Addiction Treatments of the Future: The Role of Genetics

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Prevalence of Specific Drug Abuse and Vulnerability to Develop Addictions

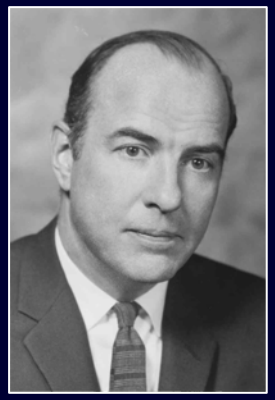
National Household Survey and Related Surveys: 2000 to 2007	
Alcohol Use – ever	~ 203 million
Alcoholism	~ 18.8 million
Cocaine Use – ever	~ 35 million
Cocaine Addiction	~ 2 to 3 million
Heroin Use – ever	~ 3.7 million
Heroin Addiction	~ 1 million
Illicit Use of Opiate Pain Medication – ever	~ 33.4 million
Addiction to Illicit Use of Opiate Pain Medications	~ ?? 1.6 million
Development of Addiction After Self Exposure	
Alcoholism	~ 1 in 8 to 1 in 15
Cocaine Addiction	~ 1 in 8 to 1 in 15
Heroin Addiction	~ 1 in 3 to 1 in 5

SAMHSA National Survey on Drug Use and Health, 2005 and 2006; NIDA, Others, 1998-2006

Development of Methadone Maintenance Treatment – 1964 Onward

Hypothesis (1964)

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.



1964: Initial clinical research on development of treatment using methadone maintenance pharmacotherapy and on elucidating mechanisms of efficacy.

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

Methadone Maintenance Treatment for Opiate (Heroin) Addiction

Number of patients currently in treatment: **~ 1 million worldwide**

- **USA: ~ 250,000**
- **Europe: ~ 500,000**
- **Rest of world: ~200,000**

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 narcotic provides steady levels of opioid at specific receptor sites.**

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

Kreek, 1972; 1973; 2008

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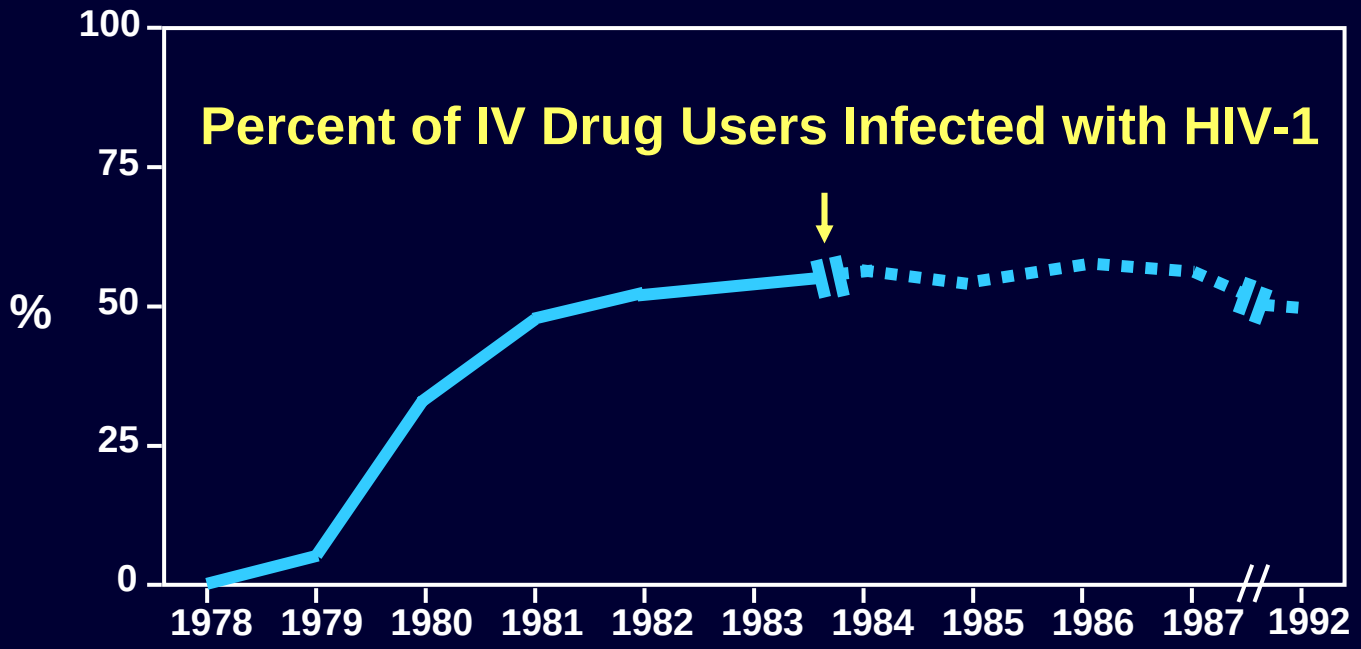
Prevalence of HIV-1 Infection in Intravenous Drug Users
New York City: 1983 - 1984
Protective Effect of Methadone Maintenance Treatment

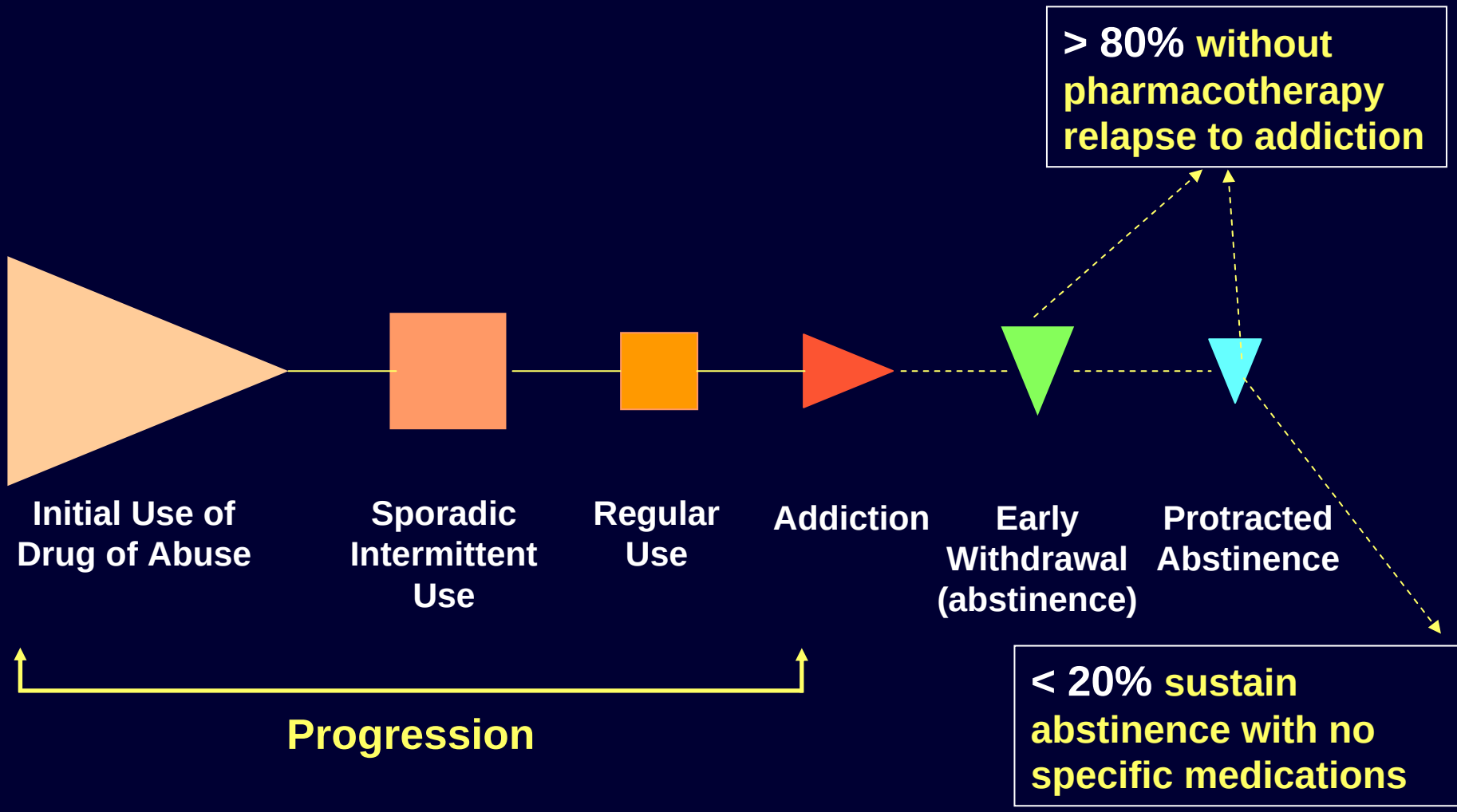


50% – 60% Untreated, street heroin addicts: positive for HIV-1 antibody

9% Methadone maintained since <1978 (beginning of AIDS epidemic): less than 10% positive for HIV-1 antibody

Kreek with Des Jarlais and others, 1984

Natural History of Drug Abuse and Addictions



Kreek et al., Nature Reviews Drug Discovery, 1:710, 2002

Few Targeted Pharmacotherapies Available for Specific Addictive Diseases

I. Opiate Addiction (Heroin and Illicit Use of Opiate Medications)
   a. METHADONE (50-80%)**
   b. BUPRENORPHINE (+ NALOXONE) (40-50%)*
   [c. NALTREXONE (<15%)]

II. Nicotine Addiction (Primarily Tobacco Smoking)
   a. NICOTINE – DIVERSE DELIVERY SYSTEMS (?)
   b. BUPROPRION (?)
   c. VARENICLINE (?)

III. Alcoholism
   a. NALTREXONE (30-40%)*
   b. ACAMPROSATE (?)

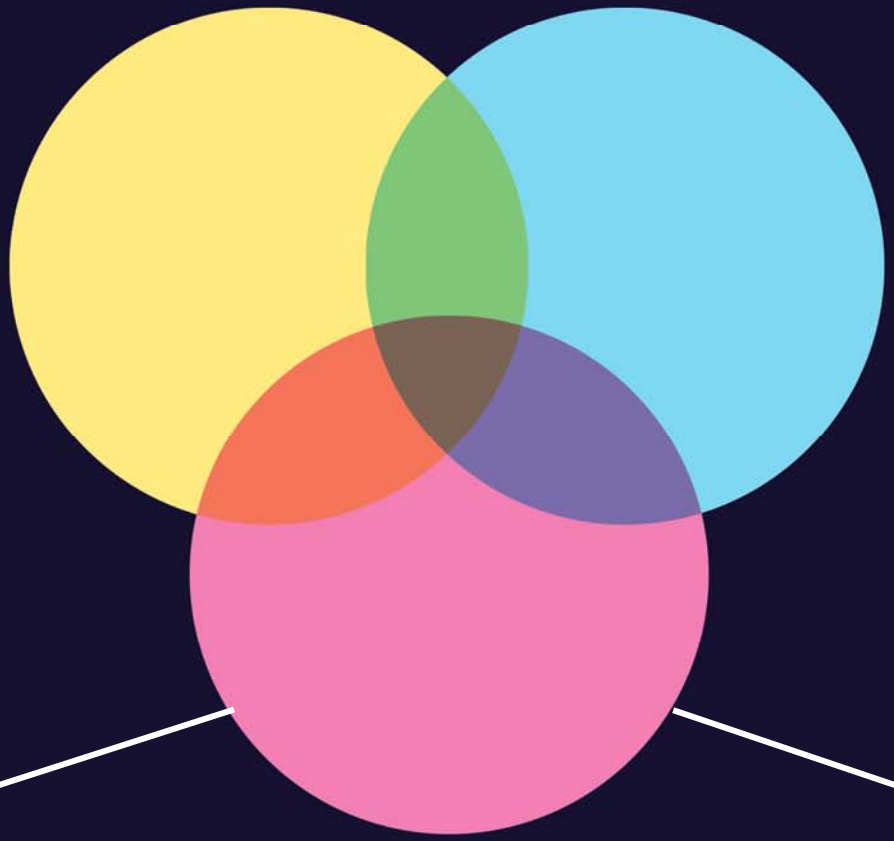
IV. Cocaine, Amphetamines and Other Stimulants
   NONE

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

Kreek, 2008

Factors Contributing to Vulnerability To Develop a Specific Addiction

Use of the drug of abuse essential (100%)



Genetic (25-60%)
- DNA
- SNPs
- other polymorphisms

Environmental (very high)
- prenatal
- postnatal
- contemporary
- cues
- comorbidity
- stress-responsivity

- mRNA levels
- peptides
- proteomics

Drug-Induced Effects (very high)

- neurochemistry
- synaptogenesis
- behaviors

Kreek et al., 2000; Kreek et al., Nature Reviews Drug Discovery, 2005

Development of an Addiction

- 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)

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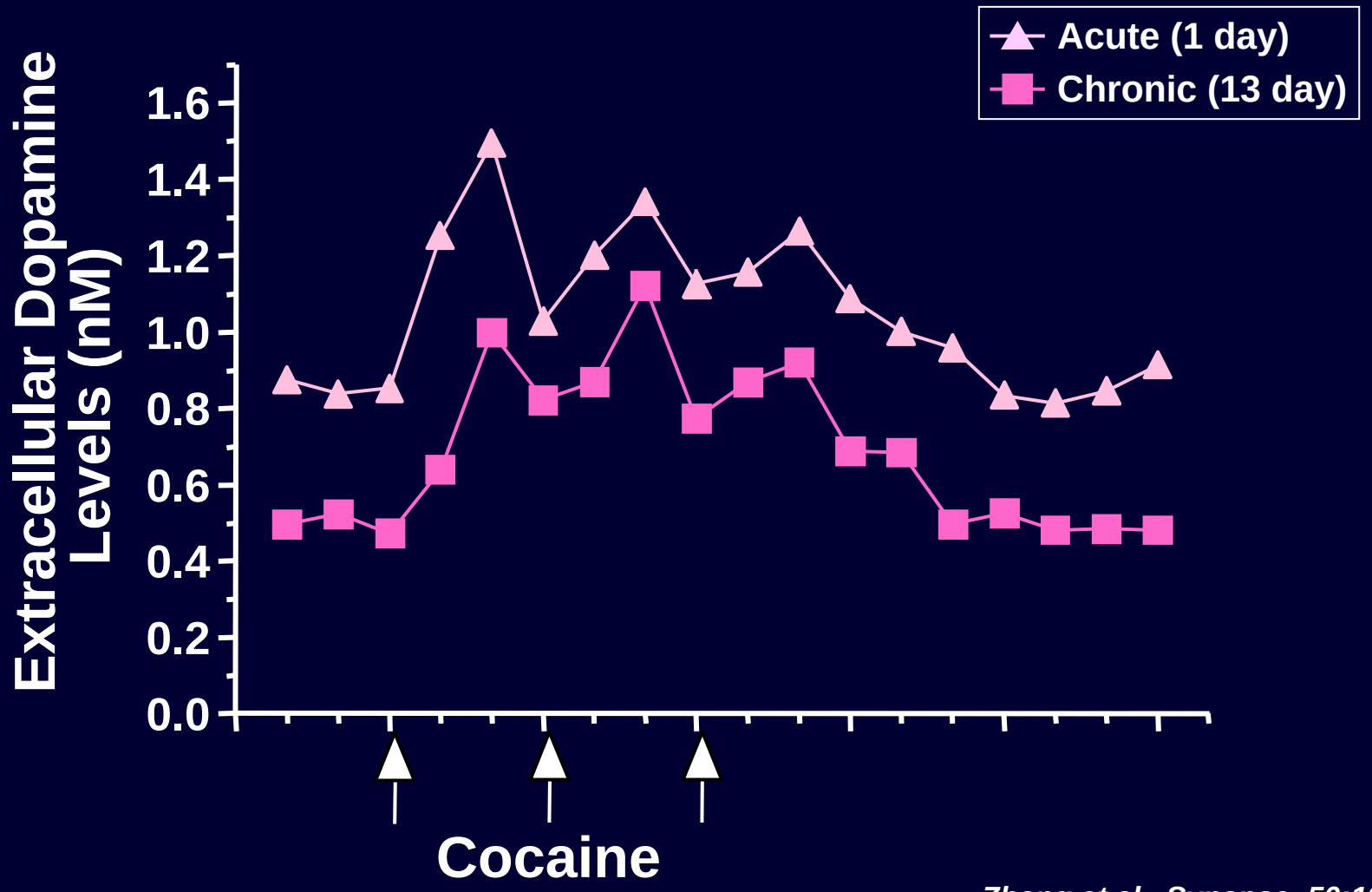
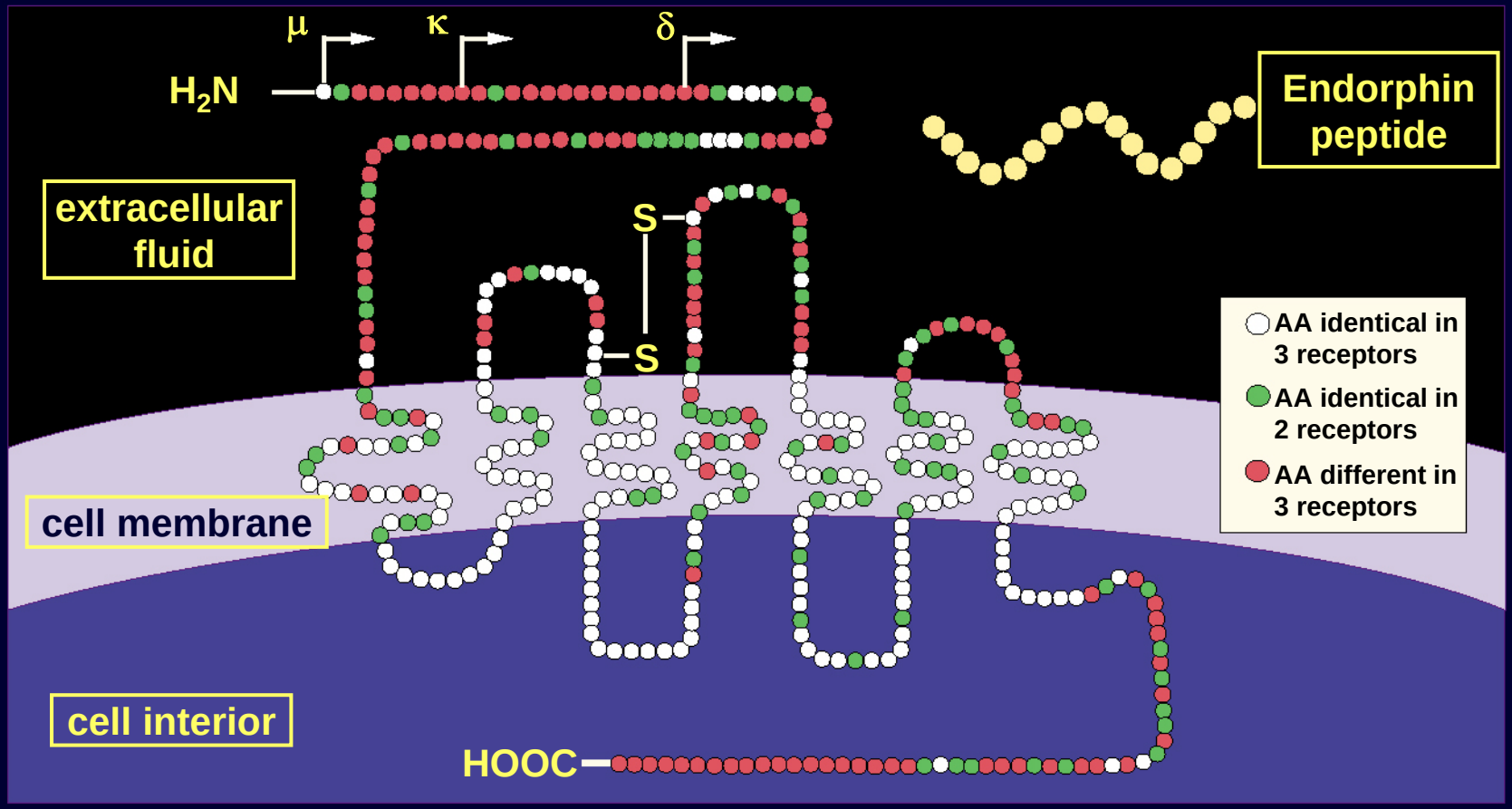
REWARD – Basal and Cocaine-Induced Increases in Extracellular Dopamine Levels Become Attenuated After Chronic "Binge" Pattern Cocaine Administration: Microdialysis (Nucleus Accumbens) Study in C57BL/6Mice



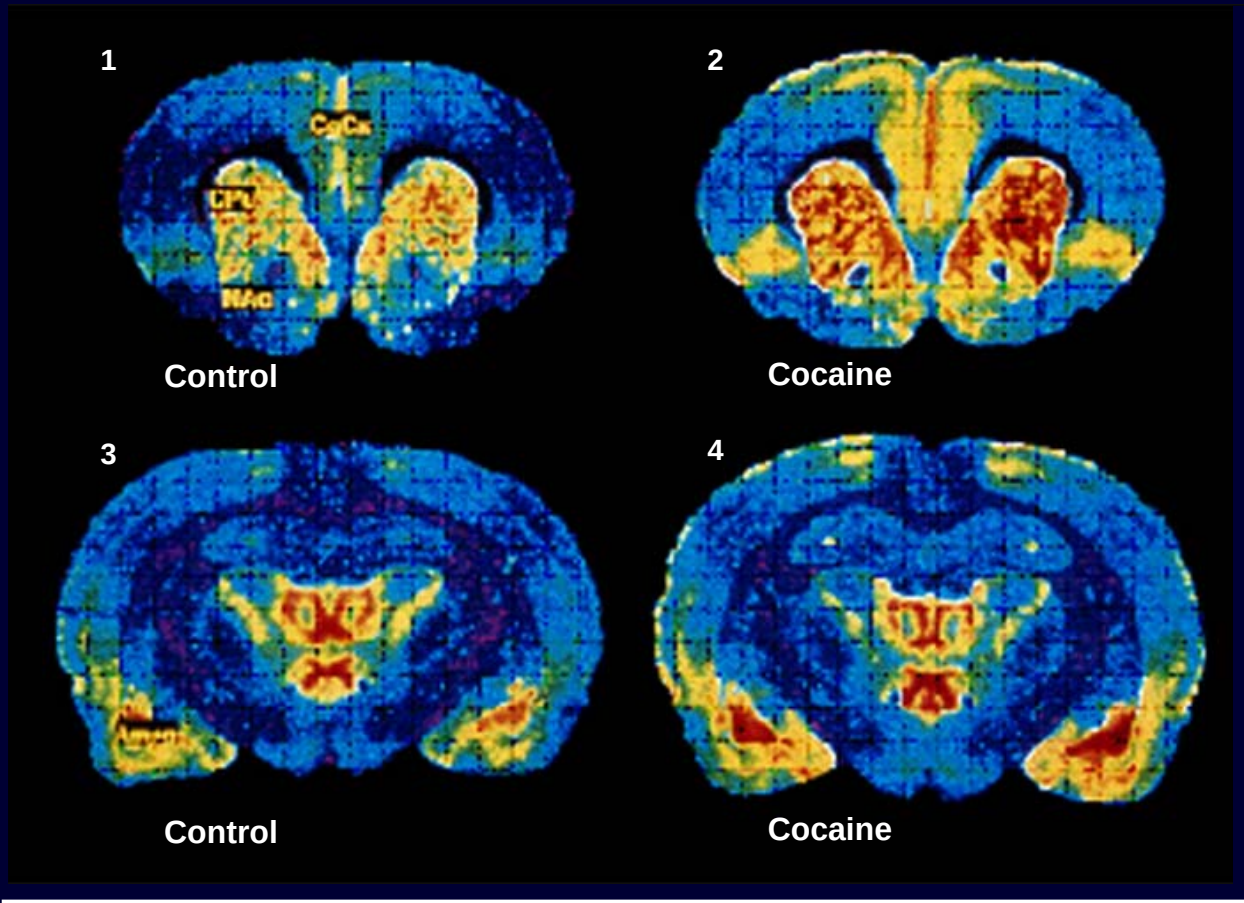
Zhang et al., Synapse, 50:191, 2003

Endogenous Opioids ("Endorphins" – 3 classes) and their Opioid Receptors (3 types)



LaForge, Yuferov and Kreek, 2000

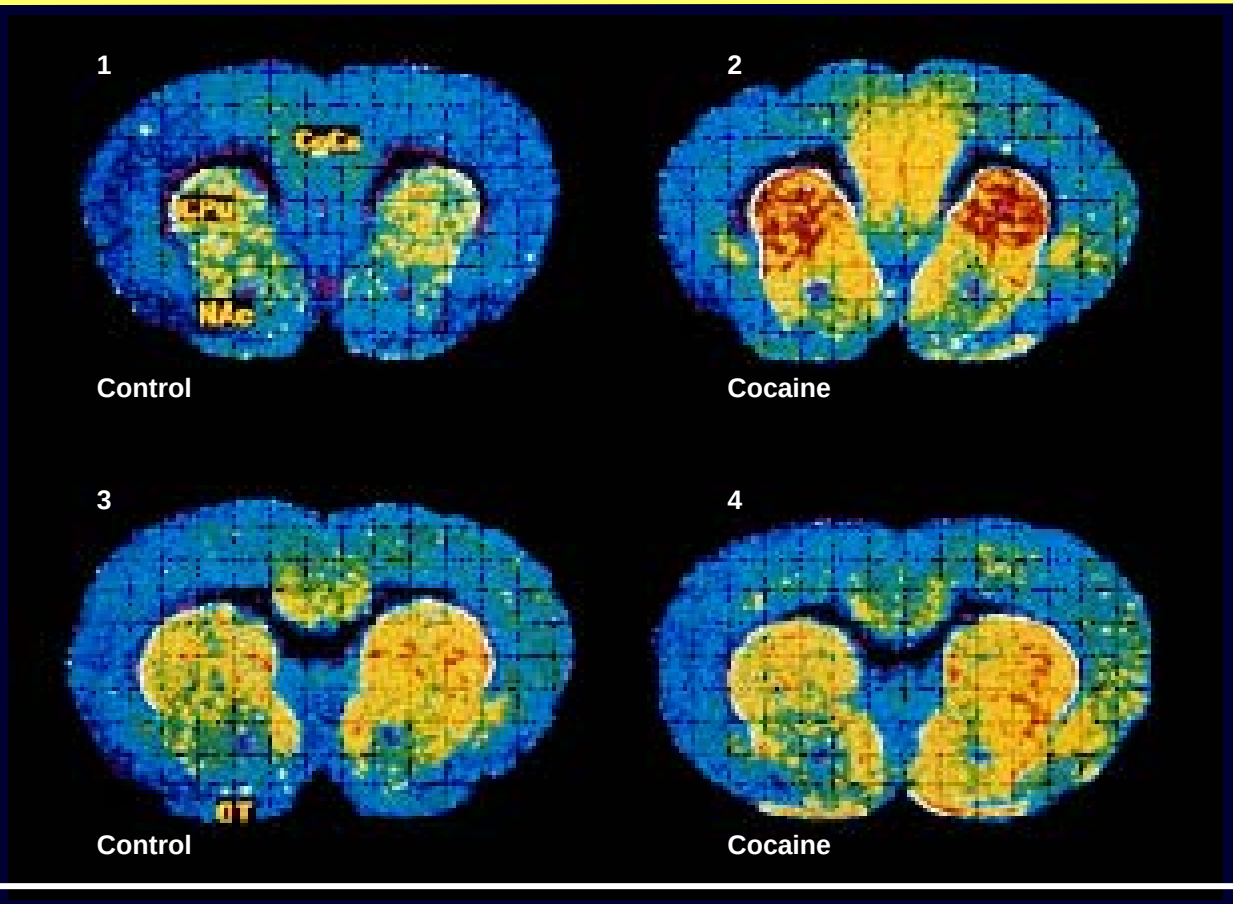
REWARD — Mu Opioid Receptor-Endorphin System: Chronic Cocaine in Rat Increases Mu Opioid Receptor Density, But With No Increase in Mu Endorphins



Relative “endorphin deficiency” develops and persists for an extended time.

Unterwald et al., Brain Res., 584:314 1992

COUNTERMODULATION – Chronic 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 et al., Mol. Brain Res., 38:71, 1996;
Unterwald et al., NeuroReport, 5:1613, 1994

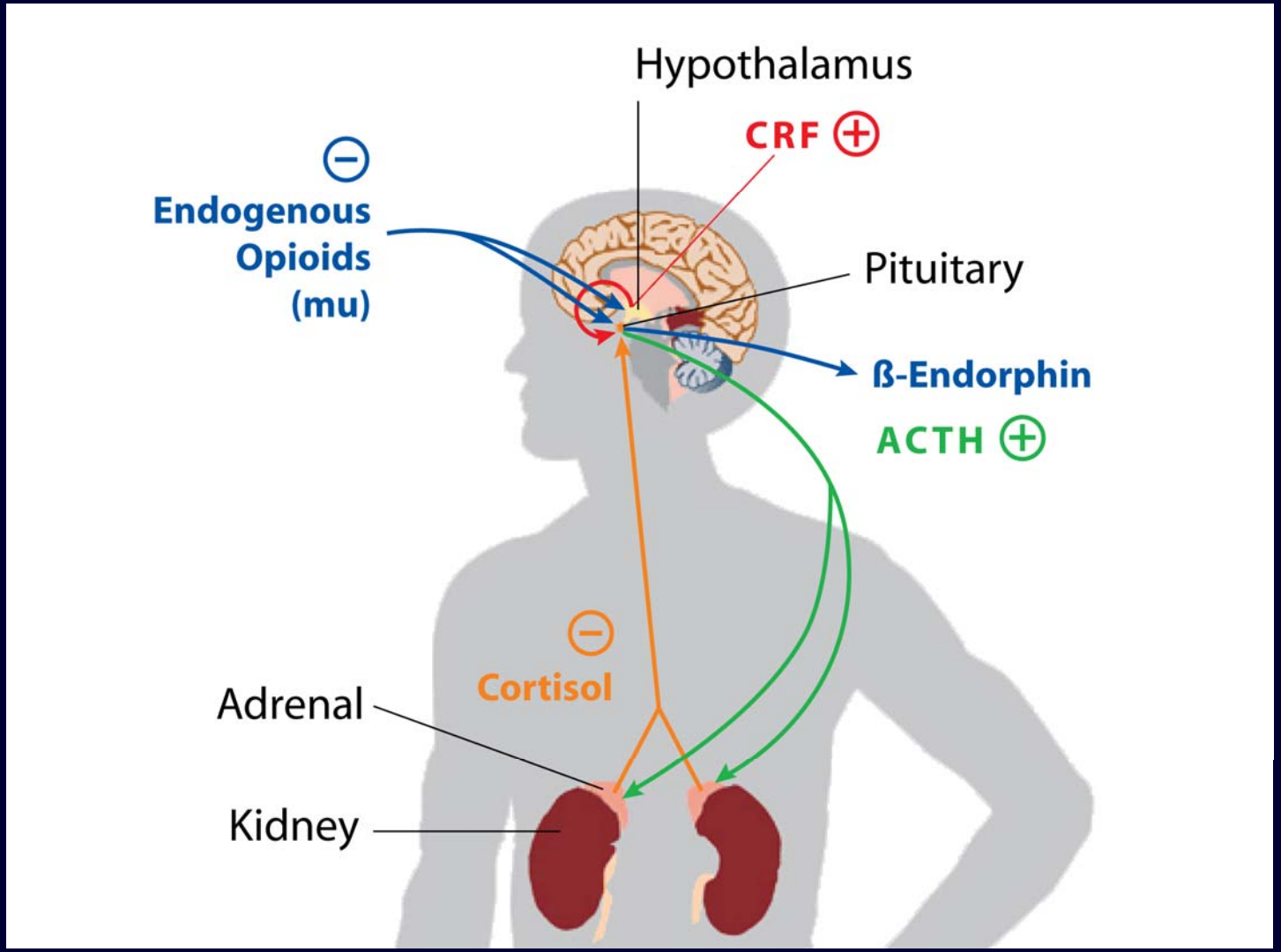
Hypothesis — Atypical Responsivity to Stressors: A Possible Etiology of Addictions

Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to, self-administration of drugs of abuse and addictions.

Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Kreek, 1972; 1981; 1984; 1987; 1992; 2001; 2008

Hypothalamic Pituitary Adrenal (HPA) Axis



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

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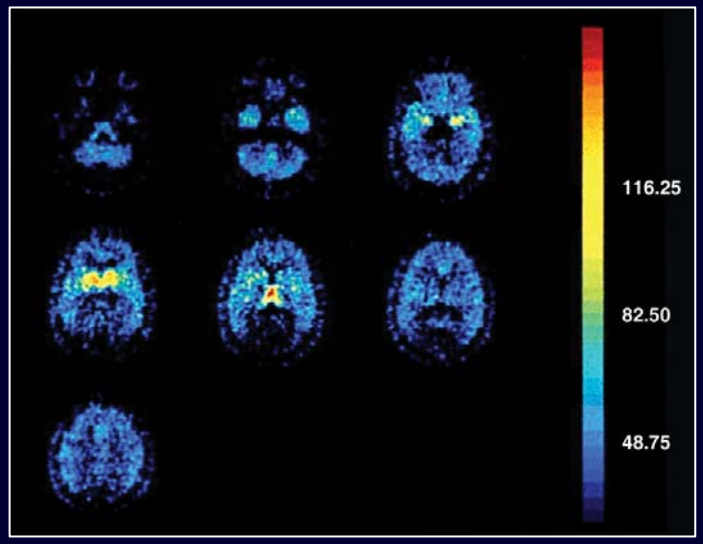
“On / Off” *versus* “Steady-State”

Disruption *versus* Normalization

- levels of gene expression and gene products (peptides)
- receptor mediated events
- physiology
- behaviors

Kreek, 1987; 2001

Normalization of Heroin Disruption Physiology During Methadone maintenance treatment: PET studies of mu opioid receptors in human brain regions



Normal volunteers n=14

MMTP volunteers n=14

(~20-30 percent reduction in mu-opioid receptor binding)

Specific Binding (ml plasma/ml tissue)

16
14
12
10
8
6
4
2
0

Thl Amy Caud Ins ACg Put MT MFr Par Crb IT Hip WMt

Region of Interest

Area related to pain response

Area with dopamine terminals involved in “reward”, mood, and decision-making

Area with dopamine terminals involved in memory, learning, and movement

Kling et al., 2000

Methadone Maintenance Treatment Allows Normalization of Endogenous Opioid-Related Physiological Functions Disrupted During Chronic Heroin Use

Neuroendocrine Function

- **Hypothalamic-Pituitary-Adrenal Axis – Stress Responsivity:** levels and circadian rhythm of release of POMC peptides (β Endorphin; ACTH and cortisol)
- **Hypothalamic-Pituitary-Gonadal Axis – Reproductive Biology:** levels and pulsatile release of LH and testosterone levels

Immune Function

- **Natural Killer Cell Activity**
- **Absolute Numbers of Cells:** T cells; T cell subset levels; B cells; NK cells
- **Immunoglobin Levels (M and G)**

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Kreek, 1972; 1973; 1978; 1987; 2001; 2008; Novick et al., 1989

Vulnerability to (or Protection from) Development of an Addiction

Genetic vulnerability to develop an addiction once self-exposed probably due to:

- **Multiple variants (different types) and of**
- **Multiple genes (as with any complex disorder, e.g., hypertension, diabetes)**
- **Probably shared and unique variants for each specific addiction**
- **Genetic contributions of comorbid conditions and personality types may play a role**

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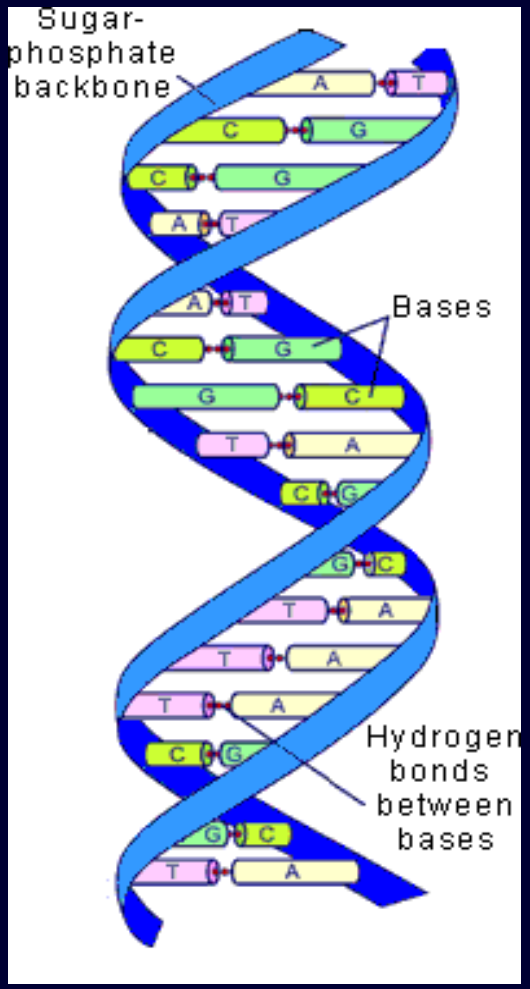
Kreek, 2008

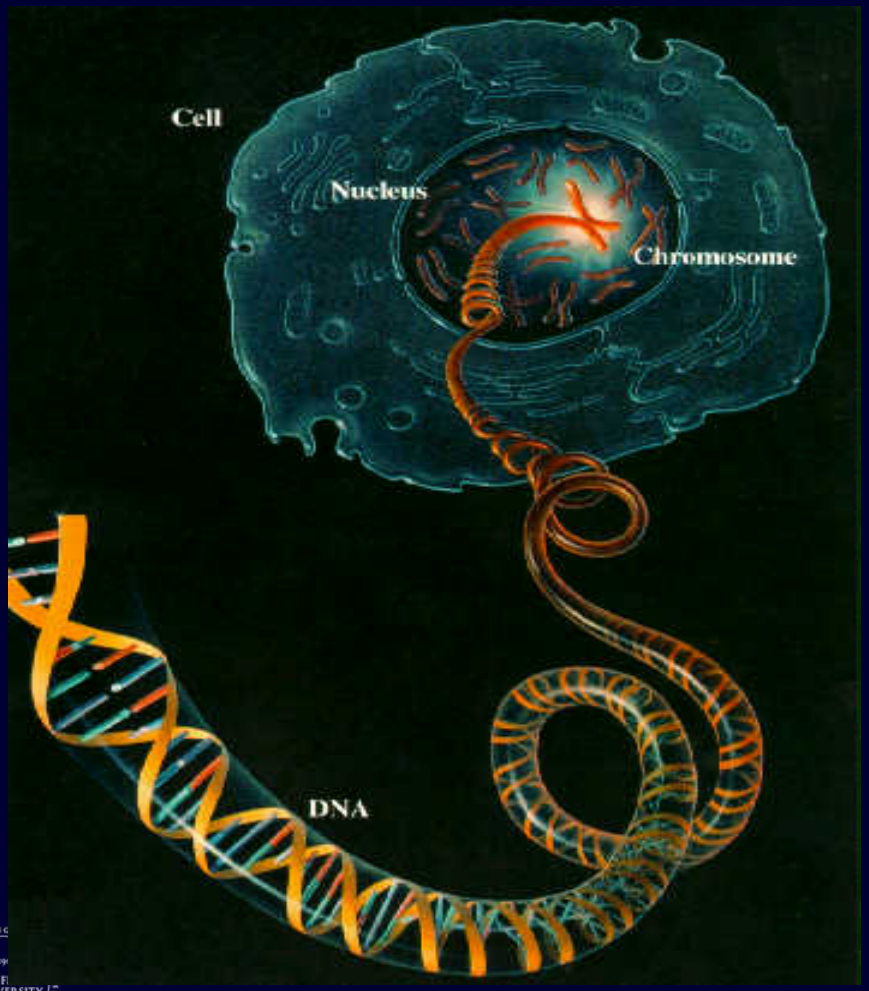
Basic Principles: DNA



- Genetic information is encoded in long, threadlike molecules called deoxyribonucleic acid (DNA).
- During fertilization, DNA comes from egg and sperm; developing offspring inherits genetic material from each parent. Thus, DNA transmits genetic information from one generation to the next.
- The entire sequence of DNA molecules in an organism is called its genome.

Hassin and Kreek, 2004

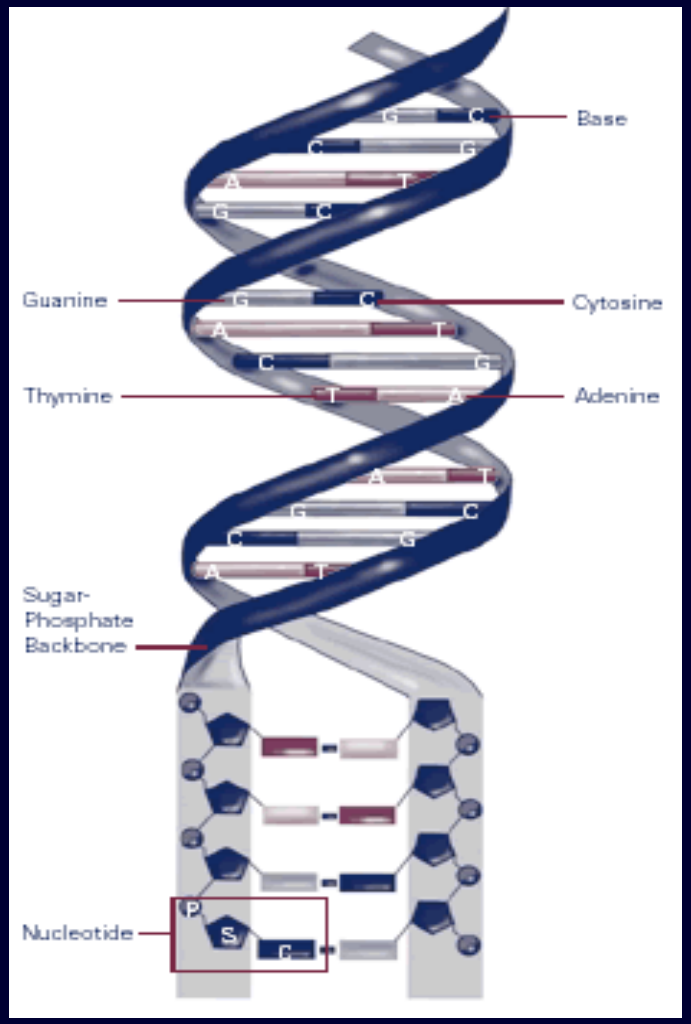
The Human Genome
(as currently understood)



- In the human genome, there are ~3 billion bases (nucleotides)
- In humans, there are estimated to be ~25,000-35,000 genes
- Each gene is a sequence of bases or nucleotides

Hassin and Kreek, 2004

Single Nucleotide Polymorphisms (SNPs) in Genes: Definitions



- **SNP — a single nucleotide polymorphism, that is, a gene variant involving one nucleotide or base of any base pair**
- **Allelic Frequency:**
  - **<1% low or rare**
  - **1–5% intermediate**
  - **>5% high, frequent**

Hassin and Kreek, 2004

Human Gene Diversity is One Basis of Variations and Differences in Humans

SNPs and Other Polymorphims (i.e., allelic variants of genes):

- **usually neither "good" nor "bad"**
- **may (or may not) have any functional significance (e.g., yield different peptides and proteins; alter levels of gene expression)**
- **may (or may not) contribute to altered response to therapeutic agents, i.e., medications, "pharmacogenetics" and "pharmacogenomics"**
- **may (or may not) contribute to altered response to endogenous peptides (e.g., hormones, enzymes)– "physiogenetics" and "physiogenomics"**

Kreek, 2000

Role of Mu Opioid Receptor and Related Endorphin Systems in Normal Physiological Functions*

- Neuroendocrine Functions
  - Stress responsive systems including hypothalamic-pituitary-adrenal axis
  - Reproductive function including hypothalamic-pituitary-gonadal axis
- Response to Pain
- Immunological Function
- Gastrointestinal Function
- Cardiovascular Function
- Pulmonary Function
- ? Mood, Affect; Cognition

* *All disrupted by chronic abuse of the short acting opiate, heroin*

Kreek, 2000

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]

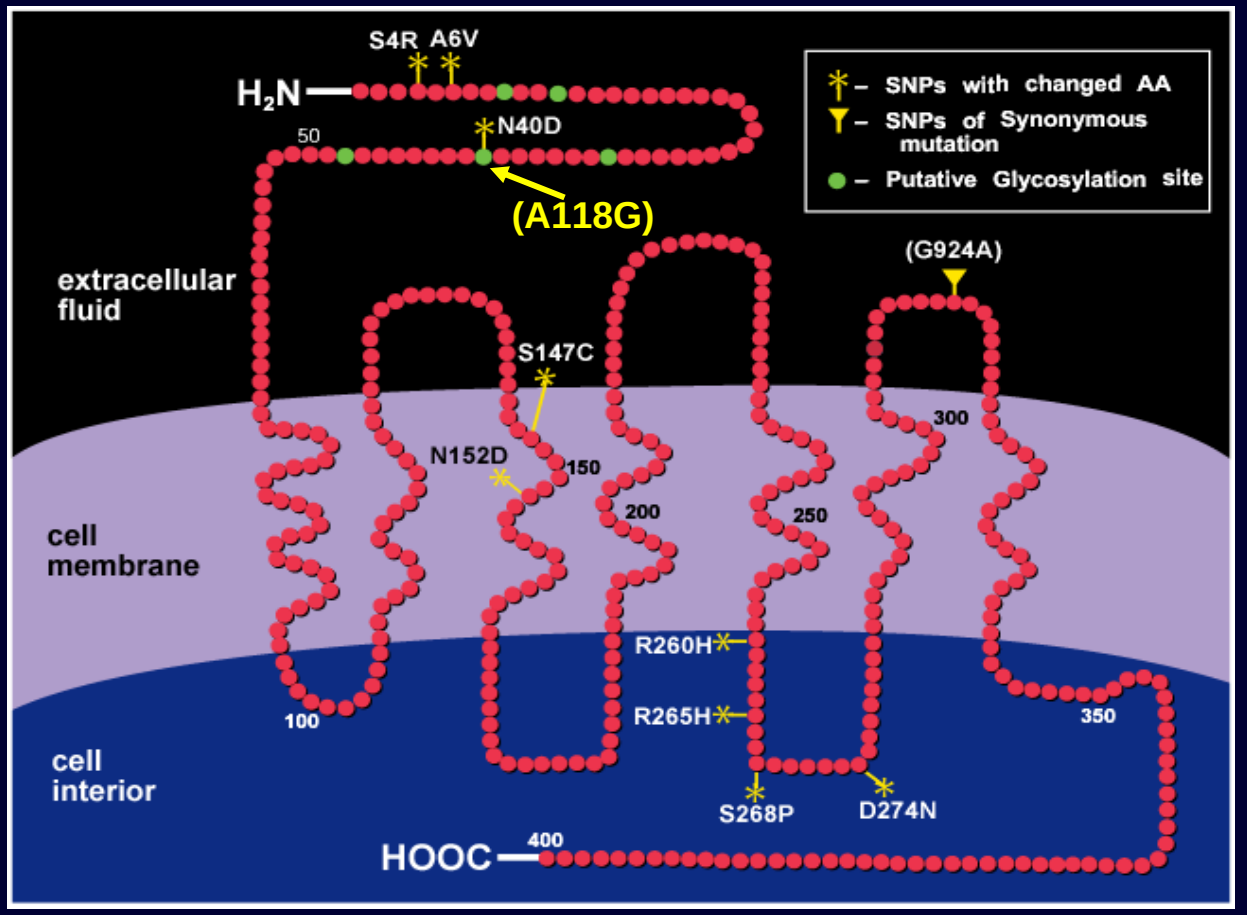
Reviewed in *Kreek et al., Nature Reviews Drug Discovery, 1:710-726, 2002*

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

HYPOTHESIS

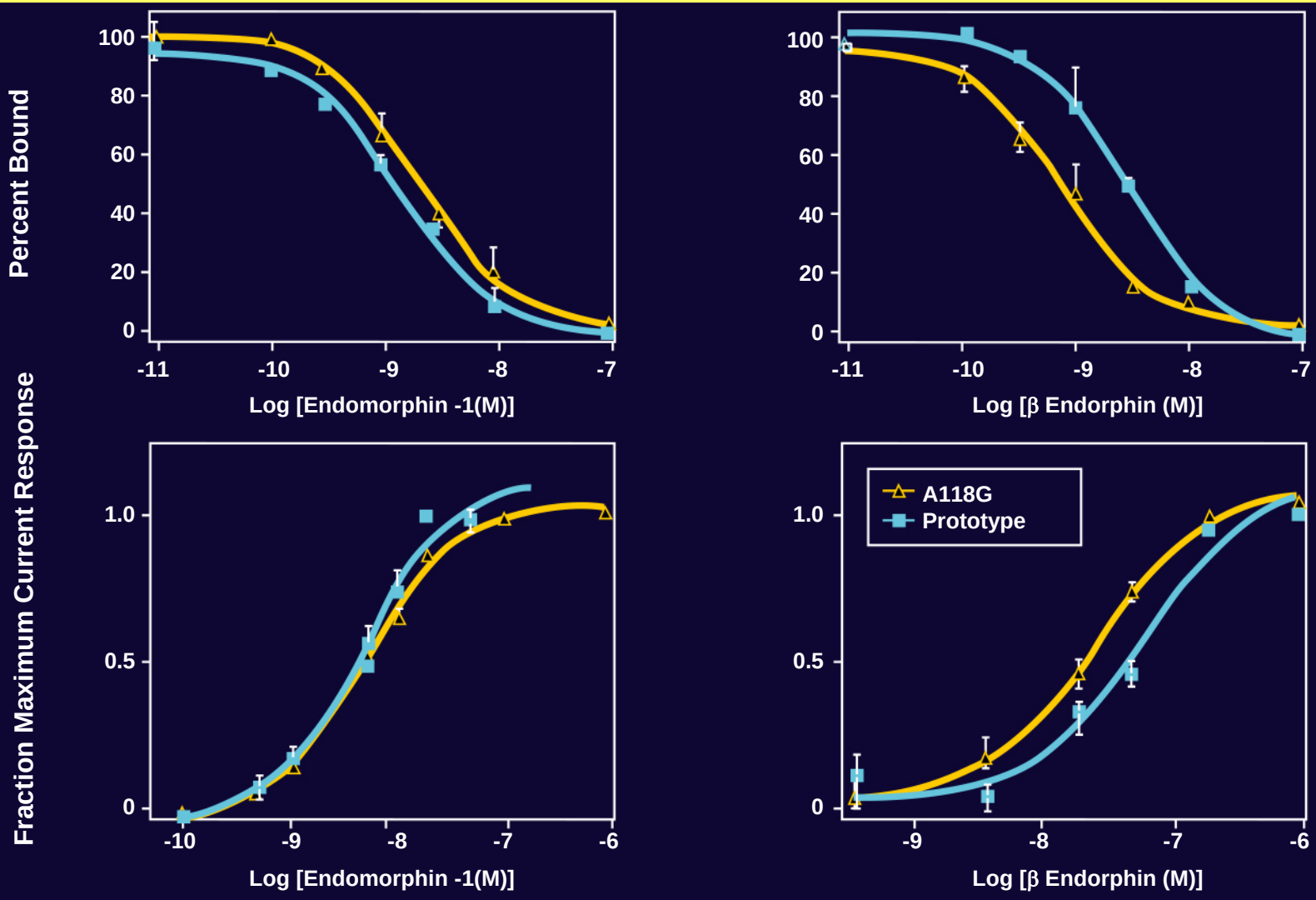
Gene variants:

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



Bond, LaForge… Kreek, Yu, PNAS, 95:9608, *1998*

Binding and Coupling to G Protein-Activated, Inwardly Rectifying K^+(GIRK) Channels by Endogenous Opioid Peptides to the Prototype and A118G Variant Mu Opioid Receptor



Bond, Laforge et al., PNAS, *1998*

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

Genotype	All Subjects		Swedish with Both Parents Swedish	
	Controls (n=170)	Opiate Dependent (n=139)	Controls (n=120)	Opiate Dependent (n=67)
A/A	147 (0.865)	98 (0.705)	104 (0.867)	46 (0.687)
A/G	21 (0.123)	39 (0.281)	15 (0.125)	19 (0.283)
G/G	2 (0.012)	2 (0.014)	1 (0.008)	2 (0/030)

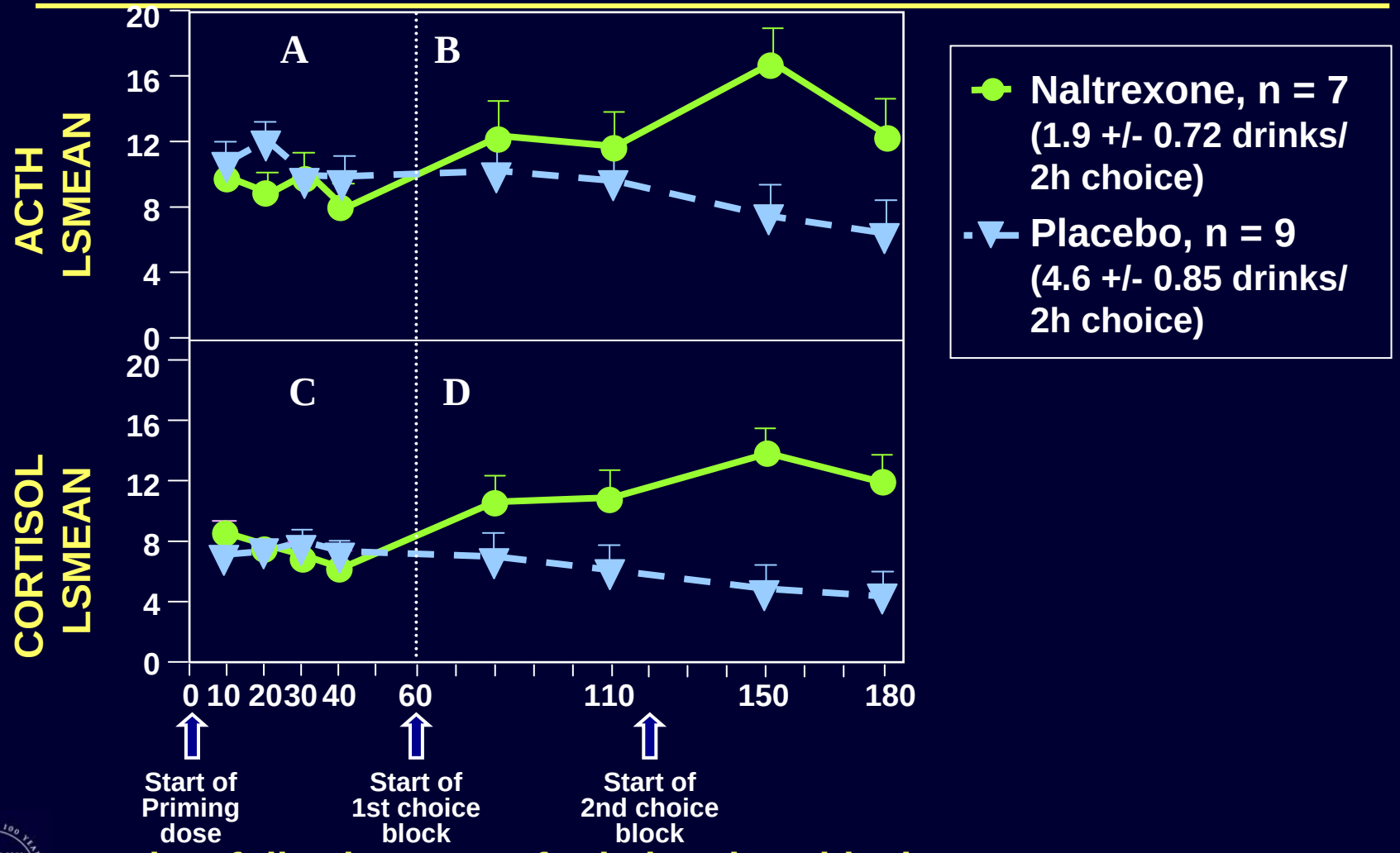
RR = 2.86 $\chi^2_{(1)}$= 13.403 P = 0.00025* RR = 2.97 $\chi^2_{(1)}$= 8.740 P = 0.0031*

	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 in this population: 18%
Attributable Risk due to genotypes with a G allele in Swedes w/ Swedish parents: 21%
(with confidence interval ranges from 8.0 to 28.0%)

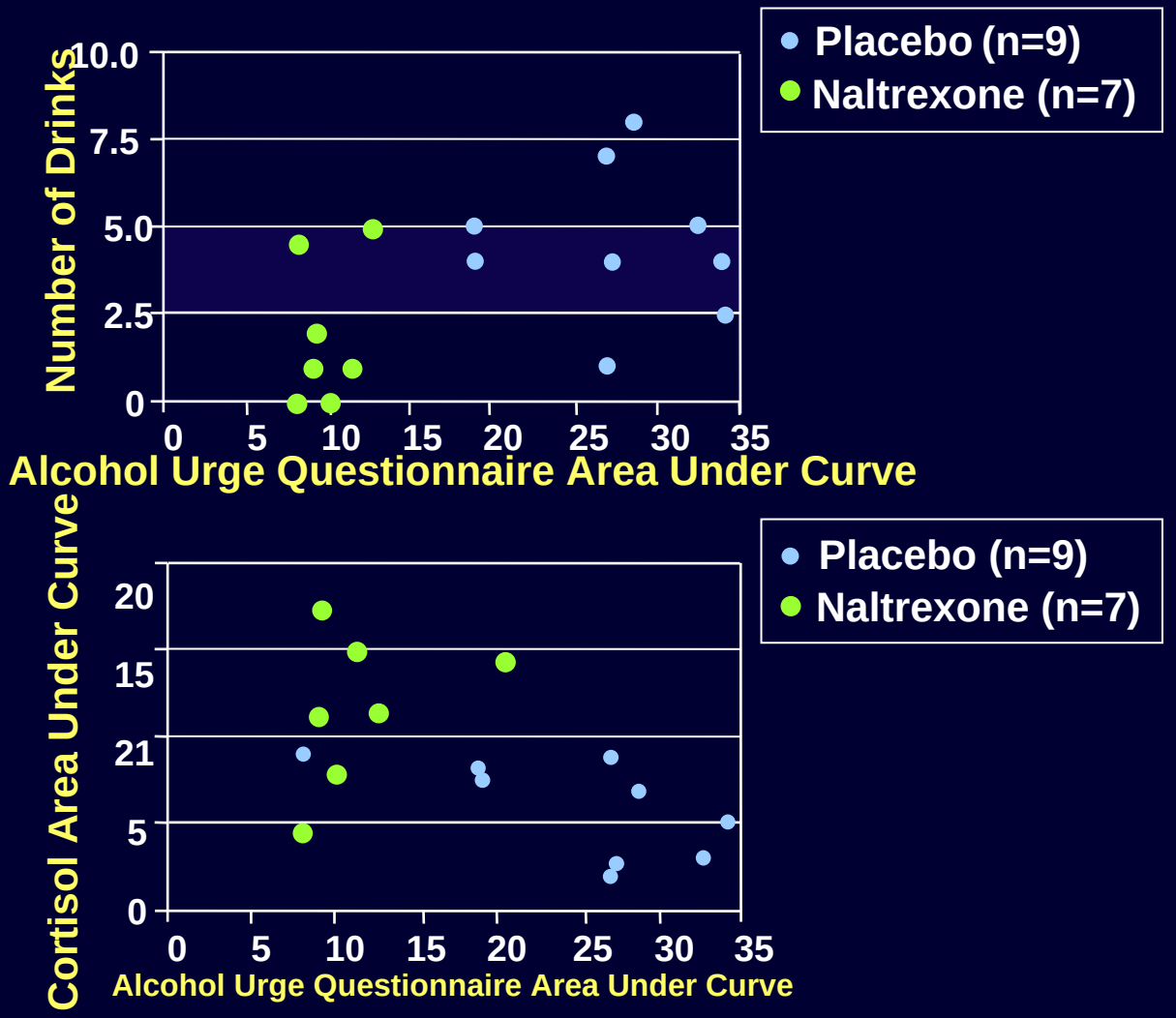
Bart G , Heilig M, LaForge KS… Ott J, Kreek MJ, et al., Molecular Psychiatry, 9:547-549, 2004

ACTH and Cortisol Levels 6 Hours After Administration of Naltrexone or Placebo: Effects of Alcohol Consumption with "Priming Drink" and Up to 4 Drinks in Each of Two 2 Hour Consecutive Sessions



O'Malley et al, Psychopharmacology, *2002*

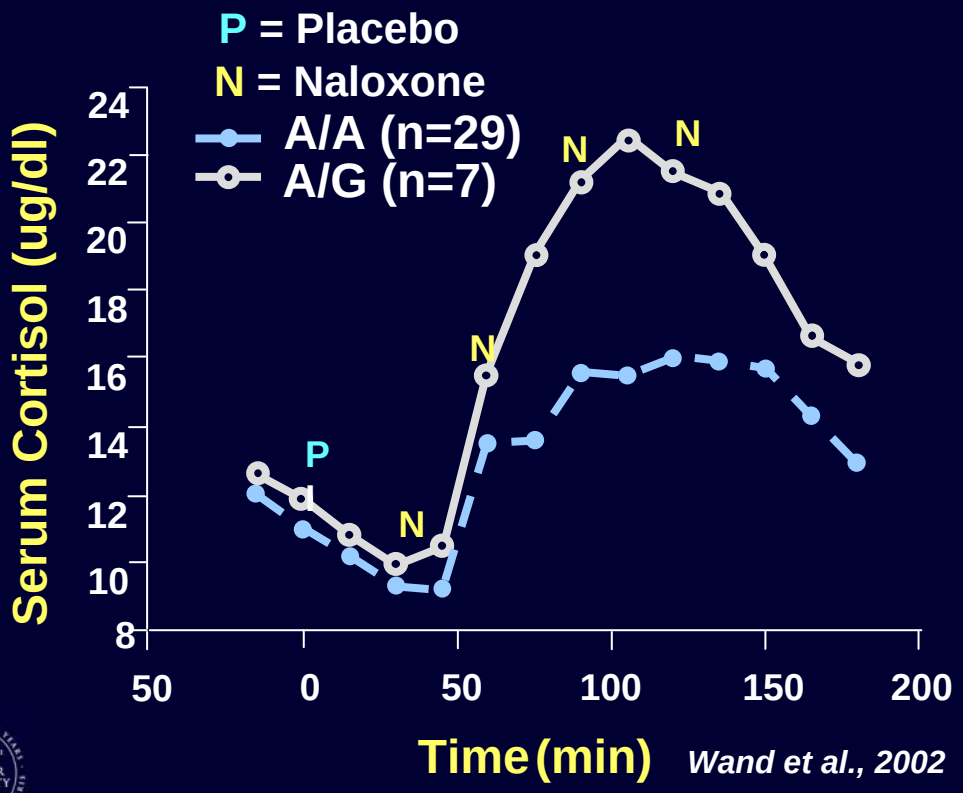
Alcohol Urge Questionaire (AUQ) 6 Hours After Oral Naltrexone or Placebo During Two 2 Hour Consecutive Drinking Choice Sessions



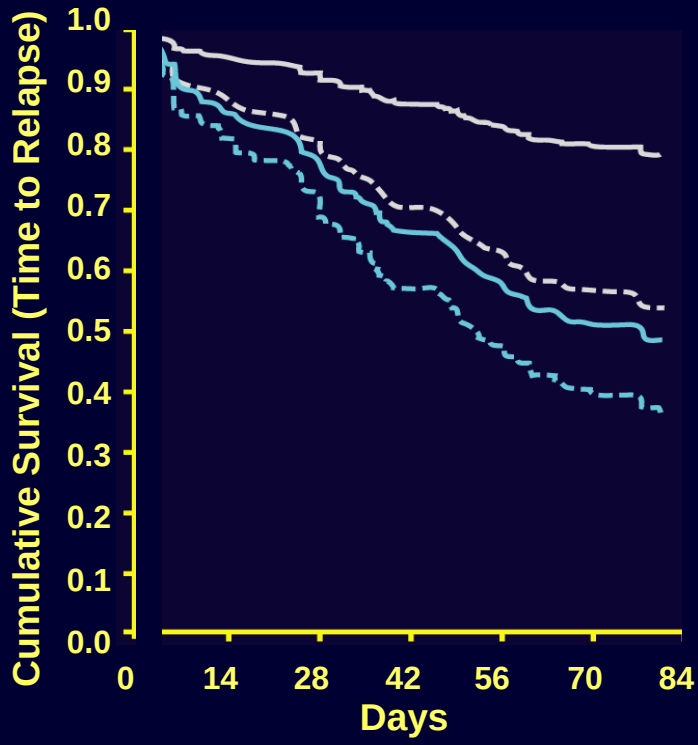
O'Malley et al, Psychopharmacology, *2002*

"Physiogenetics" and "Pharmacogenetics" Related to A118G Variant of Human Mu Opioid Receptor Gene – Altered Stress Responsivity

Basal plasma levels of cortisol significantly higher in persons with the A118G variant.
Bart et al., 2006



Wand et al., 2002



Naltrexone/ A/G, G/G (n=23)
Naltrexone/ A/A (n=48)
Placebo/ A/G, G/G (n=18)
Placebo/ A/A (n=41)
Oslin et al., 2003

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

	Swedish with two Swedish parents		Non-Swedish without Swedish Parents	
	Alcohol Dependent (n=193)	Control (n=120)	Alcohol Dependent (n=196)	Control (n=50)
A118	158	104	141	43
A118G, G118G	35	16	55	7

OR=1.92 $\chi^2_{(1)} = 7.18$, p = 0.0074

	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*

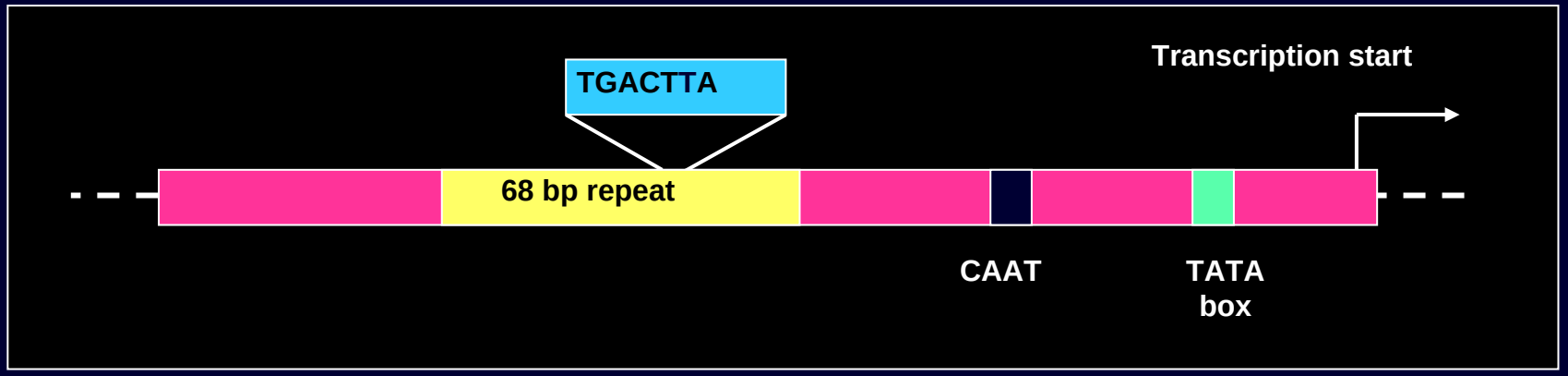
Thus, in the entire study group in this central Swedish population:

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, et al., Neuropsychopharmacology, 2005

Repeat Polymorphism of Dynorphin Gene – Grouped by Frequency of Cocaine Use and Cocaine/Alcohol Dependent versus Controls



Genotype		Cocaine / Alcohol dependent Long	Cocaine / Alcohol dependent Long/Short	Cocaine / Alcohol dependent Short	Controls Long	Controls Long/Short	Controls Short
Caucasian American	n	6	6	1	27	19	9
		46%	46%	8%	49%	35%	16%
African American	** n	25	26	10	14	16	19
		41%	43%	16%	29%	33%	39%
Hispanic American	n	4	4	2	8	3	1
		40%	40%	20%	67%	25%	8%

Long = 3,3; 3,4; 4,4
Long/Short = 1,3; 1,4; 2,3; 2,4
Short = 1,1; 1,2; 2,2

** Significant difference between control and cocaine and alcohol dependent. Fisher's Exact test, p = 0.01.

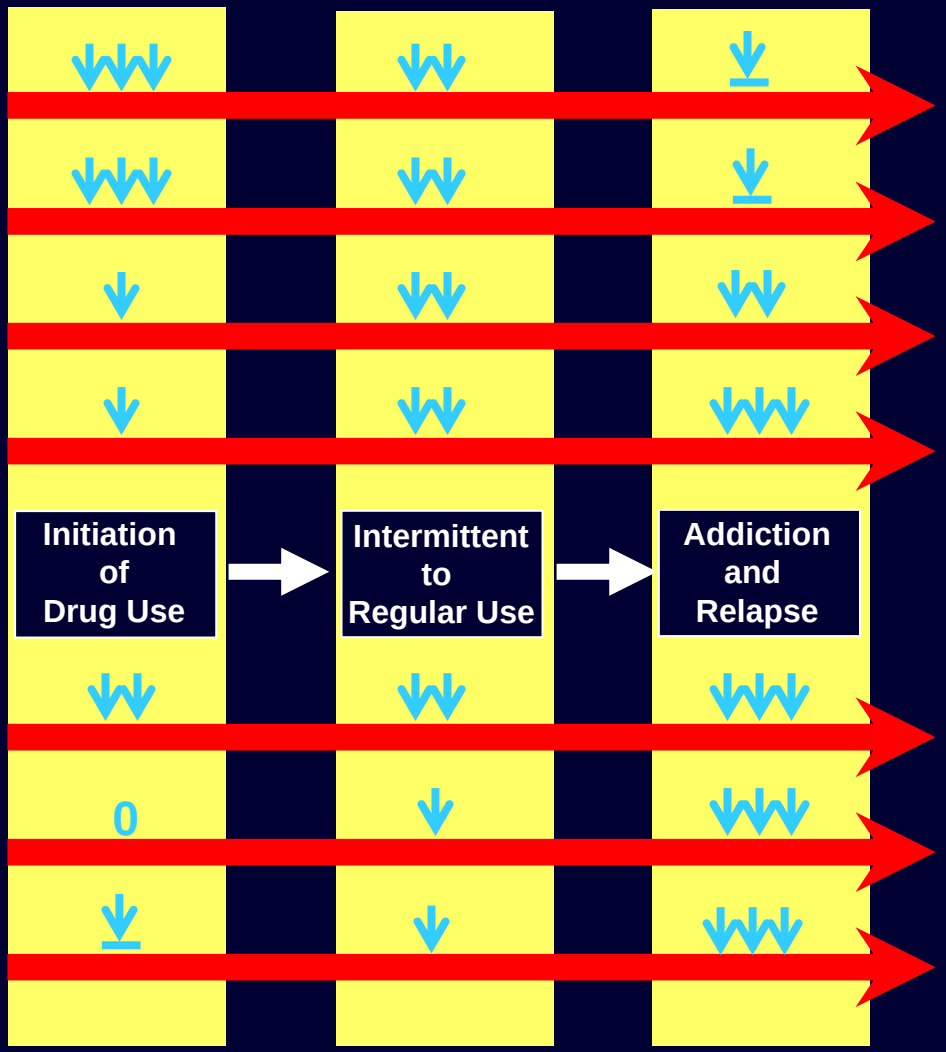
Williams et al, 12:496, 2007

Impulsivity* *(genetics?)*

Risk Taking* *(genetics?)*

Comorbidity *(genetics)*

Stress Responsivity-atypical *(genetics)*



Environmental Factors
(~100% contribution to addiction)

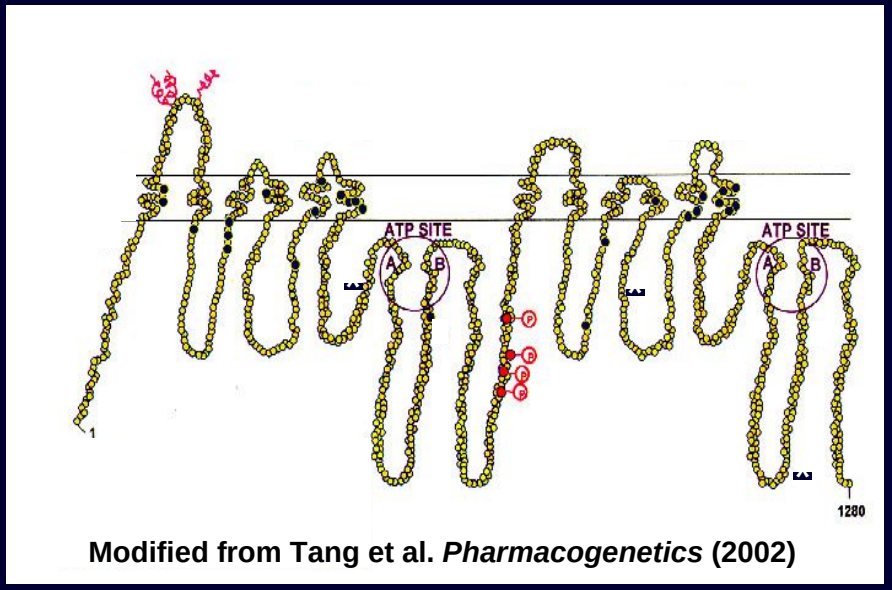
Drug Induced Effects (w/ some genetic factors)
(~100% contribution to addiction)

Genetic Factors for addiction
(30-60% contribution to addiction)

** Relative scale of contributors to stage of drug use/addiction:

Kreek, Nielsen, Butelman & LaForge, Nat Neurosci., *8:1450, 2005*

P-glycoprotein (MDR1, ABCB1)

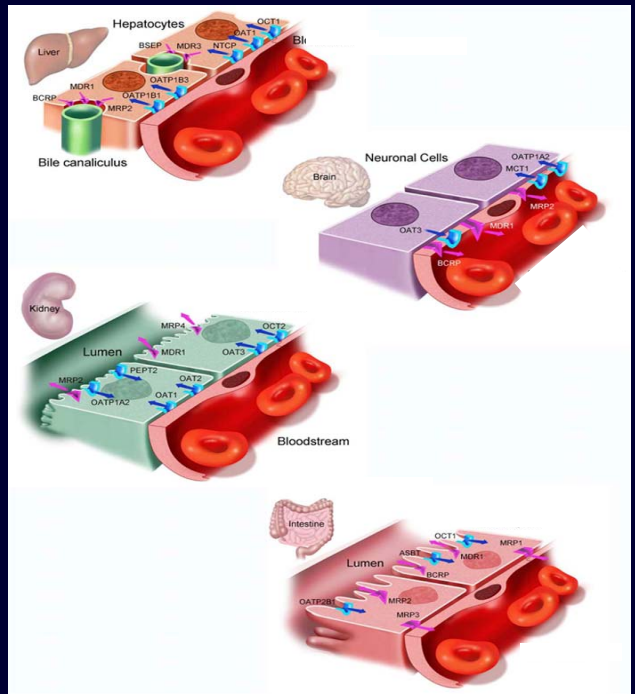


Modified from Tang et al. *Pharmacogenetics* (2002)

Out

membrane

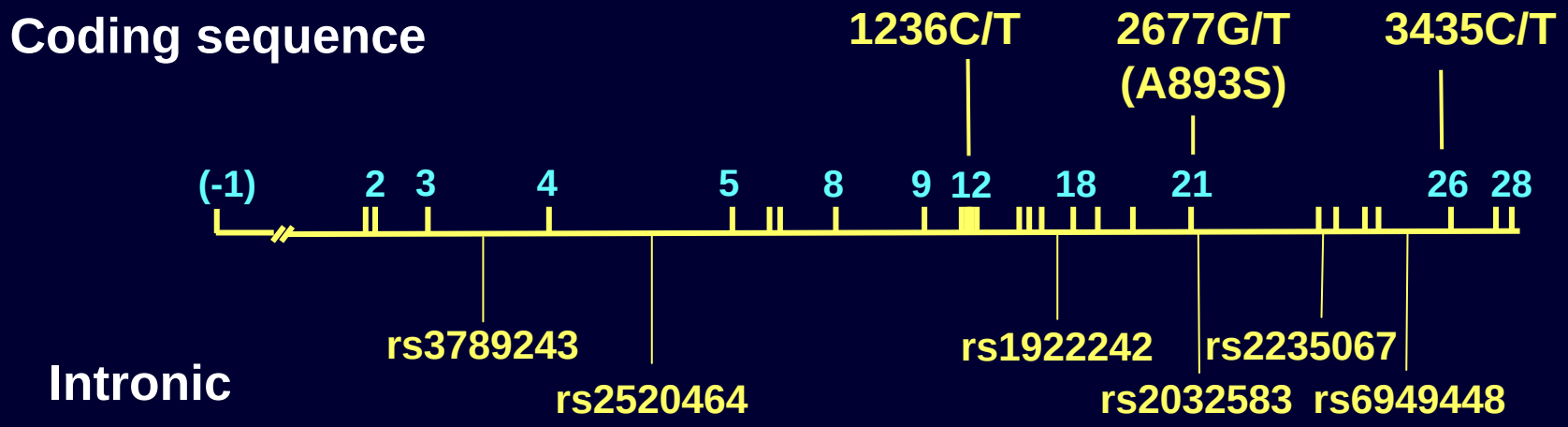
In



P-gp is expressed in tissues with barrier function like the endothelial cells lining of the Blood-Brain Barrier

Adapted from Ho et al. *Clinical Pharmacology & Therapeutics* (2005)

Selected *ABCB1* SNPs and Study Design



Methadone dose

← 150 mg/day →

"Low" | "High"

Tests for association:

Single SNP

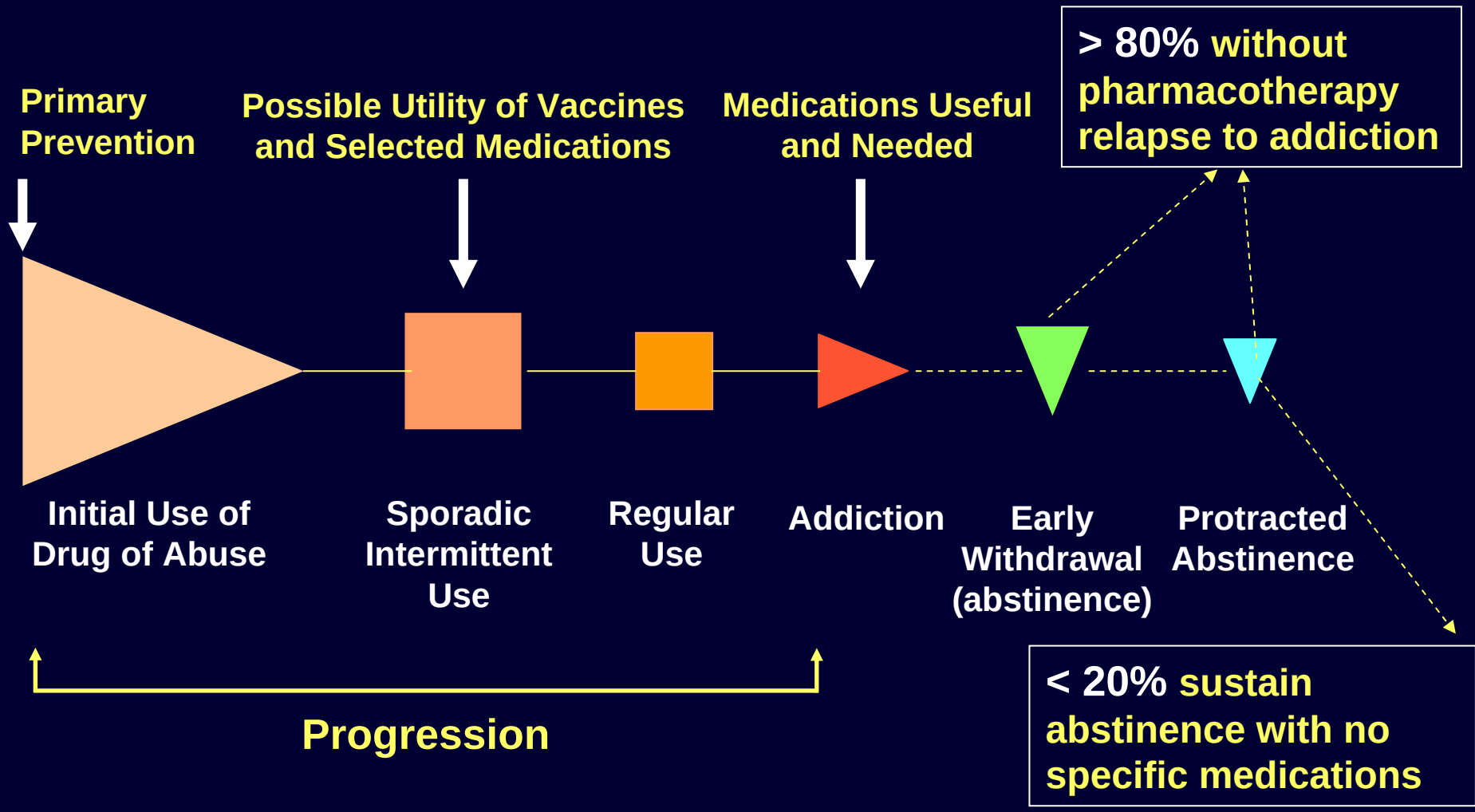
- Allele frequency
- Genotype frequency

Multi locus genotype pattern:

- 3 - locus (coding region)
- 9 - locus

Levran et al., 2008

Natural History of Drug Abuse and Addictions



Kreek et al., Nature Reviews Drug Discovery, 1:710, 2002

Genetics and Addiction: The Community Treatment Perspective

Louise Haynes
Director of Research, Lexington/Richland Alcohol and Drug Abuse Council (LRADAC)

Allan J. Cohen
Director of Research and Training
Bay Area Addiction Research and Treatment (BAART)


MAY 21 2003

Genetics and Addictions

The thoughts, understandings and misunderstandings of two community treatment providers

Today

- Science – Mary Jeanne Kreek
- The CTN- getting started in genetics studies – Louise Haynes
- The START Genetics Study – Allan Cohen

PLATYPUS

Decoded Platypus Genome Spells Out 'Hybrid‘
2008

NIDA Clinical Trials Network

In the beginning there was

Research **Scientists, laboratories and stuff)**


© Robert Rathe

. . .and there was Treatment

(counselors, groups, urine and stuff)

But, as you have heard, there was a problem

Research Meets Treatment
Mission of the CTN

- Develop dialogue between the research and treatment communities:
- Bring state-of-the-art treatments from the laboratory to the clinic
- Rigorous investigation of existing treatment practices/systems

Community Treatment Programs in the CTN

- There are 16 “nodes” in CTN
- Node = University + 5-10 CTPs
- More than 100 CTPs affiliated with the CTN
- All shapes, sizes and flavors

We are a diverse group

- Therapeutic Communities
- Narcotic Treatment Programs
- VA Center
- Drug Free Intensive Outpatient
- Short-term and Long-term Residential Care
- Small Community Clinics
- Large Urban Clinics
- Hospital Based
- University Based Programs

Genetics Studies in the CTN

- Special Interest Group- Andy Saxon, Mary Jeanne Kreek, Tom Crowley, John Rotrosen, Allan Cohen, Louise Haynes
- NIDA Genetics Consortium – Joni Rutter
- The START Genetics Study – collaborative effort

One of the questions we discussed in the Genetics Special Interest Group:

What is the Role of Community Treatment Programs in Genetics Research?

Genetics and the CTN

- Detroit Blending Meeting
- Mary Jeanne Kreek
- Introduction and Overview Workshop
- Engage community treatment programs
- Seattle Blending Mtg
- Laura Bierut- Workshop on Nicotine Addiction and Genetics
- Plenary – Mary Jeanne Kreek

Brings us to the 2008 Blending Meeting

Review with you some of what we have heard at this meeting about genetics and addiction

Its not simple

The role of genetics in the development of addiction


CHARLIE F.
DEC. 9, 2005
ADDICT

Although genetic characteristics may predispose individuals to be more or less susceptible to becoming addicted, genes do not doom one to become and addict.

Many Factors Influence the Development of Addiction

- Not just a matter of nature vs. nurture
- Agent - variability in addictive potential
- Host – individual genetics
- Environment – culture, norms
- Behavior
- Life experience – ie. early childhood trauma
- Life experiences/environmental stressors may change genetic expression

Theories of a single addiction gene have been replaced by current understanding that multiple genes are at work

“Addiction has one of the highest hereditary interactions of any of the diseases we treat”

Charles O’Brien MD
NIDA Blending Meeting 2008

CTN: A natural resource for genetics research

- Geographical diversity
- Large populations of SUD
- Variety of different treatments
- Different drugs
- Staff/Patient education

What might genetics bring to addictions treatment/community treatment programs in the future?

- Knowledge and understanding of our patients and the addiction process
- Prevention
- Ability to predict treatment effects
- Ability to "fit" treatment to the individual
- Significant reductions in "treatment non-responders"

“The ability to pinpoint genes in the human genome responsible for disease has the potential to revolutionize our ability to treat and even prevent diseases."

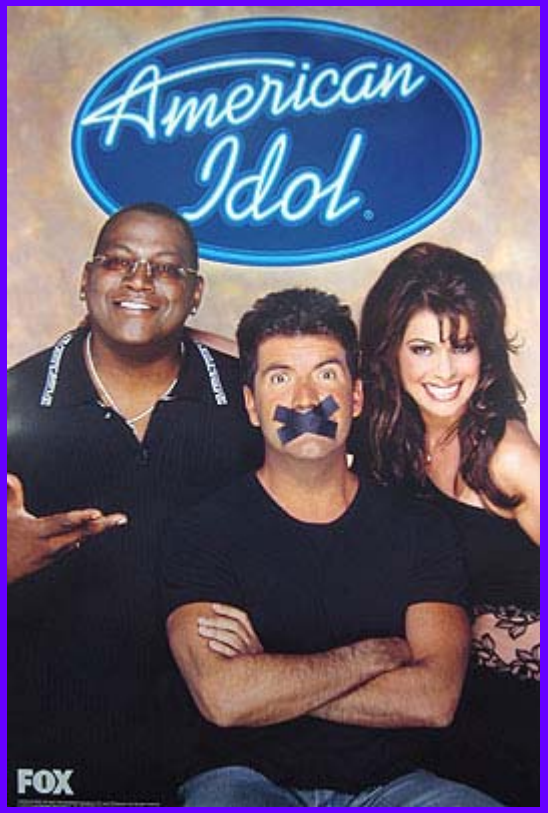
Elias A. Zerhouni
Director, Nat’l Institute
Of Health

I'm Al Cohen and the following is a true story…

“Reality Shows” Past and Present

Survivor

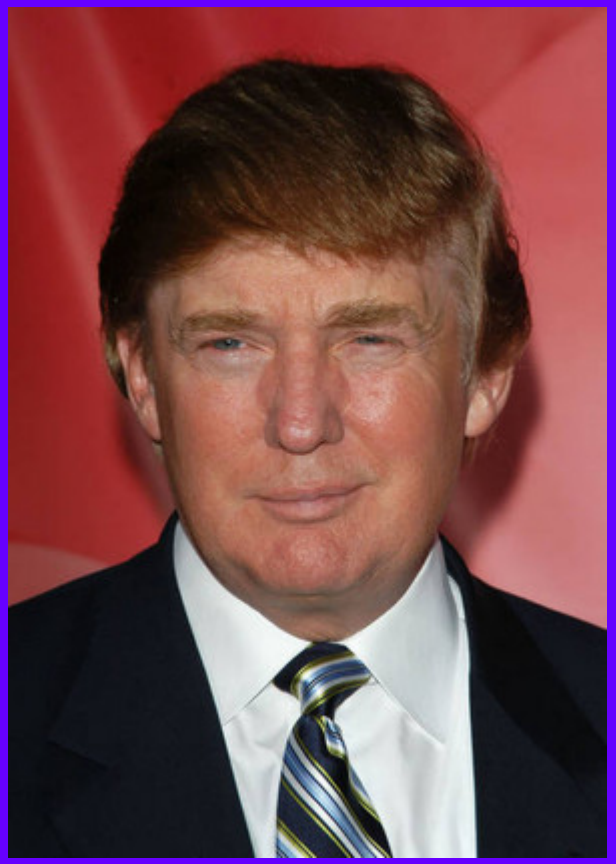
Dancing with the Stars


American Idol
FOX

American Idol

…and who could ever forget

“The Apprentice”



The Newest "Reality Show"

(Reality in the truest sense of the word)

START Genetics

(a sub-study of START)

Genetics and the Community Treatment Program

(a success story in the making)

START and START GENETICS

CTN 0027 & CTN 0027A

A "Main (or parent) and a Sub-study"

Parent and “sub”

You get the point…

NIDA-CTN-0027

Starting Treatment with Agonist Replacement Therapies (START)


THE CLINICAL TRIALS NETWORK
MEDITER-RANEAN AVENUE
COLLECT $200.00 SALARY AS YOU PASS
START
BOARDWALK
LUXU TAX
$60

Study Objectives

The Food and Drug Administration (FDA) has requested a study comparing buprenorphine/naloxone (BUP/NX) and methadone (MET) on indices of hepatic safety.

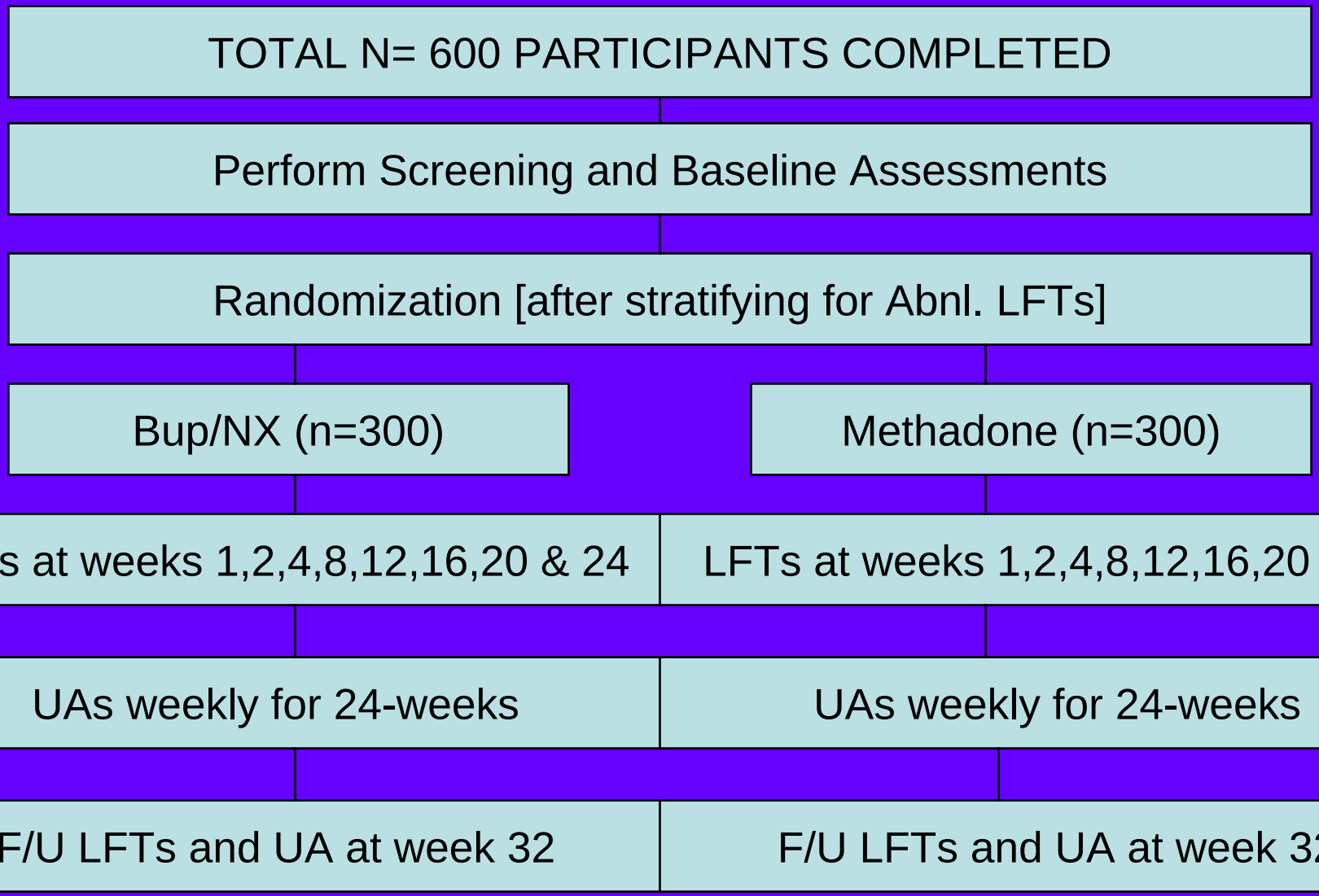
PRIMARY

Compare changes in liver enzymes related to treatment with BUP/NX to changes in liver enzymes related to treatment with MET.

SECONDARY

Assess abstinence from illicit substances. Assess abstinence from alcohol. Identify risk factors at baseline and during treatment that could contribute to interactions with BUP/NX or MET causing liver dysfunction.

START Study Schema



Participating Sites

Node	CTP	CTP Director for START
California-Arizona	Bi-Valley Medical Clinic	Garrett Stenson, MSW
New England	Connecticut Counseling Centers, Inc.	Richard Bilangi, MS
New England	Hartford Dispensary	Paul McLaughlin, MA
Delaware Valley	Northeast Treatment Center	John Carroll, CAC
Oregon-Hawaii	CODA, Inc.	Tim Hartnett, MSW, MHA
Pacific Region	Bay Area Addiction Research & Treatment Matrix Institute	Allan Cohen, MA MFT Dan George, MPH
Washington	Evergreen Treatment Services	Ron Jackson, MSW

START STEPS

Introduce/Prescreen

Consent

Randomize

Induct

Data collection/treatment up to 32 weeks

START Pharmacogenetics Sub-study (CTN 0027A)

Dr. Wade Berrettini PI for Week 2 Samples

Dr. Lindsay DeVane, PI for Week 12 Samples

START GENETICS is the first but hopefully not last genetics study conducted within the CTN

Purpose

- To better understand the potential genetic influence on opioid addition (wk 2 visit)
- To better understand how opioid dependent individuals metabolize buprenorphine and methadone (wk 12 visit)
- To evaluate feasibility of conducting a genetics sub-study within the CTN

Sample #1:

At week 2 or after START sites will obtain blood samples and ship to the NIDA repository in New Jersey. Some of the genetic material will be sent to U. Penn(Berrettini) to be evaluated to see if dependence on opioids or response to study medications are linked to specific genes.

Sample #2:

At week 12 or after a second blood sample will be obtain along with a urine samples and will sent to the Medical University of South Carolina (DeVane) . There researchers will study the relationship between treatment drug plasma concentrations and gene variants associated with how our bodies absorb, distribute, metabolize and eliminate these medications (pharmacogenetics).

Q: Will Community Treatment Programs and their Clients Accept Genetic Studies?

- **Concerns include:**

- **Misunderstand/Misinformation**
- **Confidentiality**
- **Will this be used against me in future?**
- **It's not the "usual and customary"**

START-Genetics is a "sub-study" of the parent or "main" START study (CTN 0027). Important Note: Individuals may participate in START without being compelled to participate in the Genetics sub-study

The inverse does not apply…

CTPs	START Endorsement Date	GENETICS Endorsement Date	MONTHS prior to start of Genetics
PA Matrix Institute	12-Feb-07	9-Apr-07	2
NE Hartford Dispensary	29-Jun-06	16-Apr-07	10
PA BAART	1-Jun-06	23-Apr-07	11
CA/AZ Bi-Valley	24-May-06	29-May-07	12
DV NET Steps	14-Sep-06	25-Jun-07	9
PN Evergreen Treatment	27-Apr-06	13-Jul-07	15
OR/HI CODA	14-Jul-06	6-Aug-07	13
NE CT Counseling	13-Jun-06	10-Oct-07	16
NY ARTC	13-Jun-06	NA	NA
All Sites			

These 8 START sites had advantages for conducting the genetics study:

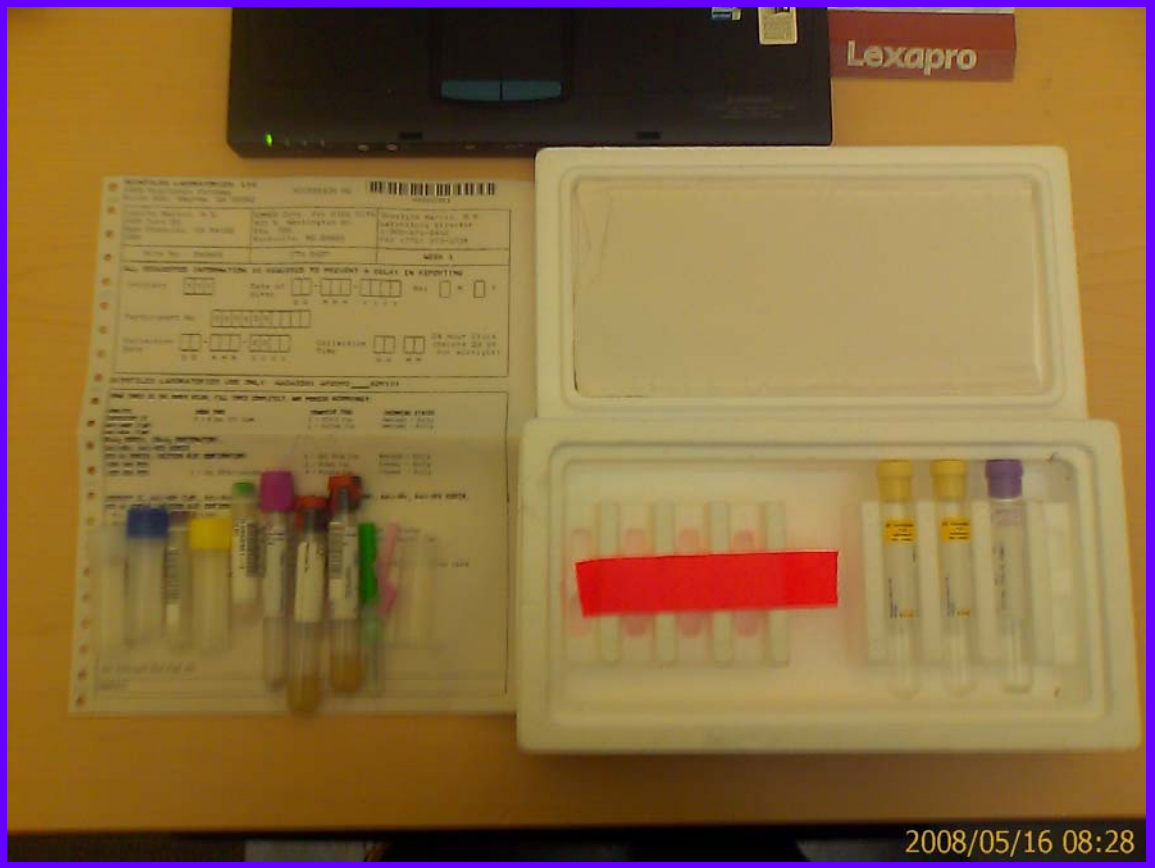
- All are Opioid Treatment Programs
- As such all had medical staff
- Not new to labs and blood draws
- Already drawing blood for START

START Genetics Steps

- Early in START “genetics” is introduced
- If participant agree - Consent (Participate and Level)
- Two serum samples drawn; one around/after week 2 and week 12 “ concurrent” with scheduled START draws
- One urine sample collected week 12 or after

Genetics cont'd

- **Participant is compensated - $25.00 X 2 cash/voucher**
- **Specimens are prepared and shipped**
- **Verification of receipt of specimen e-mailed**
- **Group Hug!**


Lexapro
2008/05/16 08:28

Ubiquitous Urine Test

The next two slides may provoke hallucinations….

CTP	TOTAL START Randomizations (thru 3/31/08)		OF TOTAL START RANDOMIZATIONS						
			CONSENTED TO GENETICS						
	Randomizations PRIOR TO Start of Genetics	Randomizations AFTER Start of Genetics	of those randomized PRIOR TO (%)	of those randomized AFTER (%)	# INVITED	# REFUSED	% AGREED	# Week 2 collected	# Week 12 collected
PA Matrix Institute	48		33 69%		36	3	92%	32	20
	8	40	4 50%	29 73%					
NE Hartford Dispensary	85		62 73%		66	4	94%	57	39
	32	53	19 59%	43 81%					
PA BAART	101		59 58%		60	1	98%	54	37
	53	48	16 30%	43 90%					
CA/AZ Bi-Valley	113		70 62%		70	0	100%	67	51
	60	53	24 40%	46 87%					
DV NET Steps	93		43 46%		44	1	98%	40	22
	48	45	18 38%	25 56%					
PN Evergreen Treatment Services	66		32 48%		34	2	94%	28	17
	44	22	18 41%	14 64%					
OR/HI CODA	102		37 36%		43	6	86%	37	20
	60	42	14 23%	23 55%					
NE CT Counseling Centers	71		26 37%		30	4	87%	23	12
	46	25	9 20%	17 68%					
NY ARTC	2								
	2	NA							
All Sites	681		362 53%		383	21	95%	338	218
	353	328	122 35%	240 73%					

CTP	TOTAL START Completers (Evaluables) (thru 3/31/08)		OF TOTAL START COMPLETERS (EVALUABLES)									
	Completed PRIOR TO Start of Genetics	Completed AFTER Start of Genetics	%OF COMP MISSED	# INVITED	# REFUSED	# CONSENTED	% AGREED	%OF ALL COMP ENROLLED	%OF POSSIBLE COMP ENROLLED	# Week 2 collected	# Week 12 collected
PA Matrix Institute	18		0%	18	3	15	83%	83%	83%	15	14
	0	18									
NE Hartford Dispensary	40		8%	36	3	33	92%	83%	89%	32	28
	3	37									
PA BAART	38		26%	28	1	27	96%	71%	96%	27	26
	10	28									
CA/AZ Bi-Valley	49		33%	32	0	32	100%	65%	97%	32	32
	16	33									
DVNET Steps	30		10%	20	0	20	100%	67%	77%	19	15
	4	26									
PN Evergreen Treatment Services	37		32%	24	2	22	92%	59%	88%	21	12
	12	25									
CRI-H CODA	35		34%	22	4	18	82%	51%	78%	18	12
	12	23									
NE CT Counseling Centers	32		56%	10	1	9	90%	28%	64%	7	3
	18	14									
NY ARTC	0										
	NA	NA									
All Sites	279		27%	190	14	176	93%	63%	86%	171	142
	75	204									

Main START study status as of 3/31/08:

681 participants had been randomized

Of all randomized START participants as of 3/31/08:

- Some began before genetics endorsed at site
- Some had dropped out of START before genetics
- Some already completed START before genetics
- Ultimately 383 "invited" into genetics

Of these 383 START participants

- 95% agreed to participate in genetics
- Only 21 participants refused
- One participant withdrew his consent

95% of all randomized START invitees agreed

93% of all START "completers" invited agreed

***Demonstrates excellent work by research staff and great acceptance by study participants**

Levels of Consent

Level 1: Researchers may use my genetic material and medical information for the START genetics study ONLY.

Level 2: Researchers may use my genetic material & medical information for the START genetics study AND for future genetic studies of opioid dependence.

Level 3: Researchers may use my genetic material and medical information for the START genetics study AND for future genetic studies of opioid dependence, AND for future genetics studies of substance abuse and/or related medical problems.

Level 4: Researchers may use my genetic material and medical information for the START genetics study AND any kind of future genetics studies.

Levels of Consent

Level 1	6%
Level 2	4%
Level 3	23%
Level 4	66%
Unkn	1%

* Two sites max Level 3

The number who refused is very low and it's difficult to establish patterns as to why?

Some general feedback was along the lines of just not being comfortable with genetics research, we are looking at this more closely

Summary

- **Majority of eligible START participants who are invited to participate in the sub-study willingly agree to participate and sign consent to most liberal use of their genetic data.**

What can we say…

- Genetics studies can be successfully accepted and implemented in community treatment programs
- By any definition START Genetics is a great success

A really very special thanks:

Christie Thomas, M.P.H.- UCLA

Many thanks as well:

- Dr. Mary Jeanne Kreek
- All of the participating START CTPs
- Susan Sonne, Pharm.D. - MUSC
- Stephanie Gentilin, MA - MUSC
- Al Hasson, MSW UCLA - UCLA
- NIDA
- Blending Conference Program Committee

Key Personnel

- Wade Berrettini – PI for Repository Samples
- Lindsay DeVane – PI for MUSC Samples
- Andy Saxon – Liaison for START
- Susan Sonne – Co-Liaison for MUSC
- Stephanie Gentilin – MUSC Regulatory
- Jennifer Donovan – MUSC Coordinator
- Dana Witt – NIDA Repository Contact

I hope the hallucinations have stopped