

# Beyond Traditional Outcome Measures for Substance Use Disorders

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Johns Hopkins University School of Medicine

Blaustein Pain Grand Rounds  
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## Disclosures

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I have received consulting fees from Analgesic Solutions, Indivior, Innocoll and Otsuka Pharmaceutical, support from The Oak Group/VitalHub, Caron treatment program, and Pinney Associates for serving on Advisory Boards, and honoraria from Elsevier and UpToDate for editing work.

# Outline for this talk

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- I. Traditional outcome measures
- II. Other ideas for outcome measures
- III. Summary and final thoughts

# Traditional outcome measures for SUD trials

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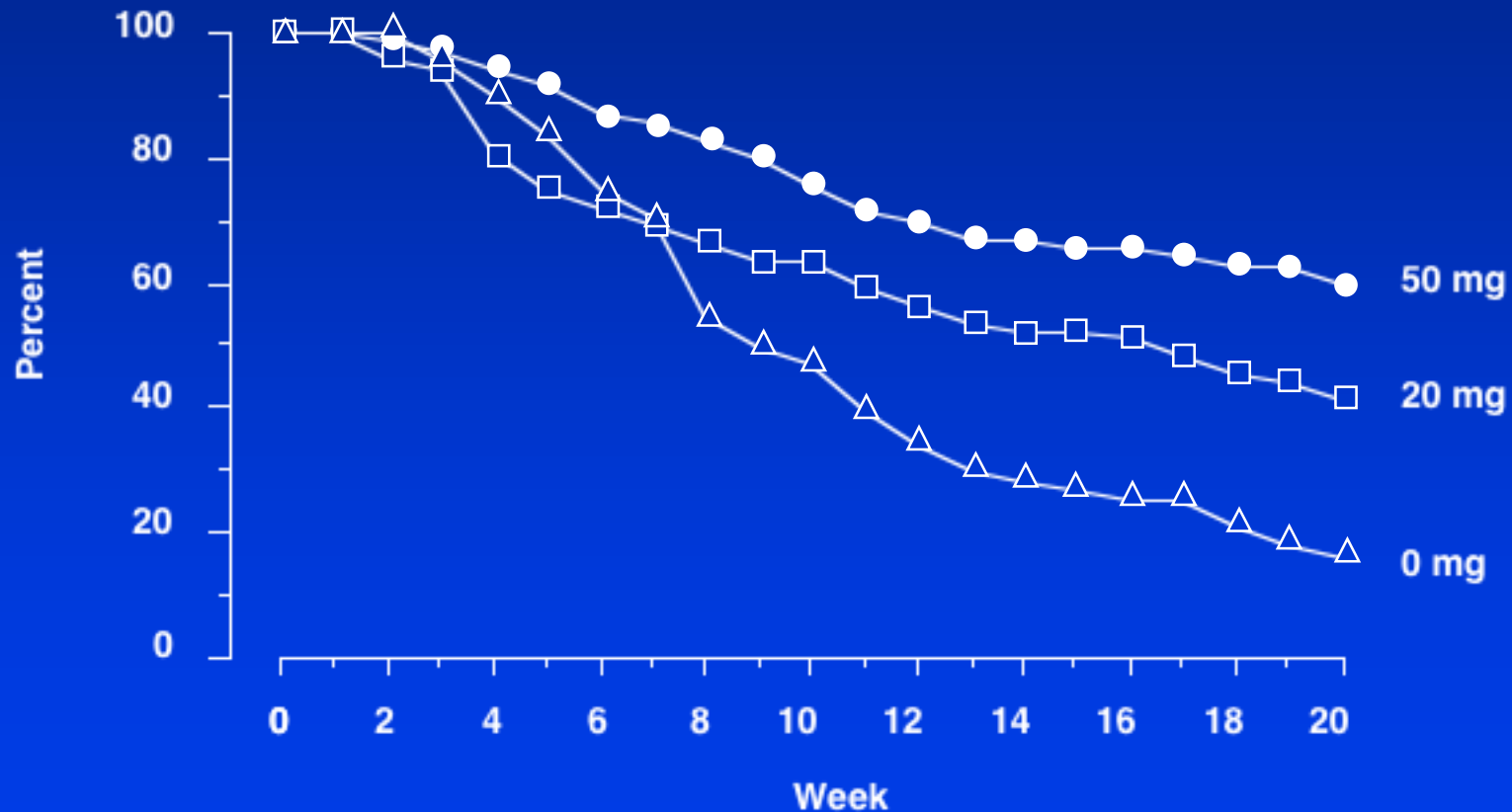
Primary outcomes typically:

## Treatment retention

Intent To Treat, some pre-defined period such as 3 or 6 months

Tends to be relatively short in the overall treatment process

# Methadone dosing: treatment retention



From Strain et al., 1993

# Traditional outcome measures for SUD trials

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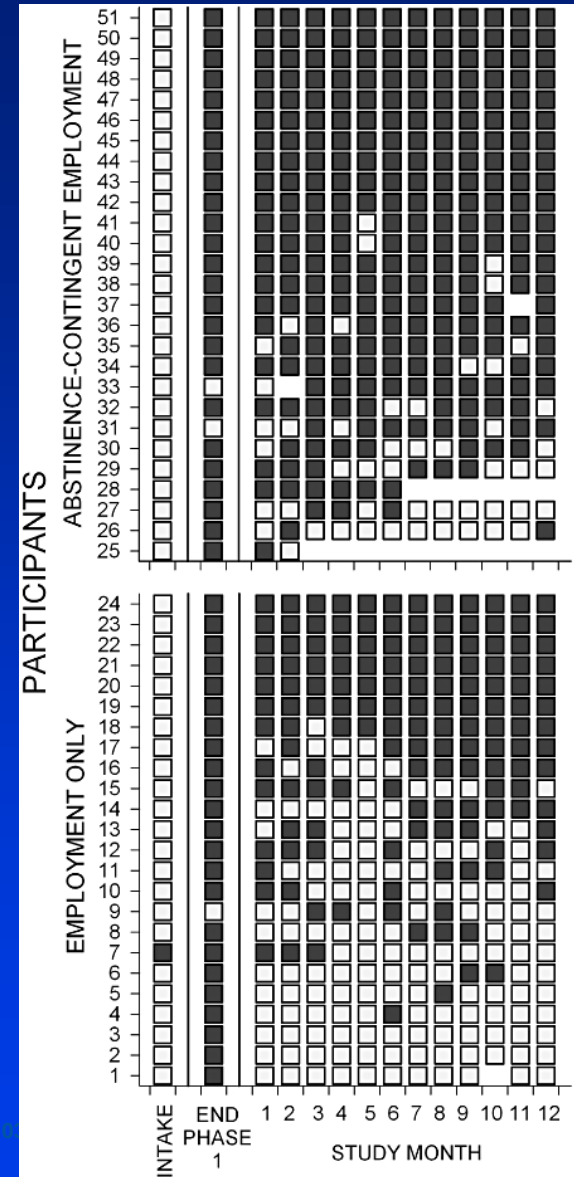
Primary outcomes typically:

Treatment retention

**Abstinence from drug use**

Often biologically-verified or some combination of biologic testing and self-report

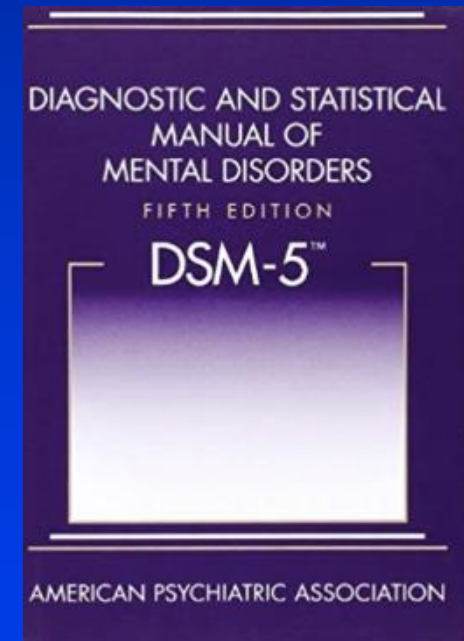
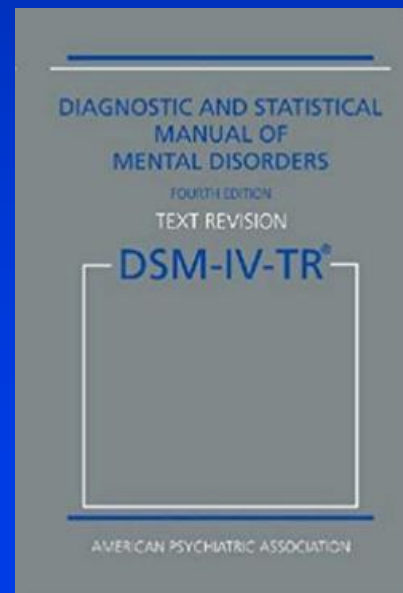
From a study by Ken Silverman and colleagues (Addiction, 2009)



# Traditional outcome measures for SUD trials

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Various forms of DSM have generally implied abstinence (i.e., remission for 12 months) as outcome of interest...





# Traditional outcome measures for SUD trials

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However, retention and abstinence may not be optimal,  
and growing recognition of this...

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

1. May be setting the bar high

Especially early in treatment, may be sporadic use of a substance

We don't necessarily require full remission with other conditions

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

2. Don't necessarily translate for all drugs of abuse

How do we validly measure cannabis abstinence?

How do we validly measure abstinence from a drug that can't be readily detected biologically, and/or has a short duration of effects?

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

3. Maybe it is good to have some retention (treatment exposure), some decrease in use (as a step forward)

We know that many patients cycle in and out of treatment before it seems to “take”

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

4. Patients may have other concerns and goals for treatment

Will come back to this, but what if the patient is more concerned with something else besides staying in treatment with you (no matter how fabulous you and your program)?

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

5. Novel interventions may not map on to traditional outcome measures

For example, apps or online interventions don't necessarily align with ideas of retention in treatment

# Traditional outcome measures for SUD trials

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The problem with these outcomes:

1. May be setting the bar high
2. Don't necessarily translate for all drugs of abuse
3. Maybe it is good to have some retention (treatment exposure), some decrease in use (as a step forward)
4. Patients may have other concerns and goals for treatment
5. Novel interventions may not map on to traditional outcome measures

# Traditional outcome measures for SUD trials

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What do patients and their families want?

What bothers them?

Data (not good, but data) from an FDA listening session in 2018...



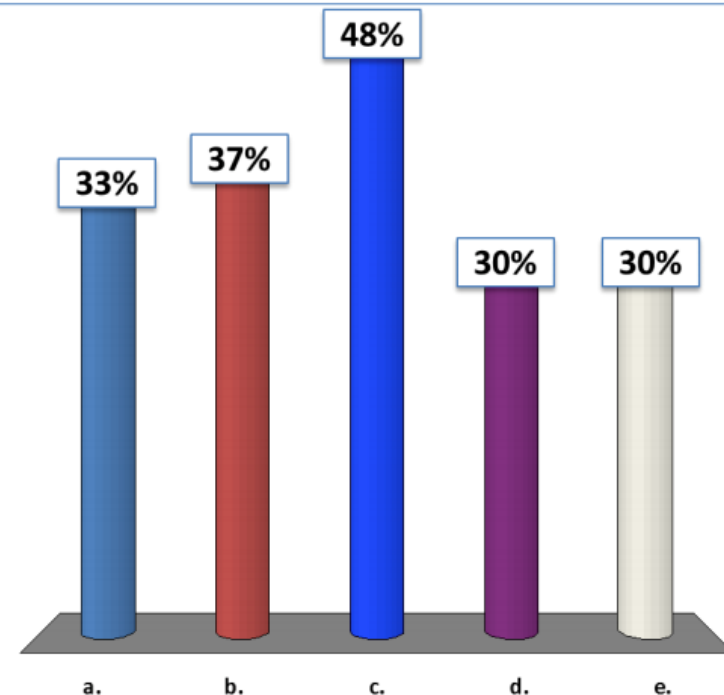
# Polling from FDA session held on 4/17/18 (Patient-Focused Drug Development Meeting on OUD)

In general, what are the most bothersome health effects related to your/your loved one's opioid use disorder?

Please choose up to two answers.

- a. Health effects associated with use of opioids (*such as confusion, constipation, sleepiness*)
- b. Symptoms associated with opioid withdrawal (*such as nausea, diarrhea*)
- c. Symptoms associated with opioid "cravings"
- d. Symptoms related to an underlying health condition (*such as unmanaged pain*)
- e. Other health effects not mentioned

**NOTE:** Due to a technical error, the original response percentages were recorded incorrectly. The correct percentages have been listed below, and may not match the height of the bars in the graph.



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# Traditional outcome measures for SUD trials

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Another way to think about this may be in terms of target symptoms...

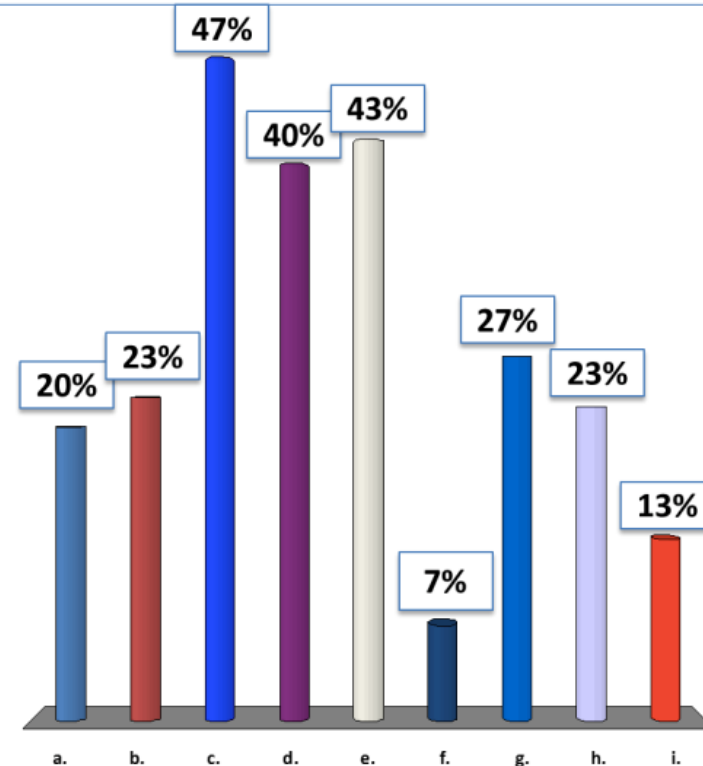
# Polling from FDA session held on 4/17/18 (Patient-Focused Drug Development Meeting on OUD)

Thinking specifically of reducing use or abstaining from opioids, what have been the most bothersome symptoms?

Please choose up to three answers.

- a. Fatigue or lack of energy
- b. Cognitive effects (*such as inability to concentrate, or "brain fog"*)
- c. Anxiety, irritability, or jitteriness
- d. Depression, apathy, or boredom
- e. Insomnia or sleep issues
- f. Nausea, vomiting, or diarrhea
- g. Flu-like symptoms, such as fever or body aches
- h. Pain
- i. Other symptoms not mentioned

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# Traditional outcome measures for SUD trials

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What constitutes “success” for a patient in treatment?

What if a patient is in treatment and abstaining, but struggles (sleeps poorly, craves every day, feels anxious all of the time)?

What might it mean to get beyond traditional outcomes?

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I. Traditional outcome measures

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A. How we look at measures (the alcohol example)

B. What we look at (going beyond urine results, retention)

III. Summary and final thoughts

# How we look at measures

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## Concept of “heavy drinking days” (HDD) in alcohol field

0145-6008/03/2710-1657\$03.00/0

ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH

Vol. 27, No. 10

October 2003

### **Measuring Outcome in Interventions for Alcohol Dependence and Problem Drinking: Executive Summary of a Conference Sponsored by the National Institute on Alcohol Abuse and Alcoholism**

John P. Allen

Key Words: Medication Development, Efficacy, Outcome, Assessment Measures, Surrogate Endpoints.

**O**N DECEMBER 3 and 4, 2001, the National Institute on Alcohol Abuse and Alcoholism convened an expert panel to consider issues surrounding measurement of

research issues surrounding assessment of treatment outcome. Dr. John Finney reports on use of various outcome measures in previous research on alcohol treatment

# How we look at measures

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## Heavy drinking day (HDD)

5 or more standard drinks per day for men, 4 or more per day for women

(Alcohol field has the advantage of “standard drink”, which don’t have for illicit substance use disorders...)



# How we look at measures

## What Is a Standard Drink?

12 fl oz of  
regular beer

=

8-9 fl oz of  
malt liquor  
(shown in a  
12 oz glass)

=

5 fl oz of  
table wine

=

1.5 fl oz shot of  
distilled spirits  
(gin, rum, tequila,  
vodka, whiskey, etc.)



about 5%  
alcohol



about 7%  
alcohol



about 12%  
alcohol



about 40%  
alcohol

Each beverage portrayed above represents one standard drink (or one alcohol drink equivalent), defined in the United States as any beverage containing .6 fl oz or 14 grams of pure alcohol. The percentage of pure alcohol, expressed here as alcohol by volume (alc/vol), varies within and across beverage types. Although the standard drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes.

# How we look at measures

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## Why the interest in HDD?

Frequency of HDDs related to risk of alcohol-related consequences:

Medical (e.g., AUDs, tobacco use, liver disease, cardiovascular disease)

Social (divorce/separation, neglect of school or work duties, loss of driver's license)

## How we look at measures

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FDA has accepted HDD changes as an outcome measure in clinical trials

This has prompted interest in re-thinking abstinence as a goal for other substance use disorders



ELSEVIER

Contents lists available at ScienceDirect

## Drug and Alcohol Dependence

journal homepage: [www.elsevier.com/locate/drugalcdp](http://www.elsevier.com/locate/drugalcdp)



### Review

## Measures of outcome for stimulant trials: ACTION recommendations and research agenda



Brian D. Kiluk<sup>a,\*</sup>, Kathleen M. Carroll<sup>a</sup>, Amy Duhig<sup>b</sup>, Daniel E. Falk<sup>c</sup>, Kyle Kampman<sup>d</sup>, Shengan Lai<sup>e</sup>, Raye Z. Litten<sup>c</sup>, David J. McCann<sup>f</sup>, Ivan D. Montoya<sup>f</sup>, Kenzie L. Preston<sup>f</sup>, Phil Skolnick<sup>f</sup>, Constance Weisner<sup>g</sup>, George Woody<sup>h</sup>, Redonna Chandler<sup>f</sup>, Michael J. Detke<sup>i</sup>, Kelly Dunn<sup>e</sup>, Robert H. Dworkin<sup>j</sup>, Joanne Fertig<sup>c</sup>, Jennifer Gewandter<sup>j</sup>, F. Gerard Moeller<sup>k</sup>, Tatiana Ramey<sup>f</sup>, Megan Ryan<sup>c</sup>, Kenneth Silverman<sup>e</sup>, Eric C. Strain<sup>e</sup>



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### Review

## The state of clinical outcome assessments for cannabis use disorder clinical trials: A review and research agenda



Mallory J.E. Loflin<sup>a,b</sup>, Brian D. Kiluk<sup>c,\*</sup>, Marilyn A. Huestis<sup>d</sup>, Will M. Aklin<sup>e</sup>, Alan J. Budney<sup>f</sup>, Kathleen M. Carroll<sup>c</sup>, Deepak Cyril D'Souza<sup>c</sup>, Robert H. Dworkin<sup>g</sup>, Kevin M. Gray<sup>h</sup>, Deborah S. Hasin<sup>i</sup>, Dustin C. Lee<sup>j</sup>, Bernard Le Foll<sup>k</sup>, Frances R. Levin<sup>l</sup>, Joshua A. Lile<sup>m</sup>, Barbara J. Mason<sup>n</sup>, Aimee L. McRae-Clark<sup>h</sup>, Ivan Montoya<sup>e</sup>, Erica N. Peters<sup>o</sup>, Tatiana Ramey<sup>e</sup>, Dennis C. Turk<sup>p</sup>, Ryan Vandrey<sup>j</sup>, Roger D. Weiss<sup>q,r</sup>, Eric C. Strain<sup>j</sup>

## How we look at measures

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The big issue with creating a HDD for an illicit substance is that we have not got a standard drink equivalent (and field has struggled with this)

But, has led to thinking in other ways (e.g., reduction in symptom counts for a DSM diagnosis)

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# Examples of new ideas to consider

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Craving

Sleep

Depression/anxiety

Functioning



# Ideas to consider

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## Craving

FDA Commissioner Gottlieb expressed an interest:

For example, one endpoint that's relevant to the treatment of addiction is the craving that fuels continued drug use. Craving is an endpoint that the FDA has included in labeling for smoking cessation products. The FDA intends to provide assistance to develop a validated measurement of "craving" or "urge to use" illicit opioids to complement other endpoints and to determine how it supports the goal of sustained abstinence.

# Ideas to consider

JAMA Psychiatry  
Viewpoint (2019)  
following a  
meeting we had  
on craving

## VIEWPOINT

### Time to Reconsider the Role of Craving in Opioid Use Disorder

**Bethea A. Kleykamp, PhD**  
School of Medicine and Dentistry, University of Rochester, Rochester, New York.

**Roger D. Weiss, MD**  
McLean Hospital, Harvard Medical School, Belmont, Massachusetts.

**Eric C. Strain, MD**  
Behavioral Pharmacology Research Unit, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland.

**Craving** has long been acknowledged by patients and clinicians as a significant feature of substance use disorders and especially opioid use disorder (OUD), as noted in a 2018 public meeting hosted by the US Food and Drug Administration (FDA).<sup>1</sup> Craving is a subjective experience that can be unpredictable in its onset, variable in its intensity, and potentially overwhelming to a person when attempting to resist drug use.<sup>2,3</sup> Patients may use a variety of terms besides or in addition to craving to describe this experience, such as having an urge, hunger, or desire to use a substance; this variability in terminology reflects some of the inherent difficulty in studying the concept (“I have really strong urges but no cravings”). Craving is not unique to drug use, and as anyone who has attempted to diet or abstain from a habit can attest, this phenomenon appears to be a part of human nature that can make changing an ingrained behavior pattern particularly problematic.

The drug abuse clinical and research fields have

novel treatments assist patients in needs to address

#### Develop a Psychology of Craving

Developing a psychology of craving is a critically important component of research on treatments for OUD. Craving measurement is a complex task; however, it is not adequately evaluated. Varying patient preferences tend to be limited to opioids more generally (2019). Additionally, it is important to systematically incorporate patient input into their early content validity. Metrically sound

## Ideas to consider

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But “craving” is a squishy concept (one person’s craving is another person’s urge, or desire, or hunger, or...)

# Examples of new ideas to consider

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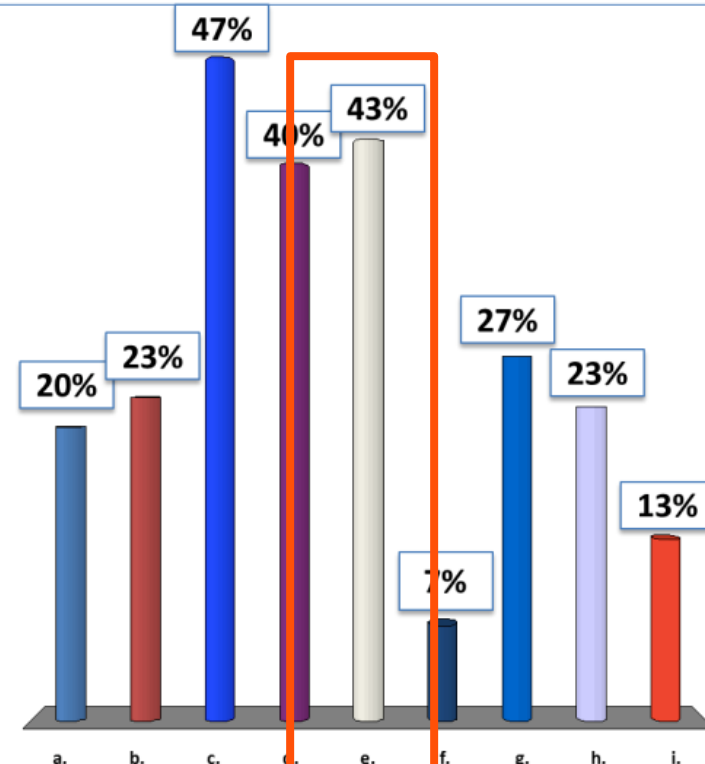
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- d. Depression, apathy, or boredom
- e. Insomnia or sleep issues**
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# Ideas to consider

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## Methadone patients; 84% with poor sleep quality

ELSEVIER Journal of Substance Abuse Treatment 26 (2004) 175–180 Treatment

Regular article

**Sleep disturbances among methadone maintained patients**

Michael D. Stein, M.D.<sup>a,b,\*</sup>, Debra S. Herman, Ph.D.<sup>a,b</sup>, Shaughna Bishop<sup>b</sup>, Joanna A. Lessor<sup>b</sup>,  
Marjorie Weinstock, Ph.D.<sup>b</sup>, Jennifer Anthony, Ph.D.<sup>b</sup>, Bradley J. Anderson, Ph.D.<sup>b</sup>

<sup>a</sup>*Brown University Medical School, 75 Waterman Street, Providence, RI 02912, USA*  
<sup>b</sup>*Rhode Island Hospital, Division of General Internal Medicine, 593 Eddy Street, Providence, RI, USA*

Received 18 May 2003; received in revised form 3 October 2003; accepted 2 November 2003

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**Abstract**

We examined the relationship of sleep disturbance and demographic, mental health, drug use and other factors among 225 methadone-maintained individuals. The cohort was 78% Caucasian and 54% male with a mean age of 41 years. Sleep disturbance was measured using the Pittsburgh Sleep Quality Index (PSQI) with a score >5 indicating poor global sleep quality.

Eighty-four percent of subjects had PSQI scores of six or higher. In multivariate analysis, depressive symptoms, anxiety symptoms, greater nicotine dependence, bodily pain, and unemployment were associated with poorer global sleep quality ( $p < .01$ ).

Targeting modifiable psychological and medical risk factors that are most strongly associated with sleep disturbance may improve quality of life in drug treatment. © 2004 Elsevier Inc. All rights reserved.

# Ideas to consider

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Up to 75% CUD patients with insomnia during withdrawal

## Reviews and Overviews

### Review of the Validity and Significance of Cannabis Withdrawal Syndrome

**Alan J. Budney, Ph.D.**

**John R. Hughes, M.D.**

**Brent A. Moore, Ph.D.**

**Ryan Vandrey, M.A.**

The authors review the literature examining the validity and significance of cannabis withdrawal syndrome. Findings from animal laboratory research are briefly reviewed, and human laboratory and clinical studies are surveyed in more detail. Converging evidence from basic laboratory and clinical studies indicates that a withdrawal syndrome reliably follows discontinuation of chronic heavy use of cannabis or tetrahydrocannabinol. Common symptoms are primarily emo-

tional and behavioral, although appetite change, weight loss, and physical discomfort are also frequently reported. The onset and time course of these symptoms appear similar to those of other substance withdrawal syndromes. The magnitude and severity of these symptoms appear substantial, and these findings suggest that the syndrome has clinical importance. Diagnostic criteria for cannabis withdrawal syndrome are proposed.

*(Am J Psychiatry 2004; 161:1967–1977)*

## Ideas to consider

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But commonly-used sleep meds (benzodiazepines) have abuse potential, and non-pharmacological treatments (CBT-I) don't seem to always work well with this population

("I tried that doc, but it just doesn't work – can't you prescribe me something?")



# Examples of new ideas to consider

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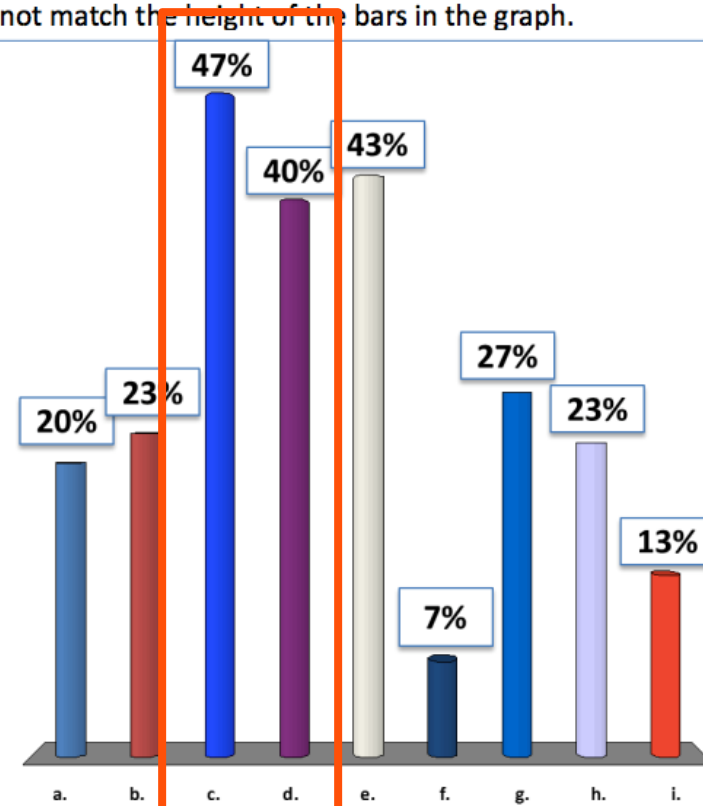
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## Ideas to consider

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Depression and anxiety may be areas most amenable to readily available treatment interventions

(But, risk of some patients attributing on-going drug use to being depressed or anxious – and provider has not gotten them the right medicine yet)

# Examples of new ideas to consider

---

Craving

Sleep

Depression/anxiety

Functioning

# Ideas to consider

---

## Functioning

Alcohol field has the idea that a reduction in “heavy drinking days” can be used as a measure of improved functioning

# Ideas to consider

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## Functioning

Treatment of whole person

Engagement in meaningful life

Quality interpersonal relationships

(The other end of the spectrum  
from harm reduction?)

# Examples of new ideas to consider

---

Craving

Sleep

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Could well be other outcome measures we need to consider...

# Outline for this talk

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- I. Traditional outcome measures
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## Final thoughts (I of II)

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Outcome measures have tended to come from opioid misuse and in some ways are tailored to opioids and the methadone treatment system (retention, ability to frequently collect and test urine samples)

The rise of other drugs of abuse and the interest in trying to develop medications for these drugs raises the opportunity to consider other outcome measures

## Final thoughts (II of II)

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These outcomes may also relate to the need to address symptoms that can be present in patients who are “doing well” (in treatment, not using), but still have distress (e.g., poor sleep, frequent craving)

While there is an important role for retention and abstinence, is an opportune time to think broader about the outcome measures we are using – especially as this may relate to new medications being considered