Methadone and Beyond:
Medication and its Role in Treating Addiction

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Blending Clinical Practice and Research:
Forging Partnerships to Enhance
Drug Addiction Treatment

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Hypothesis (1963–1964)

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.
Impact of Short-Acting Heroin As Used on a Chronic Basis in Humans - 1964 Study

Dole, Nyswander and Kreek, 1966
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

- Orally effective
- Slow onset of action
- Long duration of action
- Slow offset of action

# Heroin versus Methadone*

<table>
<thead>
<tr>
<th></th>
<th>Heroin</th>
<th>Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>intravenous</td>
<td>oral</td>
</tr>
<tr>
<td>Onset of action</td>
<td>immediate</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Duration of action</td>
<td>3–6 hrs</td>
<td>24–36 hrs</td>
</tr>
<tr>
<td>Euphoria</td>
<td>first 1–2 hrs</td>
<td>none</td>
</tr>
<tr>
<td>Withdrawal symptoms</td>
<td>after 3–4 hrs</td>
<td>after 24 hrs</td>
</tr>
</tbody>
</table>

* effects of high dosages in tolerant individuals

Kreek, 1973; 1976; 1987
Long-Acting Methadone Administered on a Chronic Basis in Humans - 1964 Study

Dole, Nyswander and Kreek, 1966
Plasma Methadone Levels in an Individual Maintained on 100 mg/day

# Opioid Agonist Pharmacokinetics: Heroin Versus Methadone

<table>
<thead>
<tr>
<th>Compound</th>
<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>Heroin</td>
<td>Limited (&lt;30%)</td>
<td>3 m (30 m for active 6-actyl-morphine metabolite) (4-6 for active morphine metabolite)</td>
<td>Successive deacetylation and morphine glucuronidation</td>
</tr>
<tr>
<td>Methadone</td>
<td>Essentially Complete (&gt;70%)</td>
<td>24 h (48 h for active $l$-enantiomer)</td>
<td>N-demethylation</td>
</tr>
</tbody>
</table>

“On-Off” versus “Steady-State”

Disruption versus Normalization

• levels of gene expression
• receptor mediated events
• physiology
• behaviors

Kreek, 1987; 2001
Early Formal Linkage Between Academic Centers and Community-Based Treatment Programs

1969  Initiation of special research-based methadone maintenance treatment program for youthful (16 to 21 yo) long-term heroin addicts (more than 3 years of multiple, daily self-administrations of heroin) (*Dole, Nyswander, and Kreek, later joined by Millman and Khuri at the Rockefeller Hospital*)

1971  Relocation of this “Adolescent Development Program” as a community-based treatment facility, with ties to Cornell-New York Hospital and continuing ties to Rockefeller University (*ADP headed by Drs. R. Millman and E. Khuri*)

1973  Creation of a second, separate community-based methadone maintenance treatment facility, the “Adult Clinic”, for adult long-term heroin addicts, also with ties both to Cornell-New York Hospital and to the Rockefeller University (*AC headed by Dr. Aaron Wells*)

Kreek, 2002
Methadone Maintenance Treatment for Opiate (Heroin) Addiction

Number of patients in treatment: 179,000

Efficacy in “good” treatment programs using adequate doses:

Voluntary retention in treatment *(1 year or more)* 60 – 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 mu receptor sites *(methadone found to be a full mu opioid receptor agonist which internalizes like endorphins and which also has modest NMDA receptor complex antagonism)*

Kreek, 1972; 1973; 2001; 2002; Inturrisi et al, in progress; Evans et al; in progress

Percent of IV Drug Users Infected with HIV-1

Kreek et al., 1984; Des Jarlais et al., 1984; 1989

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, 1984; Des Jarlais et al., 1984; 1989
Co-Infection Status - Hepatitis C and HIV-1 in Methadone Maintained Patients

- HCV-/HIV+ 0.5%
- HCV+/HIV+ 25.9%
- HCV+/HIV- 40.8%
- HCV-/HIV- 32.8%

Piccolo, 2001
Factors Contributing to Vulnerability to Develop a Specific Addiction

- Use of the drug of abuse essential (100%)
- Environmental (very high)
- Genetic (25-40%)
- Drug-induced effects (very high)

Kreek et al., 2000
<table>
<thead>
<tr>
<th>Drug</th>
<th>Category</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>Depressant</td>
<td>Acts primarily on endogenous opioid system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also affects dopaminergic system</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Stimulant</td>
<td>Acts primarily on dopaminergic system, as well as on serotonergic and noradrenergic systems</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also affects opioid system</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Stimulant &amp; Depressant</td>
<td>Undefined primary site of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Affects dopaminergic, serotonergic and opioid systems</td>
</tr>
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</table>

Endogenous Opioids and Their Receptors

<table>
<thead>
<tr>
<th>Opioid Classes</th>
<th>Opioid Receptor Types</th>
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<tbody>
<tr>
<td>Endorphins</td>
<td>Mu</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>Delta</td>
</tr>
<tr>
<td>Dynorphins</td>
<td>Kappa</td>
</tr>
<tr>
<td>Endomorphins (?)</td>
<td></td>
</tr>
</tbody>
</table>

Kreek, 2001
Human Opioid Receptors $\mu$, $\delta$, and $\kappa$

LaForge, Yuferov and Kreek, 2000
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.

Genetic, environmental and direct drug effects may each contribute to this atypical stress responsivity.

Kreek, 1972; 1987; 1992; 2001
Hypothalamic-Pituitary-Adrenal Axis and the Endogenous Opioid System Have Interrelated Roles in the Biology of Addictive Diseases

Neuroendocrine Effects of Opiates, Cocaine, and Alcohol in Humans: Hormones Involved in Stress Response

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g. heroin addiction)
  - Suppression of HPA Axis
- Opiate withdrawal effects
- Opioid antagonist effects
- Cocaine effects
- Alcohol effects
  - Activation of HPA Axis
- Chronic effects of long-acting opiate (e.g. methadone maintenance treatment)
  - Normalization of HPA Axis

HPA – Hypothalamic-pituitary-adrenal axis (involved in stress response)

Kreek, 1972; 1973; 1987; 1992; 2001
Metyrapone Testing: a Chemically-Induced “Stress”

- Heroin addicts
  - hyporesponsive
- Methadone maintained former heroin addicts
  - eureponsive
- Drug-free, opioid medication-free former heroin addicts
  - hyperresponsive
- Cocaine addicts- recently abstinent
  - hyperresponsive
- Cocaine addicted, methadone maintained former heroin addicts
  - hyperresponsive

Kreek, 1972; 1973; 1984; 1987; 1992; Kreek et al., 1984; Schluger et al., 2001
[\textsuperscript{18}F] Cyclofoxy (a Selective Opioid Antagonist) Binding in Human Brain: Normal Volunteer PET Study - NIH

Eckelman, Rice and the NIH PET group, 2000
Plasma Methadone Levels in Long-Term, Methadone-Treatment Patients Sampled Across the 90-min PET Scan Session: 22.5 to 24h After Last Oral Dose of Methadone

Kling et al., 2000
Selected Regions of Interest for Addictive Disease and Pain Research: PET Imaging Using $[^{18}F]$ Cyclofoxy

Control Subjects (NV) and Methadone Maintained Patients

- Normal Volunteers (n=14)
- MTP volunteers (n=14)

Specific Binding

Region of Interest (ROI):
- Thl
- Amy
- Cau
- Ins
- ACg
- Put

*Kling et al., 2000*
[^18F] Cyclofoxy (a Selective Opioid Antagonist) Binding in Human Brain

Normal Volunteer

Methadone Maintained Patient Volunteer

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
- Immunoglobulin Levels (M and G)

Hypothesis: Genetic Variability and the Opioid System

Some of the individual genetic variability in susceptibility to the development and persistence of, or relapse to, opiate addiction may be due to polymorphisms of the mu opioid receptor.

Also, individual differences in responses to endogenous opioids ("physiogenetics") or pharmacotherapies ("pharmacogenetics") may be mediated by variant forms of the mu opioid receptor.

LaForge, Yuferov and Kreek, 2000
Human Gene Diversity: Single Nucleotide Polymorphisms (SNPs) in Genes

• SNP — a single nucleotide polymorphism, that is, one nucleotide or base of any base pair that is different from the “usual”, “prototypic”, (or first identified and recorded base)

• Coding region — that part of a gene which codes for a peptide (protein)

• Allelic Frequency:
  - <1% low or rare
  - 1–5% intermediate
  - >5% high or frequent
### Three Single Nucleotide Polymorphisms in Human Mu Opioid Receptor Gene

<table>
<thead>
<tr>
<th>Variant (nucleotide position)</th>
<th>Exon location</th>
<th>Protein domain</th>
<th>Corresponding amino acid change</th>
<th>Allele frequency</th>
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<tbody>
<tr>
<td>A118G</td>
<td>1</td>
<td>N-terminus</td>
<td>Asn 4 Asp (N40D)</td>
<td>10.5%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(26 heterozygous; 3 homozygous)</td>
</tr>
<tr>
<td>C17T</td>
<td>1</td>
<td>N-terminus</td>
<td>Ala 6 Val (A6V)</td>
<td>6.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(14 heterozygous; 3 homozygous)</td>
</tr>
<tr>
<td>G24A</td>
<td>1</td>
<td>N-terminus</td>
<td>Synonymous mutation</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(6 heterozygous)</td>
</tr>
</tbody>
</table>

* Nucleotide position 1 is first base of the start codon.

Bond et al., 1998
Human MOR Gene SNPs

SNPs with changed AA

Synonymous mutation

Putative Glycosylation site

Kreek, Yuferov and LaForge, 2000
Mu Opioid Receptor Gene: Evidence of Association or Linkage With Addictions

Alcohol Dependence
- For: Town, et al., 1999
- No Evidence For: Bergen, et al., 1997; Kranzler et al., 1998; Sander et al., 1998; Gelernter et al., 1999; Gscheidel et al., 2000.

Opioid Dependence
- For: Bond et al., 1998; Szeto et al., 2001.
- No Evidence For: Kranzler et al., 1998; Li et al., 2000; Franke et al., 2001.

Mixed Drug Dependence
- For: Berrettini et al., 1997; Hoeho et al., 1997.
- No Evidence for: Kranzler et al., 1998; Gelernter et al., 1999

adapted from K.S. LaForge, 2001
Pharmacotherapies for Specific Addictive Diseases

I. Opiate Addiction (primarily Heroin Addiction)*
   a. Methadone (mu-opioid receptor agonist)
   b. LAAM (mu-opioid receptor agonist)
   c. Buprenorphine + Naloxone (partial mu-opioid receptor agonist + a non-orally bioavailable mu opioid antagonist)
   d. (Naltrexone[mu-opioid receptor antagonist])**

II. Alcoholism**
   a. Naltrexone (mu-plus kappa receptor antagonist)
   b. Nalmefene (mu-plus kappa-opioid receptor antagonist)
   c. Acamprosate (NMDA antagonist)

III. Cocaine, Amphetamines and Other Stimulants Addictions
     NONE

IV. Nicotine Addiction **
   a. Nicotine replacement (patch; gum; inhaler; other nicotine delivery systems)
   b. Bupropion

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* Effective in >60% of unselected persons (high)
** Effective in >30% to 50% of unselected persons (moderate)
*** Effective in >15% of unselected persons (low)

Kreek, 2000
Future of the Role of Medications in Treating Addictions: A Few Major Needs

1) Broad acceptance of need for and implementation of combined pharmacotherapy (specific, targeted, safe, and effective) and counseling and other behavioral treatments (specific, as well as general, and effective), each in “adequate doses”, in the treatment of many long-term drug abusers and addicts, entering into and during chronic recovery.

2) Reduction (and ultimately eradication) of stigma against former drug abusers and addicts in various forms and stages of effective treatment and thus recovery, along with increased resources (fiscal and manpower) for treatment.

3) Expansion and enhancement of bidirectional (clinical-laboratory) input and support of research (neurobiological, molecular, genetic, and behavioral, as well as prevention and treatment research) for future development of improved primary prevention, early intervention, and treatment approaches.

Kreek, 2002
<table>
<thead>
<tr>
<th>Laboratory Scientists</th>
<th>Clinical Scientists</th>
<th>Administrative Staff</th>
<th>Assistants for Research</th>
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<tbody>
<tr>
<td>Ann Ho</td>
<td>Gavin Bart</td>
<td>Karen Perry</td>
<td>Abena Amoah</td>
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<tr>
<td>K. Steven LaForge</td>
<td>Lisa Borg</td>
<td>Susan Russo</td>
<td>Jonathan Ball</td>
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<td>Eduardo Butelman</td>
<td>Mark Green</td>
<td>Kitt Lavoie</td>
<td>Wan-Xin Feng</td>
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<td>Vadim Yuferov</td>
<td>Scott Kellogg</td>
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<td>David Fussell</td>
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<td>Yan Zhou</td>
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<td>Stefan Schlussman</td>
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<td>Yong Zhang</td>
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<td>Andrew Chen</td>
<td>Clinical Adjunct Scientists</td>
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<tr>
<td>Dmitri Proudnikov</td>
<td>Paola Piccolo</td>
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<td>Brian Reed</td>
<td>Joan Culpepper-Morgan</td>
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<td>Lawrence Brown</td>
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<tr>
<td>Ellen Unterwald</td>
<td>Research Nurses</td>
<td>Laboratory Worker</td>
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<td>Vanya Quinones-Jenab</td>
<td>Kathy Bell</td>
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<tr>
<td>Charles Inturrisi</td>
<td>Elizabeth Ducat</td>
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