The Modern Science of Addiction

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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol Use – ever</td>
<td>~ 260 million</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>~ 16.5 million</td>
</tr>
<tr>
<td>Marijuana Use – ever</td>
<td>~104 million</td>
</tr>
<tr>
<td>Marijuana Daily Use</td>
<td>~ 5.7 million</td>
</tr>
<tr>
<td>Cocaine Use – ever</td>
<td>~ 45.6 million</td>
</tr>
<tr>
<td>Cocaine Addiction</td>
<td>~ 2 to 3 million</td>
</tr>
<tr>
<td>Heroin Use – ever</td>
<td>~ 5.7 million</td>
</tr>
<tr>
<td>Heroin Addiction</td>
<td>~ 1 million</td>
</tr>
<tr>
<td>Illicit Use of Opiate Medication – ever</td>
<td>~ 37.1 million</td>
</tr>
<tr>
<td></td>
<td>(i.e., 14.2% of the population 12 and over)*</td>
</tr>
</tbody>
</table>

### 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

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

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)

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)

Source: National Center for Health Statistics, CDC Wonder

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
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

Drug-Induced Effects (very high)
- mRNA levels
- peptides
- proteomics
- neurochemistry
- synaptogenesis
- neuroneogenesis
- behaviors

Kreek et al., 2000; 2005; 2016
Natural History of Drug and Alcohol Abuse and Addictions

Primary Prevention  Possible Utility of Vaccines and Selected Medications  Medications Useful and Needed

60%-90% without pharmacotherapy relapse to addiction

Initial Use of Drug of Abuse  Sporadic Intermittent Use  Regular Use  Addiction  Early Withdrawal (abstinence)  Protracted Abstinence

10%-40% sustain abstinence with no specific medications

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


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

<table>
<thead>
<tr>
<th>Functional State (Heroin)</th>
<th>Functional State (Methadone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;High&quot;</td>
<td>&quot;High&quot;</td>
</tr>
<tr>
<td>&quot;Straight&quot;</td>
<td>&quot;Straight&quot;</td>
</tr>
<tr>
<td>&quot;Sick&quot;</td>
<td>&quot;Sick&quot;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic Bioavailability After Oral Administration</th>
<th>Apparent Plasma Terminal Half-life ($t_{1/2}$ Beta)</th>
<th>Major Route of Biotransformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited (&lt;30%)</td>
<td>3 min (30 min for active 6 acetyl morphine metabolite; 4 6 h for morphine and active morphine 6 glucuronide metabolite)</td>
<td>Successive deacetylation and morphine glucuronidation</td>
</tr>
<tr>
<td>Essentially Complete (&gt;70%)</td>
<td>24 h (48 h for active <a href="l">R</a> enantiomer)</td>
<td>N demethylation</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Facilities</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone Maintenance Treatment</td>
<td>1,282</td>
<td>330,308</td>
</tr>
<tr>
<td>Buprenorphine Maintenance Treatment</td>
<td>3,113</td>
<td>48,148</td>
</tr>
<tr>
<td>Extended Release Naltrexone Treatment</td>
<td>1,718</td>
<td>3,781</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Wang et al., 1999
Natural Dynorphin A<sub>1-17</sub> Lowers Basal and Cocaine Induced Dopamine Levels in Mouse Striatum

Dopamine in Dialysate (nM)

Dynorphin Dose (nmol)
- 0
- 2.0
- 1.0
- 4.4
- 4.4+nBNI (antagonist)

Infusion and Injection
- Control
- Cocaine (15mg/kg)
- Dynorphin (4.4nmol) + Cocaine (15mg/kg)

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

Endogenous Opioids (mu – inhibition) (kappa – ? activation)

Mu Opioid Receptor Antagonists

CRF

Arginine Vasopressin

β-End (↑)

ACTH (↑)

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 opiate (e.g., heroin addiction)
- Opiate withdrawal effects *
- Opioid antagonist effects
- Cocaine effects *
- Alcohol effects
- Chronic effects of long-acting opiate (e.g. methadone in maintenance treatment)

* 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)

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

Percent Bound

Log [\beta Endorphin (M)]

-11 -10 -9 -8 -7

0 20 40 60 80 100

Fraction Maximum Current Response

Log [\beta Endorphin (M)]

-9 -8 -7 -6

0 0.5 1.0

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 Psycyh, 65:135, 2008
### Association Between a Functional Polymorphism in the mu Opioid Receptor Gene and Opiate Addiction and also Alcoholism in Central Sweden

<table>
<thead>
<tr>
<th></th>
<th>Opiate Dependent (n=139)</th>
<th>Control (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G; A/G</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>A/A</td>
<td>98</td>
<td>147</td>
</tr>
<tr>
<td>118G Allele Frequency</td>
<td>0.155</td>
<td>0.074</td>
</tr>
</tbody>
</table>

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%)


<table>
<thead>
<tr>
<th></th>
<th>Alcohol Dependent (n=389)</th>
<th>Control (n=170)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G; A/G</td>
<td>90</td>
<td>23</td>
</tr>
<tr>
<td>A/A</td>
<td>299</td>
<td>147</td>
</tr>
<tr>
<td>118G Allele Frequency</td>
<td><strong>0.125</strong></td>
<td>0.074</td>
</tr>
</tbody>
</table>

*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%)

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

Females

<table>
<thead>
<tr>
<th></th>
<th>10mg/kg Heroin</th>
<th>20mg/kg Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (6)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>AA (6)</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

Males

<table>
<thead>
<tr>
<th></th>
<th>10mg/kg Heroin</th>
<th>20mg/kg Heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG (6)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>AA (7)</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Genes</th>
<th>Variant</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPRM1 (mu opioid receptor)</td>
<td>A118G (rs1799971)</td>
<td>e.g, Bond… Kreek and Yu, 1998; Stadlin et al., 2001; Haerian and Haerian, 2013</td>
</tr>
<tr>
<td>OPRD1 (delta opioid receptor)</td>
<td>rs2236861, rs3766951, rs2236857</td>
<td>Levran et al., 2008; Beer et al., 2013; Nelson et al., 2014</td>
</tr>
<tr>
<td>OPRK1 (kappa opioid receptor)</td>
<td>NSV*</td>
<td>Yuferov et al., 2004; Levran et al., 2009; Kumar et al., 2012</td>
</tr>
<tr>
<td>PDYN (dynorphin peptide)</td>
<td>NSV*</td>
<td>Wei et al., 2011; Clarke et al., 2012</td>
</tr>
<tr>
<td>AVPR1A (arginine vasopressin receptor 1A)</td>
<td>rs11174811; rs1587097; rs10784339</td>
<td>Maher et al., 2011; Levran et al., 2014</td>
</tr>
<tr>
<td>FKBP5 (FK506-binding protein 5/ corticosterone chaperone)</td>
<td>rs1360780; rs3800373</td>
<td>Levran et al., 2014a; Levran et al., 2014b</td>
</tr>
<tr>
<td>GAL (galanin)</td>
<td>rs694066</td>
<td>Maher et al., 2011, Levran et al., 2014</td>
</tr>
</tbody>
</table>

*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