What Science Can Teach Us About The Treatment of Alcohol Use Disorders

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In 2017, 5.7% (14.1 million) of people 18+ reached criteria for alcohol use disorder (AUD)

~ 88,000 people die annually from alcohol-related causes

~ 50% of all liver disease deaths attributable to alcohol misuse

Increase in the intensity of binge drinking, ED visits and hospitalizations in last 10 years

<10% of people with AUD get any treatment and fewer than 4% receive pharmacotherapy

“Deaths of Despair”

All-cause mortality, ages 45-54 for US White non-Hispanic (USW), US Hispanics (USH) and six comparison countries

Increase in mortality among US White non-Hispanics aged 45-54

Deaths per 100,000

Year

Flow of Talk

1. **The Science:** Neurocircuitry Overview of Alcohol Use Disorder (AUD) - Neurofunctional domains, Hyperkatifeia

3. **Diagnosis:** Addiction Neuroclinical Assessment, Alcohol Biosensor

4. **Treatment:** Novel Treatments for AUD and ALD

5. **Emerging Challenges for AUD:** Extreme Binge Drinking, Drinking in Women and Aged, AUD and Comorbidity, Pain and AUD, Sleep and AUD, and Medical Education
Drug Addiction

Addiction — Defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability, defined as “hyperkatifeia”) when access to the drug is prevented.
Conceptual Framework for Neurobiological Bases Driving Substance Use Disorders

Hyperkatifeia

1. Defined as the increased intensity of negative emotional/motivational symptoms and signs observed during withdrawal from abused drugs

2. Derived from the Greek word *katifeia* for dejection, sadness, or negative emotional state

3. “Hyperkatifeia” refers to the increases in emotional distress and emotional pain experienced by individuals with addiction during abstinence.

4. “Hyperkatifeia” is hypothesized to represent elements such as dysphoria, irritability, alexithymia, or simply symptoms often described as ill at ease, uncomfortable within one’s own skin, or simply not hedonically normal, symptoms historically difficult to define.

Positive and Negative Reinforcement - Definitions

Positive Reinforcement — the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug taking paradigms).

Negative Reinforcement — a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal - defined as “hyperkatifeia”) increases the probability of a response (dependence-induced drug taking).
Etiology of Addiction

Progression of the Addictive Process

Individual factors: Genetics, Life Stress

Reward
- DA, 5-HT, GABA, GLU
- Opioid Peptides
- Glucocorticoids

Dependence
- Dysregulation of reward neurotransmitters
- Dysregulation of Brain Stress Systems
  - CRF, Dynorphin, Substance P, Hypocretin, NPY, Nociceptin, Oxytocin
  - Glucocorticoids

Relapse
- Glutamate
- Dopamine
- CRF
- Glucocorticoids

Escalating/Compulsive Use

Dependence/Withdrawal

Protracted Abstinence

Relapse
Neurocircuitry/ Neurochemistry of the Withdrawal Negative Affect Stage

Stress Neurotransmitters
- Corticotropin-releasing factor (CRF)
- Norepinephrine
- Dynorphin
- Vasopressin
- Orexin (hypocretin)
- Substance P
- Glucocorticoids
- Neuroimmune factors

Anti-stress neurotransmitters
- Neuropeptide Y
- Nociceptin (orphanin FQ)
- Endocannabinoids
- Oxytocin

Diagnosis: Neuroclinical Assessment
Associations with Neurocircuits Provides a Framework for improved Diagnosis, Prevention and Treatment

Adapted from Koob. Curr Top Behav Neurosci. 2011

This study examined three key neurobiological domains that are critical to the addiction cycle (incentive salience, negative emotionality, and executive function) in a large, diverse clinical sample of individuals representing the spectrum of AUD.

Measures of addiction, personality, cognition, behavior, and exposure to early-life stress were collected. Using a multiple indicators, multiple causes approach, the study confirmed the relevance of the three neurofunctional domains to AUD.

Diagnosis: Wearable Alcohol Biosensor Challenges

• Winning prototype submitted by BACtrack, a company known for designing and selling portable breath alcohol testers for consumer use
  • Their entry, the BACtrack Skyn:
    – Worn on the wrist
    – Detects alcohol using a fuel cell technology similar to that used in roadside testing devices
    – Offers continuous, non-invasive BAC monitoring
    – Stores data to a smartphone via Bluetooth
  • Opportunity to spread the word - NIAAA will issue additional challenges to stimulate inventors to create and adapt different technologies that measure alcohol directly in blood or interstitial fluid for real time quantification in a wearable device.

1st Prize: $200,000
2nd Prize: $100,000
Treatment: Developing Medications to Treat AUD

- **NIAAA Division of Medications Development:**
  - **SBIR/STTR program** facilitates studies leading to FDA IND application
  - **Human laboratory screening studies** bridge gap between preclinical and clinical trials
  - **NIAAA Clinical Investigations Group (NCIG)** conducts “fast success/fast fail” phase II clinical trials with 18 month turn-around time
- **Intramural program** conducts clinical studies on novel compounds with AUD treatment potential

![Diagram showing the flow from Molecular Targets to Clinical Trials through Animal Models and Human Laboratory Models.](chart.png)
Treatment: Novel AUD Targets by Stage of the Addiction Cycle

Dopamine receptors (DRD2)
GABA_A receptors (GABRA2)
Opioid receptors (OPMR1)
Acetylcholine receptors (CNRNA5)
Glycine receptors (GLRA1)
Serotonin receptors (HTR3A)
Serine/Threonine Kinases (MTOR)
Cannabinoid receptors (CNR1)
GIRK channels (KCNJ6)

Norepinephrine receptor (ADRB2)
Hypocretin (Orexin) receptor (HCRTR1)
Neuropeptide Y receptor (NPY1R)
CRF receptor (CRHR1)
Kappa opioid receptor (OPRK1)
Substance P receptor (TACR1)
Nociceptin receptor (OPRL1)
Oxytocin receptor (OXTR)
Vasopressin receptor (AVPR1B)
Glucocorticoid receptor (NR3C1)
Neuroimmune factors (NFKB1)

Phosphodiesterases (PDE10A)
Protein kinases (PRKCE)
Transcription factors (CREB1, FOSB)
NMDA & AMPA receptors (GRIN2B, GRIA1)
Metabotropic glutamate receptors (GRM8)
Actin cytoskeleton (ACTB)
Matrix Metallopeptidase (MMP9)
Enabling of New Drug INDs for Development of Medications to Treat Alcohol Use Disorders (U44/UT2)

• Small business (SBIR) or Small business and academic partner (STTR) opportunity

• Purpose: Translating research discoveries into new treatments for AUD or alcohol related diseases by supporting efforts to achieve an IND.

• Mechanism: U44/UT2 – cooperative agreement – work closely with NIAAA Medication’s Development staff.

• Budget: Up to $1.0M total costs per year for Phase I and up to $1.5M total costs per year for Phase II may be requested.

Emerging Issues – Extreme Binge Drinking

**Binge drinking** – 4+ drinks for women, 5+ drinks for men, on an occasion

**Extreme binge drinking** – consuming 2 or more times these thresholds
  - Nearly 32 million adults engaged in extreme binge drinking

Emerging Issues – Alcohol and Women’s Health

- Gaps between women and men are narrowing for prevalence, frequency and intensity of drinking, early onset drinking, having AUD, drunk driving, and self-reported consequences (Slade et al., 2016; White et al., 2017)

- Women more likely to experience blackouts, liver inflammation, brain atrophy, cognitive deficits, certain cancers, and to experience negative affect during withdrawal and stress or anxiety-induced relapse (Becker and Koob, 2016)

- But we still know very little about why

- Out of 230 structural neuroimaging studies on substance use over 23 years only 26% evaluated sex differences (Lind et al., 2017)

Emerging Issues – More People Aged 65+ Are Drinking and Binge Drinking

Emerging Issues: Addressing AUD and Co-Occurring Conditions

- AUD frequently co-occurs with other SUDs and mental health conditions (e.g., depression, bipolar disorder, anxiety disorders, PTSD).

- AUD patients with co-occurring mental health conditions tend to have poorer prognosis.

- NIAAA supports research to elucidate the relationship between AUD and co-occurring conditions and develop preventive and treatment interventions.

- **FOA:** Alcohol-PTSD Co-morbidity: Preclinical Studies of Models and Mechanisms
  - Issued in collaboration with Cohen Veterans Bioscience
  - To develop, validate, or apply animal models for mechanistic studies of comorbid PTSD and AUD.
Emerging Issue: Alcohol Misuse Causes Pain and Pain Causes Alcohol Misuse

16-25% chronic pain patients drink heavily or have AUD

43%-73% of individuals with AUD have moderate to severe pain

Acute alcohol (at binge levels) is analgesic (relieves pain)
T Thompson et al. (2017) Journal of Pain

Chronic alcohol and withdrawal produce hyperalgesia (increased pain sensitivity)
S Edwards et al. (2012) Neuropharmacology

Adapted from Dr. Mark Egli, NIAAA
Emerging Issue: Alcohol Use Disorder and Sleep Disturbance – A Feed Forward Allostatic Framework

Koob and Colrain, Neuropsychopharmacology Reviews, In submission
Priority: Closing the Treatment Gap

• In the US, fewer than 10% of people with AUD receive any form of treatment
• Routine health care presents a unique opportunity for prevention, early intervention, and treatment of AUD
• However, many health care providers:
  – Do not perform alcohol screening
  – Are not aware of evidence-based treatments
  – Do not know where to refer patients for treatment

Goals

*Improve physician training in substance abuse prevention and treatment at all levels* and

*Integrate prevention, early intervention, and treatment into routine health care*
In Development: NIAAA Clinician’s Toolkit

• What every clinician needs to know about alcohol
  – Presentation in primary care
  – Role in common co-occurring conditions
  – Neuroscience
  – Alcohol misuse across the lifespan
  – Diagnostic criteria, recommended drinking limits
  – Alcohol withdrawal syndrome
  – Evidence-based therapies/medications
  – Addressing stigma
  – Interactions with commonly used medications

• Suggestions for practice
  – How to start the conversation
  – Clinician’s Guide, Screening Tools, Rethinking Drinking, etc.
Gaps in Translation

1. **The framework:** The neurofunctional domain encompassing the withdrawal/ negative affect stage has been neglected.

3. **Diagnosis:** Addiction Neuroclinical Assessment measures and better biomarkers are a first step.

4. **Treatment:** Need to bridge two valleys of death: IND and phase III; Need to educate the medical community.

5. **Emerging Challenges for AUD:** Extreme Binge Drinking, Drinking in Women and Aged, AUD and Comorbidity, Pain and AUD, Sleep and AUD.
NIAAA

Your source for credible, evidence-based information about prevention, diagnosis and treatment of alcohol use disorders

www.niaaa.nih.gov