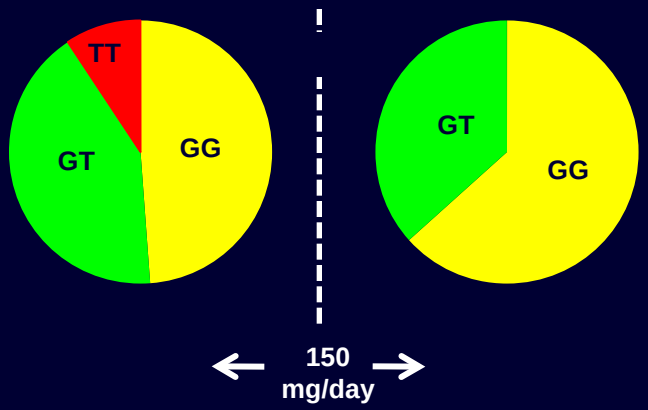
Variants of Opioid and Stress Related Genes Associated with Opiate Addiction in Caucasians Which Have Been Replicated (7 of over 15)

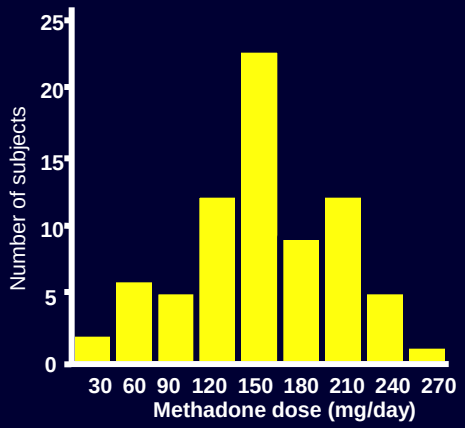
Genes	Variant	Refs
OPRM1 *(mu opioid receptor)*	A118G (rs1799971)	e.g, Bond… Kreek and Yu, 1998; Stadlin et al., 2001; Haerian and Haerian, 2013
OPRD1 *(delta opioid receptor)*	rs2236861, rs3766951, rs2236857	Levran et al., 2008; Beer et al., 2013; Nelson et al., 2014
OPRK1 *(kappa opioid receptor)*	NSV*	Yuferov et al., 2004; Levran et al., 2009; Kumar et al., 2012
PDYN *(dynorphin peptide)*	NSV*	Wei et al., 2011; Clarke et al., 2012
AVPR1A *(arginine vasopressin receptor 1A)*	rs11174811; rs1587097; rs10784339	Maher et al., 2011; Levran et al., 2014
FKBP5 *(FK506-binding protein 51/ corticosterone chaperone)*	rs1360780; rs3800373	Levran et al., 2014a; Levran et al., 2014b
GAL *(galanin)*	rs694066	Maher et al., 2011, Levran et al., 2014
*NSV – No Single Variant; replication is on association of entire genes		

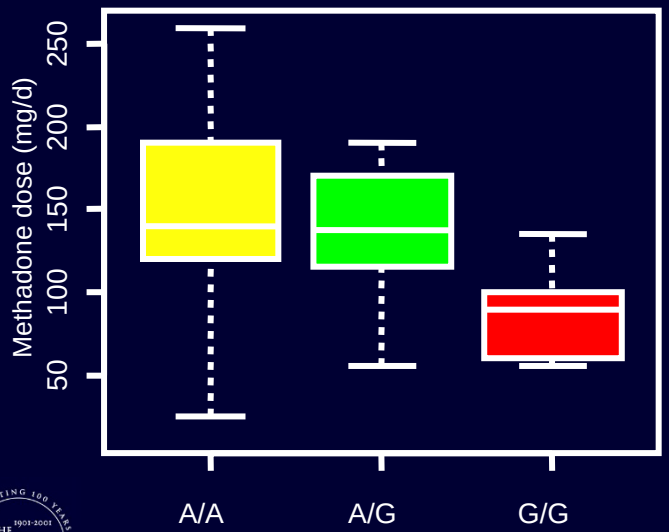
Kreek 2016; adapted from Reed et al., Current Psychiatry Reports,16(11): 504, 2014

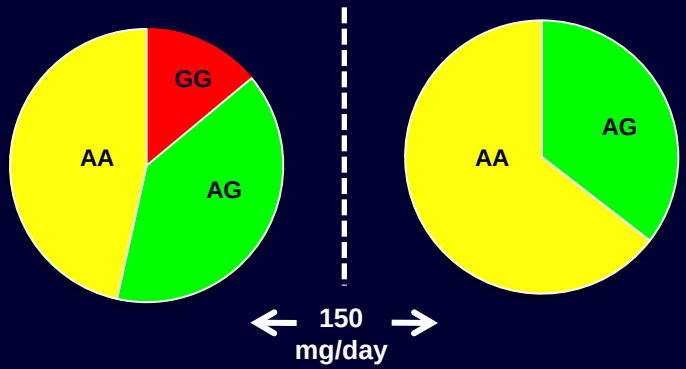
PHARMACOGENOMICS – *CYP2B6* SNPs are Associated with Effective Methadone Dose (n=74) (516G>T and 785A>G) (Replication)











Levran … Kreek, Addiction Biology, 18: 709, 2012
Dobrinas…Eap, Pharmacogenet Genomics, 23:84, 2013
Gadel et at., Drug Metab Dispos, 41: 709, 2013

September 10, 2003 – FDA Presentation "Major Issues Related to Physician Prescribing of Long-Acting Mu Opioid Receptor Agonists"

A. Lack of adequate or updated medical education concerning pharmacokinetics and pharmacodynamics of long-acting (intrinsic or by formulation) mu opioid receptor agonists and partial agonists.

B. Lack of adequate (or any) medical school education concerning any of the specific addictions and also medical approaches to assessing persons with ongoing misuse, abuse, or addiction to drugs.

C. Stigma, ingrained in physicians and other healthcare workers by their formal health-related education, against the addictive diseases, the persons suffering from addictive diseases, the providers of healthcare services to those with addictive diseases, and the medications used to treat addictive diseases (e.g., methadone and buprenorphine-naloxone).

Kreek, adapted from *Long Acting Opioids: Challenges in Pharmacotherapy* presented at the FDA September 10, 2003