CURRENT AND FUTURE CONSIDERATIONS FOR NON-ABSTINENCE OUTCOMES

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Disclosures:

Past 3 years I have consulted with Cessation Therapeutics and DemeRx and participated on a Study Steering Committee for Indivior

Research is funded by NIDA and Cure Addiction Now

OUTLINE

UNMET NEED AND CURRENT STRATEGIES

THE ALCOHOL FIELD AS AN EXAMPLE

UNIVERSAL OUTCOMES

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DSM-5 Criterion
Substance taken in greater amount than intended
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There is craving for the substance
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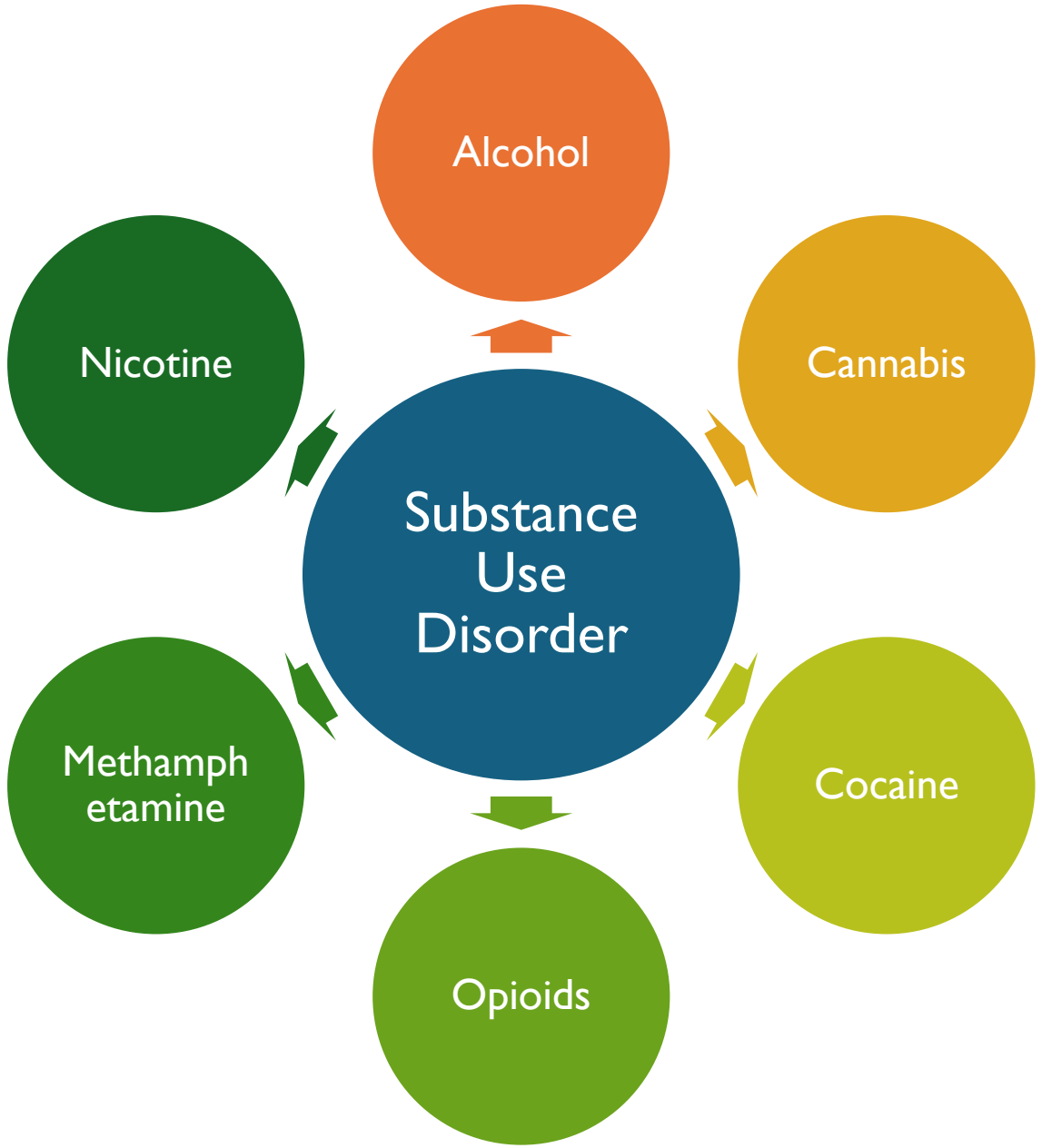
Use continues despite negative consequences in social and interpersonal situations
Valued social or work-related roles are stopped because of use
Repeated substance use occurs in potentially dangerous situations
Substance use not deterred by medical or psychiatric complication
Tolerance develops: increasing amount is needed to obtain effects
Withdrawal syndrome occurs or patient takes substance to prevent withdrawal

Lehman & Fingerhood, 2018, NEJM



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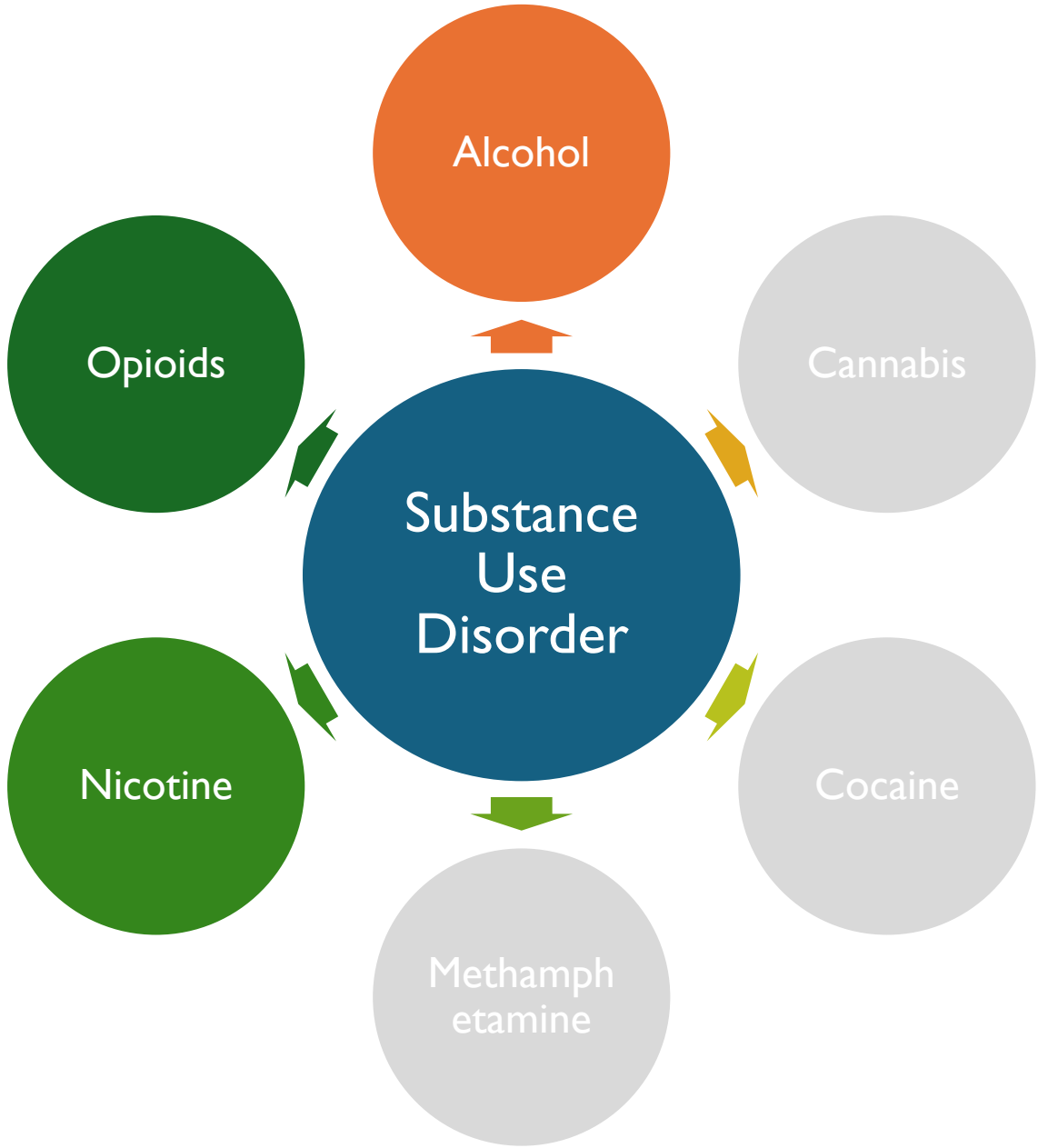
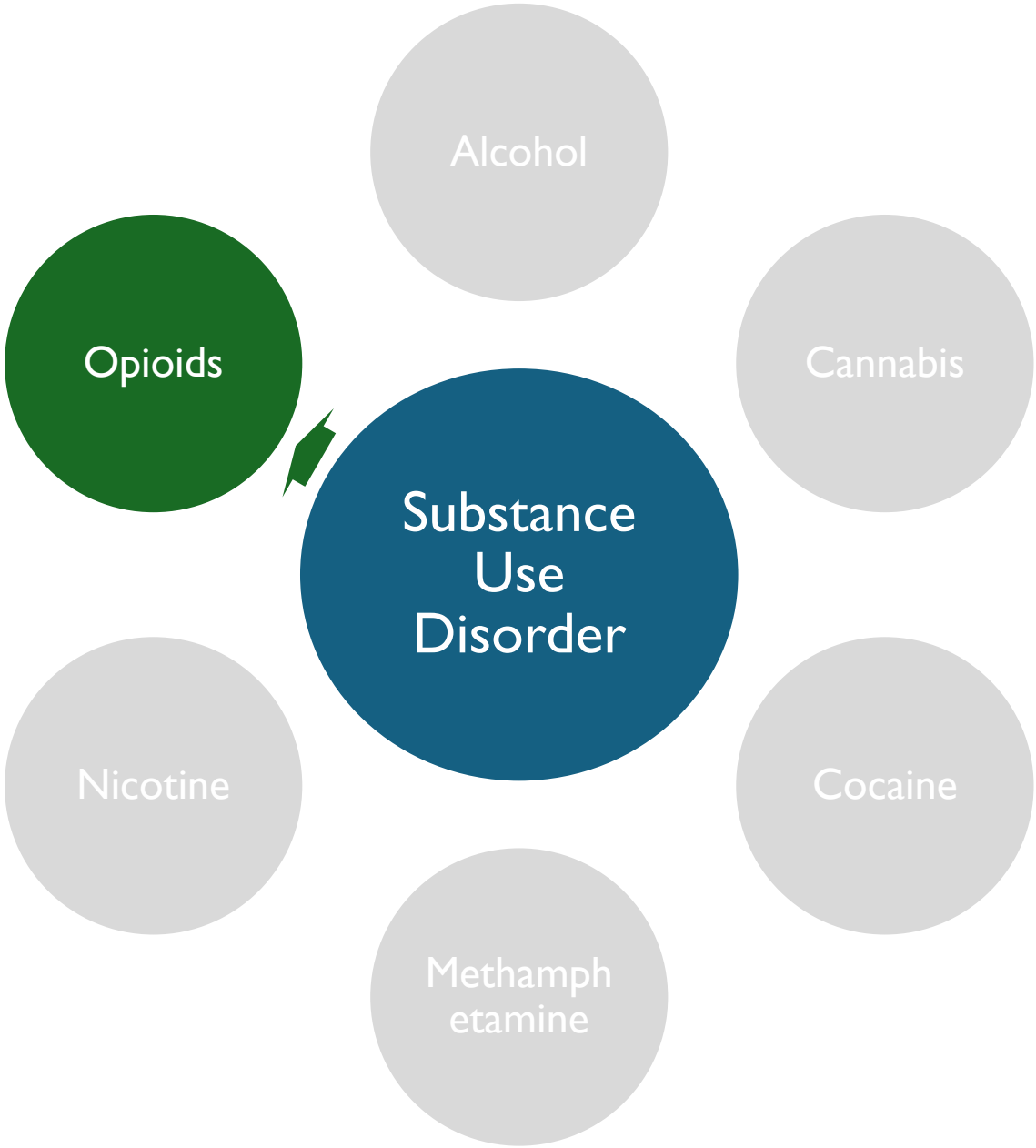


Methadone
Naltrexone
Buprenorphine
Lofexidine



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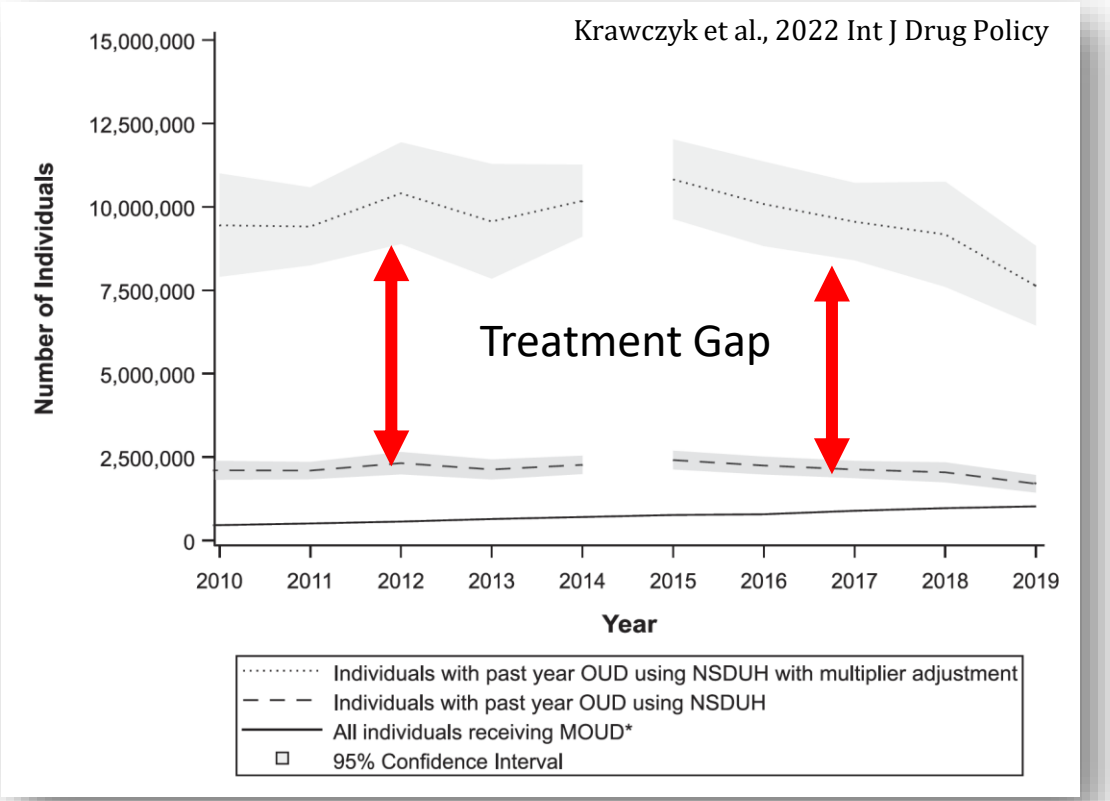
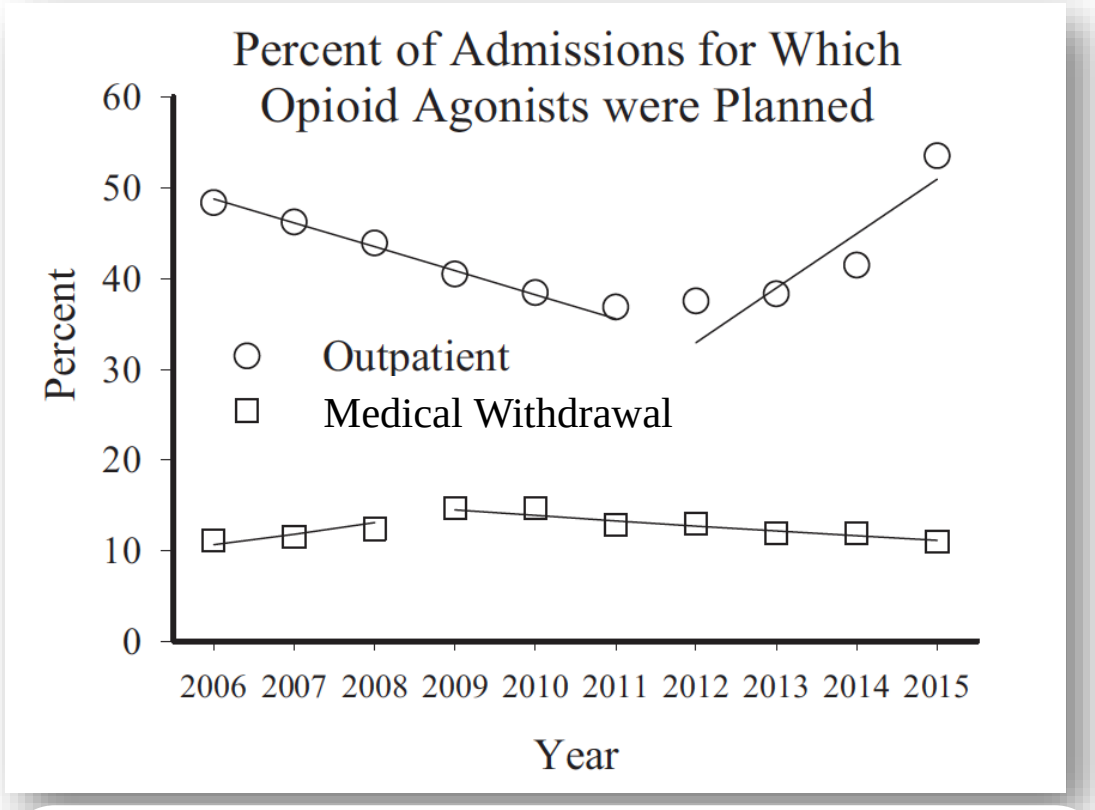
Large Treatment Gap and Huge Opportunity for Innovation



1. Millions of persons estimated to need but not be receiving opioid agonist treatment



2. Supervised withdrawal is the most common form of treatment, most do not provide opioid agonists

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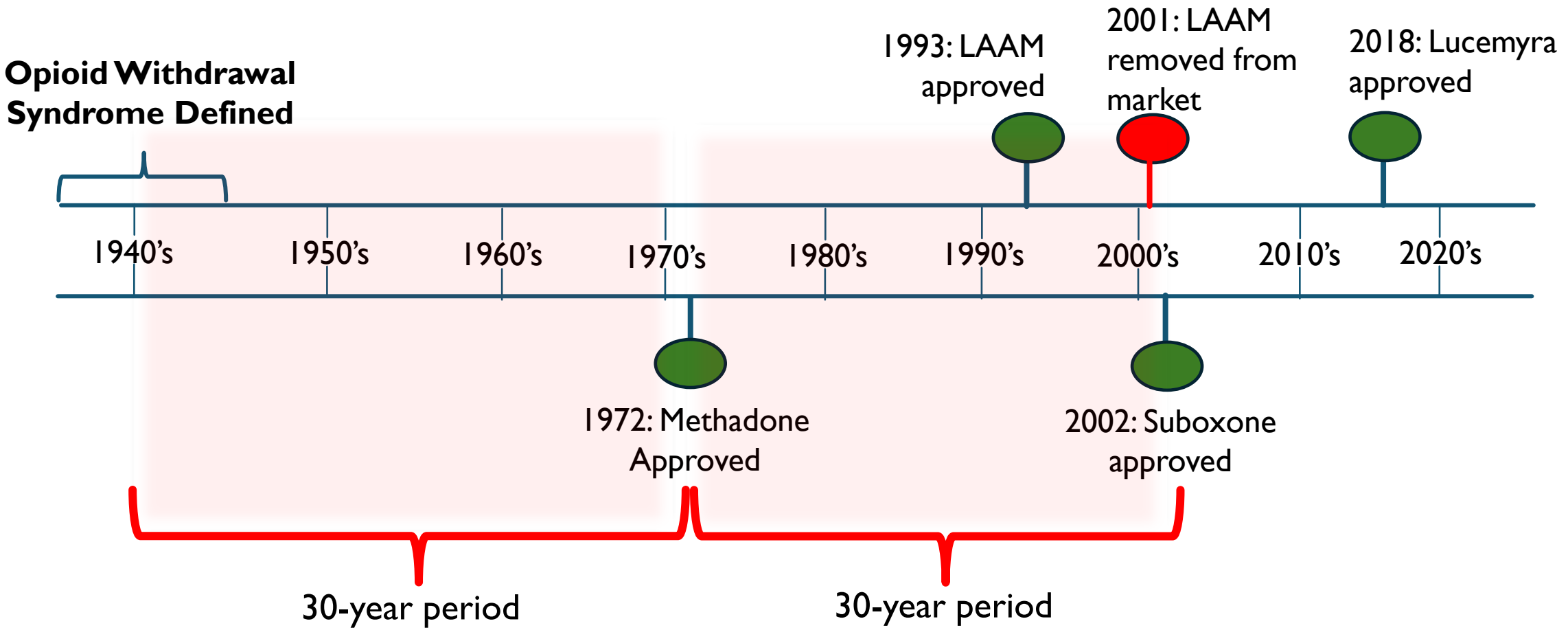
Drug discovery and innovation has been slow



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Especially relative to other conditions…

Table 1. FDA-Approved Antidepressants

Drug	Putative Mechanisms of Action
Fluoxetine	SSRI
Sertraline	SSRI; blocks DA reuptake at high doses
Paroxetine	SSRI; blocks NE reuptake at high doses
Fluvoxamine*	SSRI
Escitalopram	SSRI
Citalopram	SSRI
Vortioxetine	SSRI; 5-HT_{1A} agonist
Vilazodone	SSRI; 5-HT_{1A} partial agonist
Venlafaxine	SNRI
Duloxetine	SNRI
Levomilnacipran	SNRI
Bupropion	Unknown
Nortriptyline	TCA; primarily NE reuptake inhibitor
Imipramine	TCA; NE and 5-HT reuptake inhibitor
Amitriptyline	TCA; NE and 5-HT reuptake inhibitor
Maprotiline	Tetracyclic primarily NE reuptake inhibitor; no longer available in the U.S.
Clomipramine*	TCA; primarily 5-HT but also NE reuptake inhibitor
Protriptyline	TCA; primarily NE reuptake inhibitor
Desipramine	TCA; primarily NE reuptake inhibitor
Trimipramine	TCA; NE and 5-HT reuptake inhibitor
Phenelzine	MAOI
Tranylcypromine	MAOI
Isocarboxazid	MAOI
Selegiline Transdermal	MAOI
Mirtazapine	NASSA=alpha-2 antagonist; 5-HT_2 and 5-HT_3 antagonist
Esketamine	NMDA antagonist, MU opiate agonist

*Approved for OCD

Medicine for Depression

There are different kinds of medicine for depression.

- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)
- Tricyclic and Tetracyclic Antidepressants
- Atypical Antidepressants
- Monoamine Oxidase Inhibitors (MAOIs)
- N-methyl D-aspartate (NMDA) Antagonist
- Neuroactive Steroid Gamma-Aminobutyric Acid (GABA)-A Receptor Positive Modulator

https://psychnews.psychiatryonline.org/doi/10.1176/appi.pn.2021.11.14

https://www.fda.gov/media/132665/download

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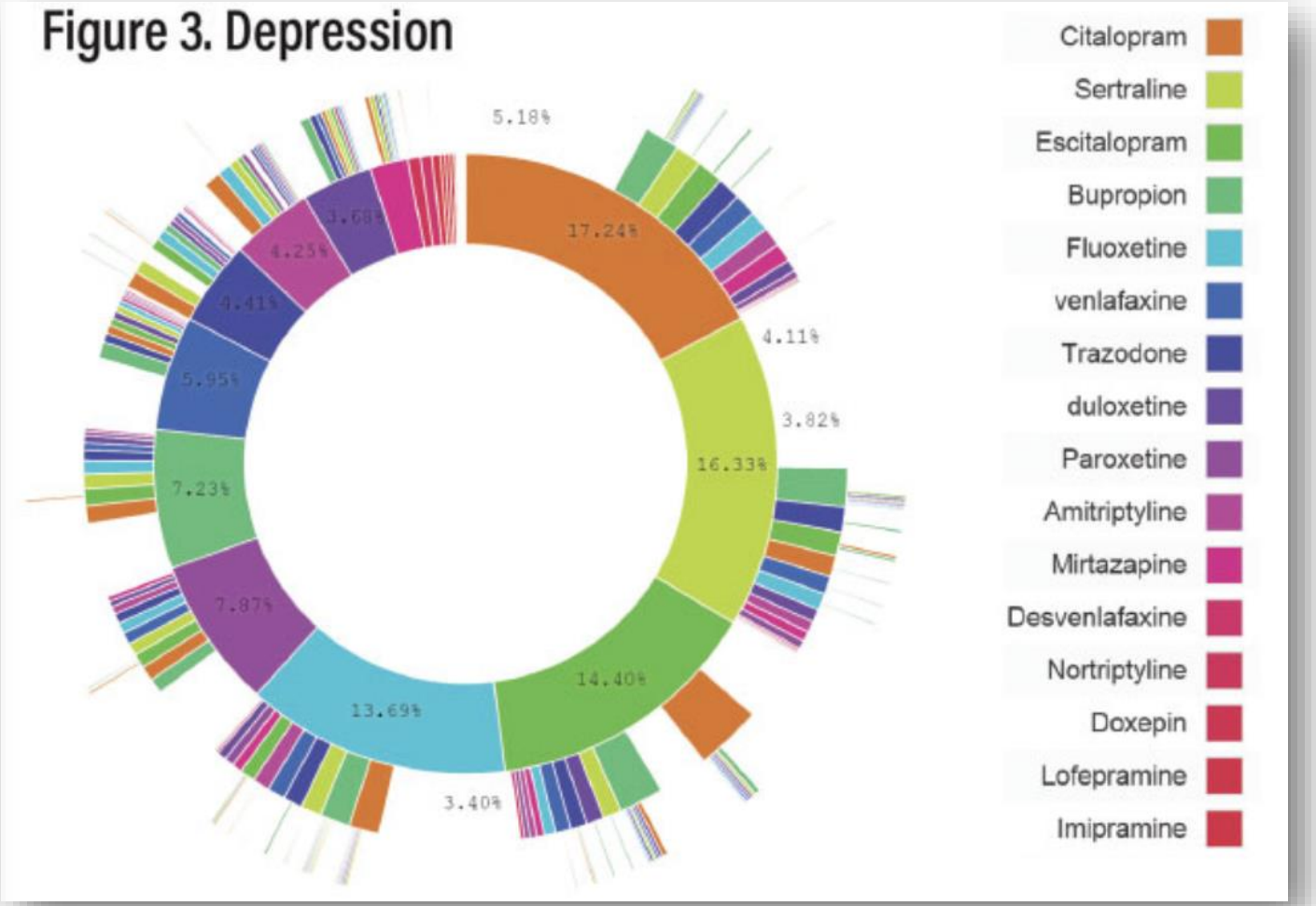

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Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2020
Clinical/Medical

Stimulant Use Disorders: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2023
Clinical/Medical

“In general, clinical trials evaluating effectiveness of drugs for treating OUD have used ***reduction in drug-taking behavior (drug use patterns)*** *as an endpoint.*

There is great interest in expanding the primary and secondary endpoints *used in clinical trials of drugs for treating OUD, including other outcome measures important to patients and their families, clinicians, and the public."*

Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment

Guidance for Industry

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October 2020
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Proportion of responders	• Prespecified, grace period permitted, cumulative responder curve
Adverse outcomes of OUD	• Changes in mortality, emergency interventions, infectious disease
Change in disease state	• Proportion of patients meeting DSM-5 criteria for remission of OUD
Change in drug use patterns	• Surrogate marker, urinalysis is a component of a responder definition
Patient reported outcomes	• Assess patient feeling or function
New entry to treatment	• Premised on challenges with the clinical condition in initiating treatment

Self-report	• Time-line followback
Urine toxicology	• Recognized as important, no guidance regarding frequency
Measures of treatment response	• Periods of nonuse or reductions in use
Change in pattern of stimulant use	• "Achieving a predefined pattern of use days per period of time"
Change in disease state	• Proportion of participants meeting early remission at end of trial
Clinical Outcome Assessments	• Change in craving, resumption of work or school, reduced justice interactions

Stimulant Use Disorders: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2023
Clinical/Medical

Additional Considerations

FDA recognizes the heterogeneity between these conditions and within stimulant use disorder

Emphasizes need for double-blind, RCTs

Does not recommend # of DSM-5 diagnostic criteria as an outcome

Recognizes urinalysis tests as *"surrogate markers"* because "they are not reflective of how a subject feels, functions, or survives"

OUTLINE

UNMET NEED AND CURRENT STRATEGIES

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UNIVERSAL OUTCOMES

Alcoholism: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2015
Clinical/Medical

Trials should measure the proportion of patients in each treatment group who attain, and sustain over the observation period, a target drinking pattern that is considered a valid surrogate for clinical benefit. The following two options can be used as target drinking patterns and do not need any additional data to support the pattern as a valid surrogate for clinical benefit. Sponsors should discuss other options with the division.

(1) **Abstinence.** As noted above, trials that use complete abstinence as the target drinking pattern can be used.

(2) **No Heavy Drinking.** Trials that use no heavy drinking as the target drinking pattern can be used. This is based on several lines of evidence that provide support for this pattern as a valid surrogate for clinical benefit. Several of these lines of support are from unpublished analyses, but there are also published studies that confirm these analyses. Support for this endpoint is summarized in Appendix 2.

Alcoholism:
Developing Drugs for Treatment
Guidance for Industry

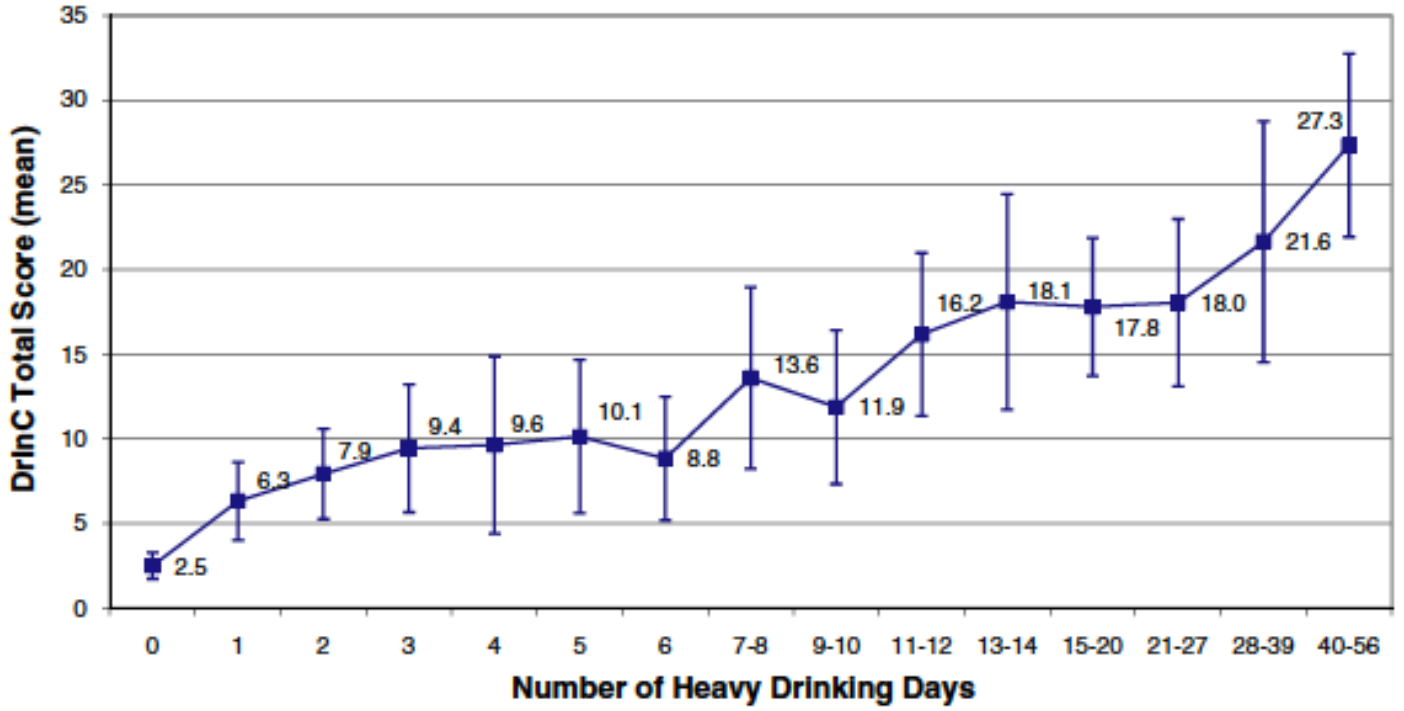
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2015
Clinical/Medical

- Secondary analyses conducted within two large uniform data sets
  - Combine study (n=1383)
  - Multisite topiramate study (n=373)
- Compared % subjects with no heavy drinking days (PSNHDD) to conventional measures
  - Defined as >3/>4 drinks per drinking day for women/men

PSNHDD Demonstrated:

- Similar performance and sensitivity relative to 7 traditional abstinence measures
- Strong association with drinking-related consequences

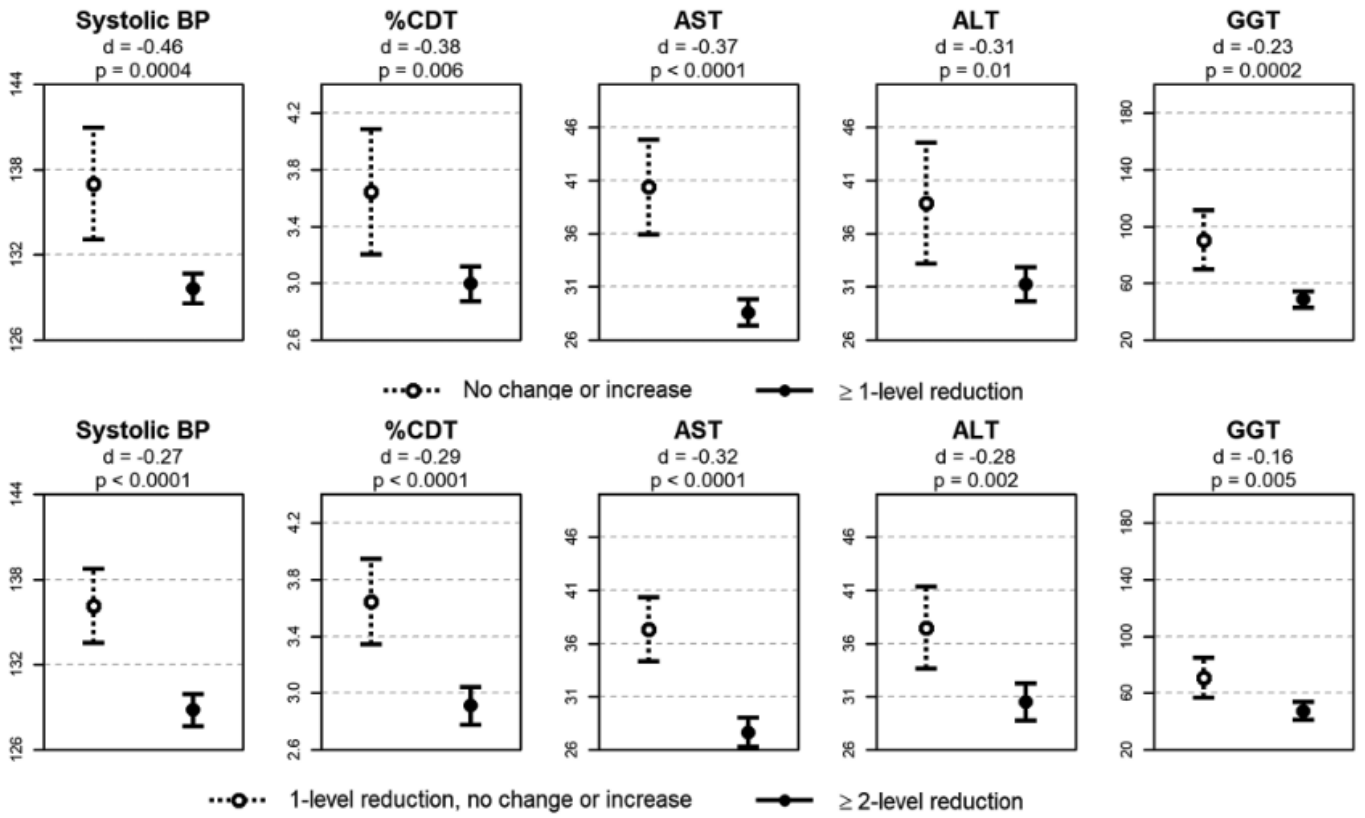


Alcoholism: Clinical and Experimental Research

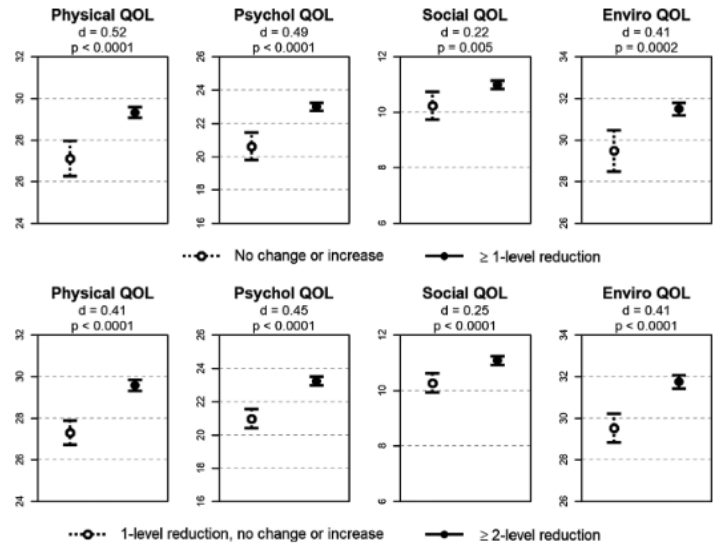
Vol. 34, No. 12
December 2010

Percentage of Subjects With No Heavy Drinking Days: Evaluation as an Efficacy Endpoint for Alcohol Clinical Trials

Daniel Falk, Xin Qun Wang, Lei Liu, Joanne Fertig, Margaret Mattson, Megan Ryan, Bankole Johnson, Robert Stout, and Raye Z. Litten



1 or 2 step decreases in WHO drinking levels associated with significant reductions in several biomarkers…

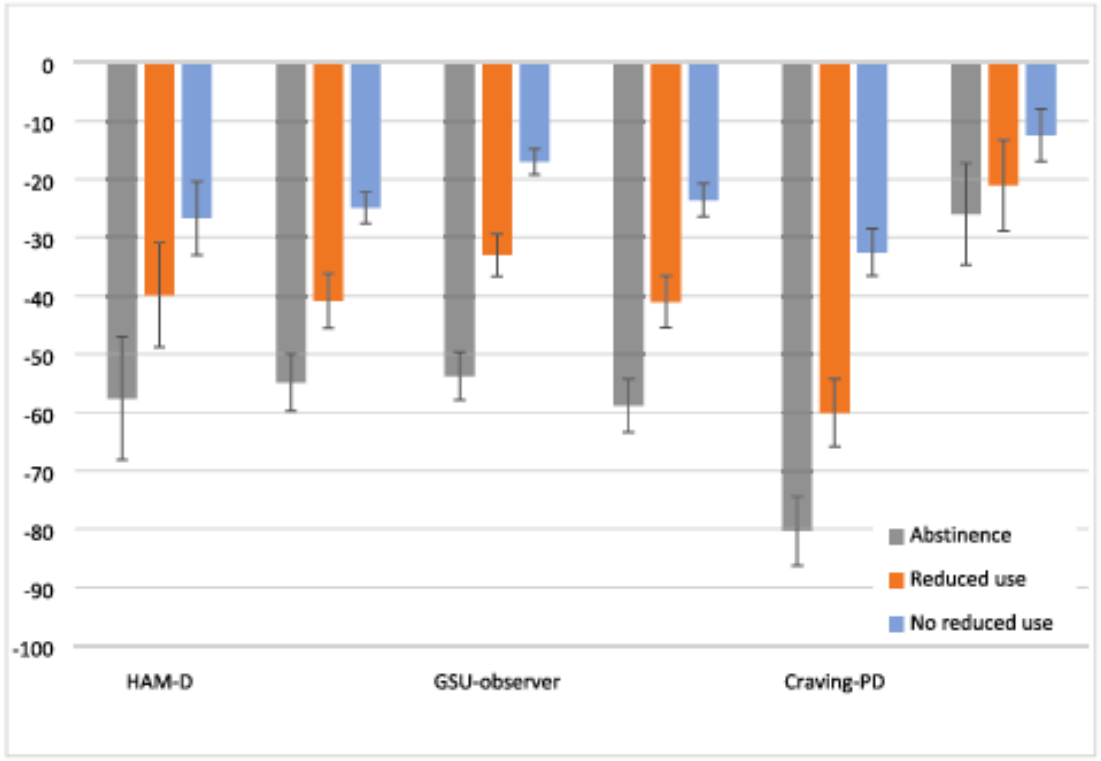


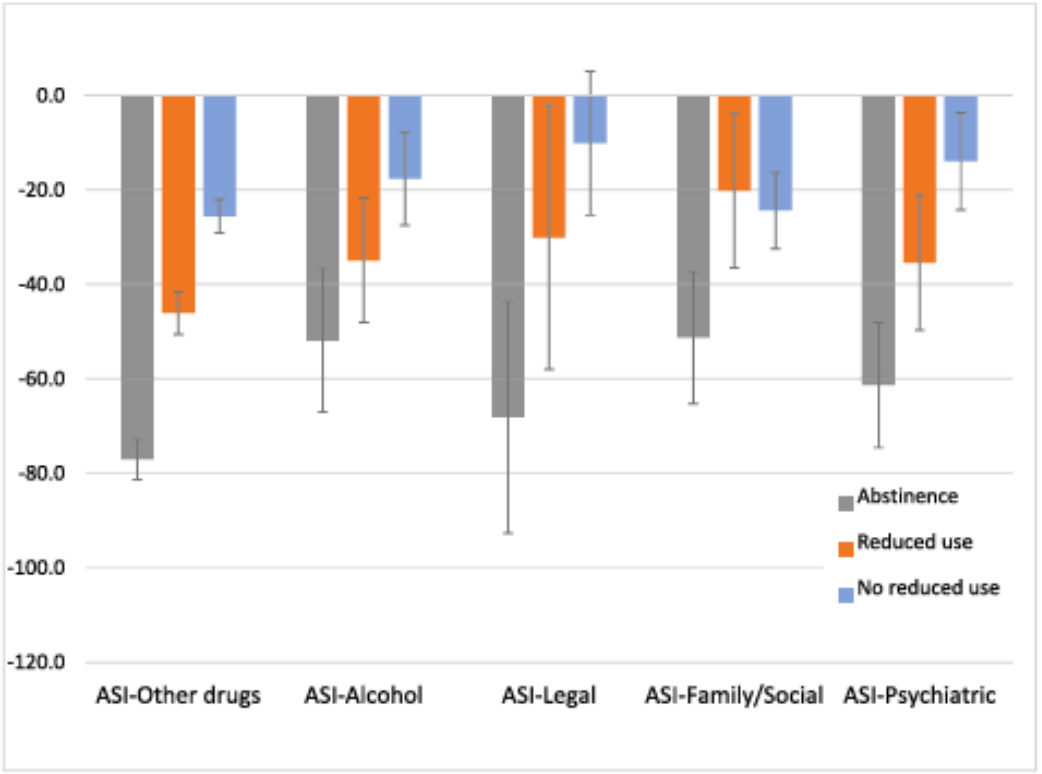
…as well as psychological endpoints

Alcoholism: Clinical and Experimental Research
Vol. 42, No. 12
December 2018

Drinking Risk Level Reductions Associated with Improvements in Physical Health and Quality of Life Among Individuals with Alcohol Use Disorder

Katie Witkiewitz, Henry R. Kranzler, Kevin A. Hallgren, Stephanie S. O'Malley, Daniel E. Falk, Raye Z. Litten, Deborah S. Hasin, Karl F. Mann, and Raymond F. Anton





- Analysis of 13 multisite trials (N=2062) for cocaine/methamphetamine use disorder examining reductions in stimulant use shows promise

Received: 20 February 2023 | Accepted: 10 November 2023
DOI: 10.1111/add.16409
RESEARCH REPORT
ADDICTION SSA

Reduced drug use as an alternative valid outcome in individuals with stimulant use disorders: Findings from 13 multisite randomized clinical trials

Masoumeh Aminesmaeili[1,2] | Mehdi Farokhnia[1,3] | Ryoko Susukida[1] | Lorenzo Leggio[3,4,5,6] | Renee M. Johnson[1] | Rosa M. Crum[1,7,8] | Ramin Mojtabai[1,8]

Additional Considerations

This effort started >15 years ago and was supported by existing large multisite trials with common data collection standards

Alcohol field has established surrogate markers (biomarkers, DrInC)

Unified understanding of a "standard drink unit"

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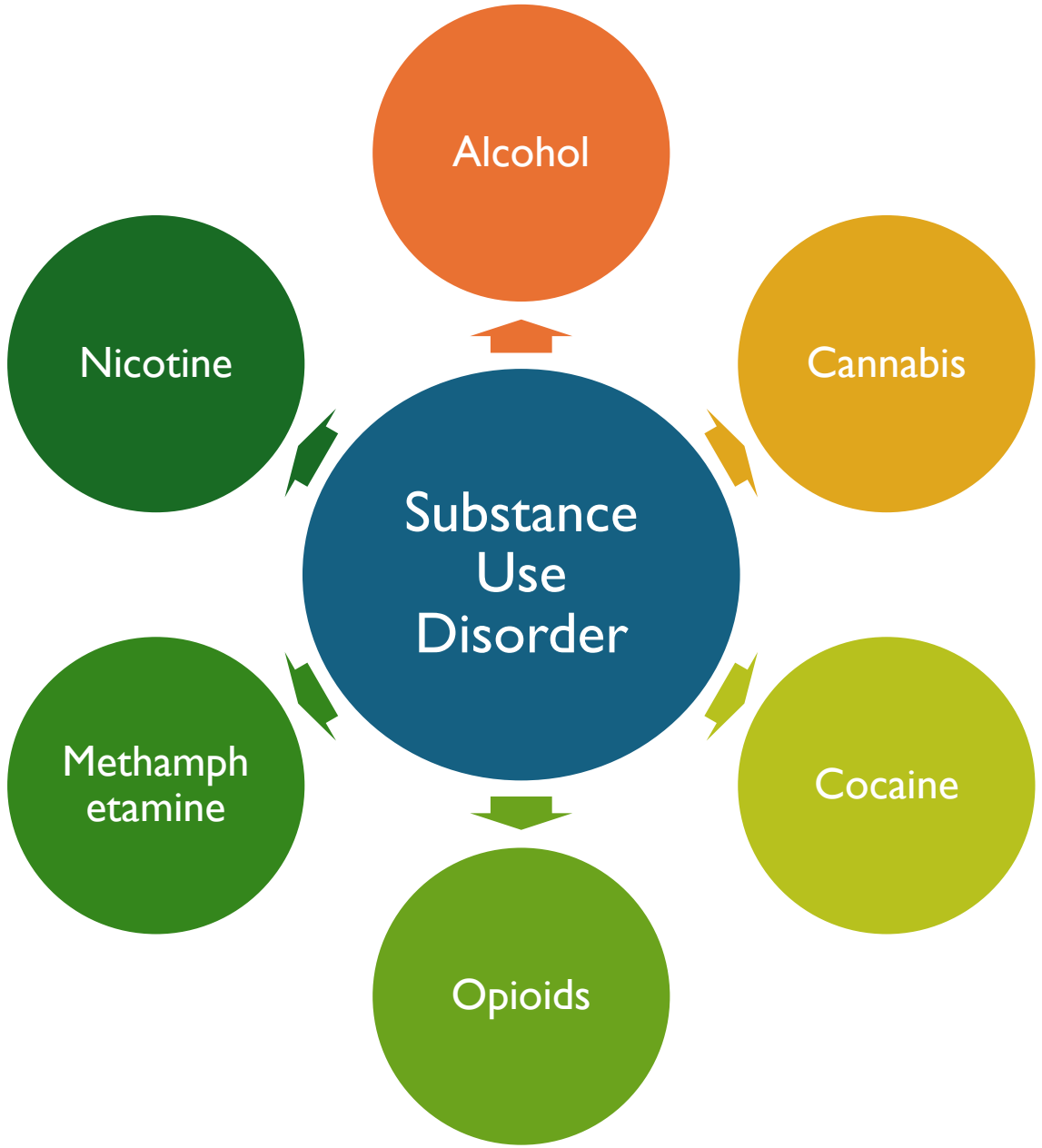
Lehman & Fingerhood, 2018, NEJM



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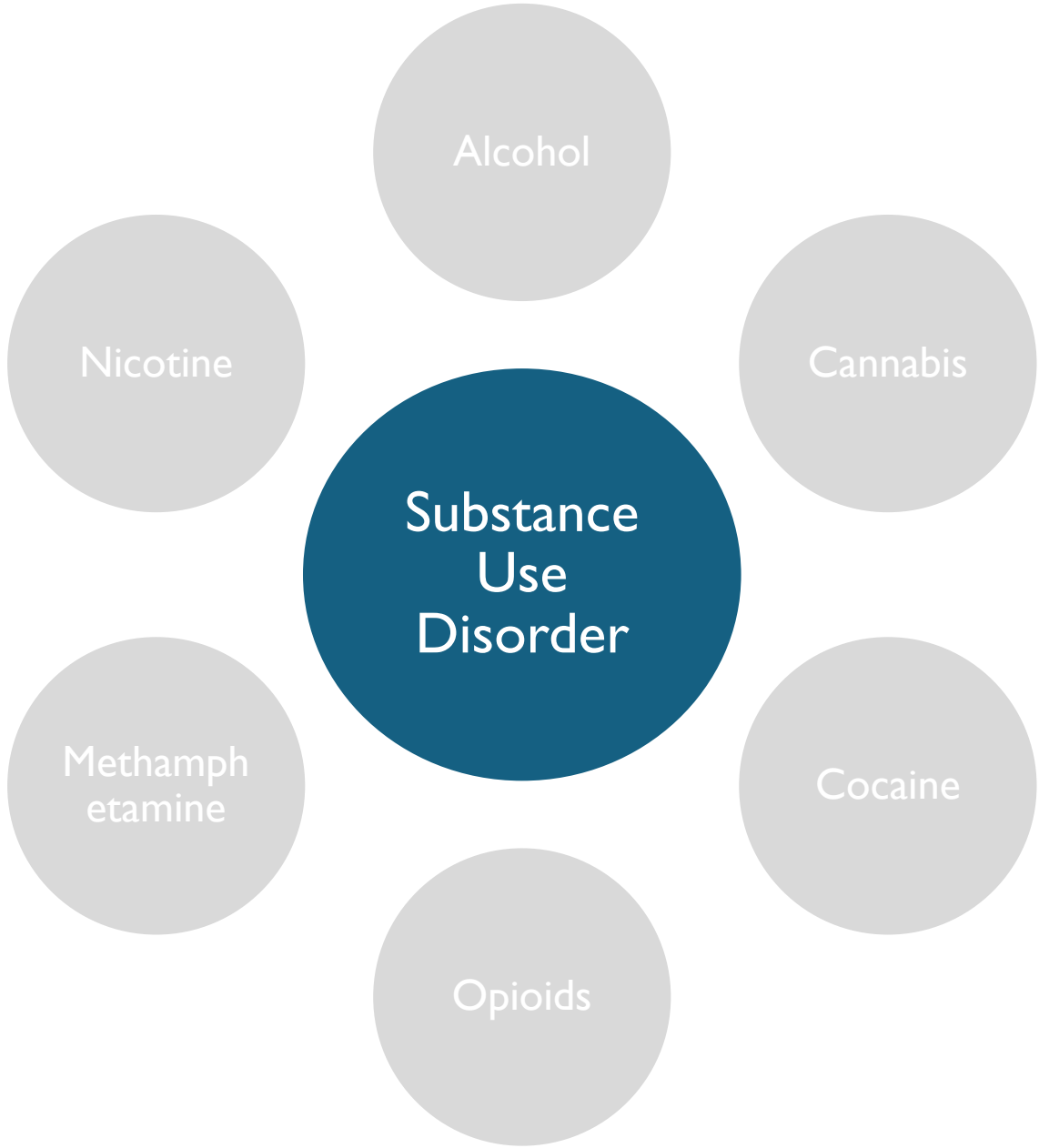

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Are we overlooking universal features of SUDs?

Universal Symptoms

- Craving
- Withdrawal
- Insomnia
- Mood Disturbance

Universal Salutary Health Outcomes

- Improved healthcare utilization
- Reduced infectious disease
- Reduced morbidity, mortality
- Improvements in QOL

Overall Conclusions

- There is substantial opportunity and unmet need for new SUD treatments
- Current strategies rely heavily on abstinence, contrary to FDA guidance
- Alcohol field is a roadmap for developing non-abstinence outcomes
- Examining universal symptoms expand our opportunities to find new solutions

Thank you to funders:

NIH National Institute on Drug Abuse
Advancing Addiction Science

CURE ADDICTION NOW