CSAM-SMCA Journal Club

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THE AMERICAN JOURNAL ON ADDICTIONS

AAP American Academy of Addiction Psychiatry

Review Article

Systematic Review and Meta-Analysis: Treatment of Substance Use Disorder in Attention Deficit Hyperactivity Disorder

CME

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Background

- **The presence of attention deficit hyperactivity disorder (ADHD) not only increases vulnerability to substance use disorder (SUD) but also influences the long-term prognosis and treatment of SUD itself.**
- **Prevalence of ADHD is 23% in all substance users.**
- **Substance Use Disorder is present in 40% of individuals with ADHD**

Background

- **Medications may treat ADHD and correct dopamine/norepinephrine deficits of ADHD.**
- **Suggested that non stimulants and stimulants be used to treat ADHD even though there is no evidence for them.**
- **Interventions target norepinephrine, dopamine, and nicotinic acetylcholine receptors.**

Meta-analysis Aims

- **Effectiveness of pharmacological interventions for reducing substance use, managing withdrawal symptoms, reducing cravings, and maintaining and promoting abstinence in ADHD patients with SUD.**
- **Investigate whether pharmacological interventions could improve ADHD symptoms.**
- **Incite more research on medications to manage SUD in ADHD patients.**

Methods

- **PRISMA guidelines and PROSPERO registered.**

INCLUSION CRITERIA:

- **RCTs with pharmacological agents to treat SUD in ADHD with control being a placebo. No restrictions on age, race, sex, country, or language.**

PRIMARY:

1. **Reduction in substance use**
2. **Management of withdrawal symptoms**
3. **Reduction in craving**
4. **Facilitating or promoting long-term abstinence**

Secondary

1. **Reduction in ADHD symptoms in participants with SUD**

Methods

PRIMARY OUTCOMES

1) Reduction in substance use
2) Management of withdrawal symptoms
3) Reduction in craving
4) Facilitating or promoting long-term abstinence

SECONDARY OUTCOMES

1) Reduction in ADHD symptoms in participants with SUD (tobacco, cocaine, amphetamine, cannabis, and alcohol).

Methods Continued

INFORMATION AND SEARCH STRATEGY

1971- 2020:

- Cochrane Central Register of Controlled Trails, PubMed, EBSCO, Google Scholar, Embase, Web of Science and Ovid MEDLINE

- Unpublished and nonpeer-reviewed documents on Open Grey, Non-Governmental Organization (NGO), Bielefeld Academic Search Engine (BASE), the WHO International Trials, Registry Platform (ICTRP) and the United States Clinical Trials Registry

Methods Continued

STUDY SELECTION AND DATA COLLECTION

- Reviewers screened all articles. Discrepancies were discussed between reviewers and 95% consensus was required for the article to move forward.
- Data was extracted using a standard data abstraction form.
- RCT must have scored greater than or equal to two on the Oxford Quality Scoring System to be included in the review

Methods Continued: Outcomes

Primary Outcome

- **Data on abstinence, craving, reduction of substance use, withdrawal symptoms, and reduction in ADHD symptoms were tabulated**
- **Open-source, Cross-platform Software for Ecological and Evolutionary Meta-analysis (OpenMEE) 17 to perform the meta-analysis**
- **Standardized mean difference (SMD) to compare two groups on a continuous dependent variable as the principle measure of effect size**
- **MD was interpreted as: small: SMD=0.2, medium: SMD = 0.5, and large: SMD = 0.8**
- **Meta – analysis was based on the random effects model known as the DerSimonian and Laird method**
- **Statistical heterogeneity between studies was assessed by the I2 statistic. The interval confidence of the observed data was set at 95%, and statical significance was set at a P value ≤ .05**

Methods Continued: Outcomes

- **The methodological quality of the trials included in the review was assessed by the criteria for quality assessment recommended in the Cochrane Collaboration Handbook.**
- **Risk of bias in randomized trials (RoB 2). T**
- **The criteria mainly focused on the description of sequence generation, allocation concealment, blinding, and completeness of outcome data, selective outcome reporting, and other potential sources of bias (such as adequate wash-out period, especially in cross-over trials).**

Results

- 54,515 electronic documents screened, 2899 of them were potentially relevant citations

- Participants were between 15 and 65 years of age.
    - 35% of the RCTs involved tobacco use disorder,
    - 29% of the RCTs involved cocaine use disorder,
    - 12% amphetamine
    - 12% alcohol use disorder
    - 12% cannabis use disorder

Risk of Bias: 95% of the studies showed no concern regarding the randomization process, missing outcome data, or deviation from the intended intervention, more than 85% of them showed “some concerns” in their selection of reported results

- Funnel Plot showed symmetry
- HETERGENITY: moderate heterogeneity with an I^2 of 35.369%

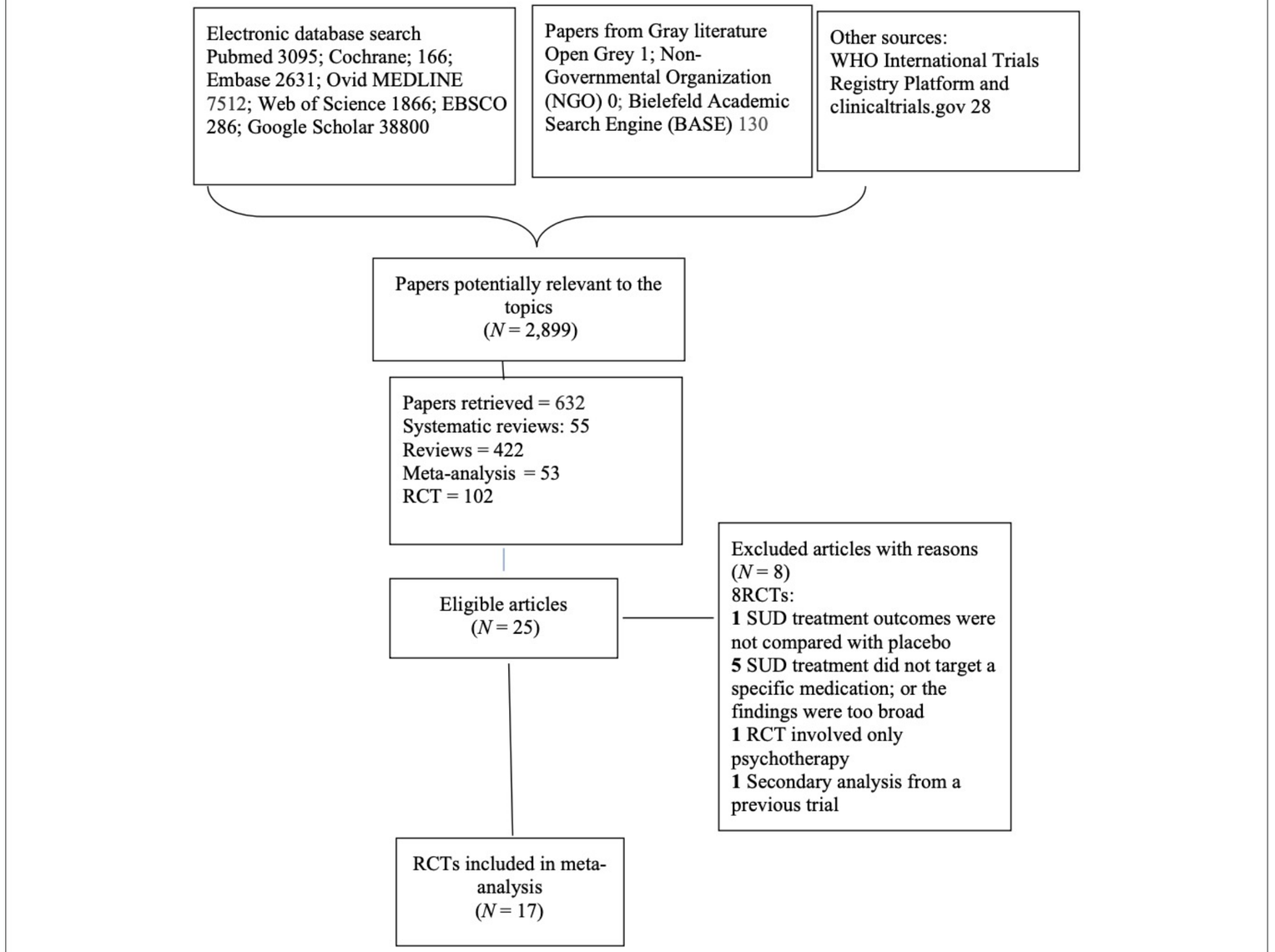

FIGURE 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Selection and sources of papers included in the review. RCTs = randomized controlled trials; SUD = substance use disorder; WHO = World Health Organization.

Results

SUBSTANCE USE REDUCTION

All substances: thirteen studies (N = 1246), four reported a moderate and large reduction in substance use, remaining studies showed small reduction.

Pooled effect size of the 13 studies on continuous measures, representing mainly self-reported quantity of use and urine drug screening, was small but significant. (SMD = 0.405, 95% confidence interval [CI]: [0.252, 0.557], P < .001
Tobacco: SMD = 0.438, 95% CI: [0.044, 0.832], P = .029
Cocaine: SMD = 0.442, 95% CI: [0.095, 0.788], P = .012
Cannabis: SMD = 0.170, 95% CI: [−0.154, 0.494], P = .305

Methylphenidate with cocaine and methamphetamines: SMD = 0.391, 95% CI: [0.097, 0.685], P = .009

Methylphenidate with methamphetamines: methylphenidate produced a moderate reduction in amphetamine use (SMD = 0.511, 95% CI: [0.058, 0.963], P = .027

Methylphenidate with cocaine: SMD = 0.346, 95% CI: [−0.080, 0.771], P = .111

Results

Withdrawal Management:
2 RCTs (N=458)
Tobacco: SMD = 0.577, 95% CI: [0.389, 0.764], P = .001

Abstinence (N= 434):
significant progression toward abstinence; 11 studies combined showed a small trend toward abstinence (SMD = 0.328, 95% CI: [0.149, 0.507], P < .001) I2 of 54.869%.

CRAVING: (N=530)
craving, data collected on alcohol, tobacco, amphetamine, and cocaine showed that the pooled effect size was small (SMD = 0.274, 95% CI:
[0.103, 0.446], P = .002). I2=0

Decrease in the Severity of ADHD Symptoms
Clinical Global Impression-Improvement (CGI) scale and the Adult ADHD Investigator Symptom Rating Scale: SMD = 0.533, 95% CI: [0.393, 0.672], P < .001). There was no statistical heterogeneity (I2 = 0%).

Reduction in the Frequency of ADHD Symptoms
small reduction in the frequency of ADHD symptoms was found (SMD = 0.420, 95% CI: [0.259, 0.582], P < .001
negative correlation between ADHD symptom improvement (severity and frequency) and substance use reduction (r(11) = −.0462).

Discussion

- meta-analysis suggests that pharmacological interventions decreased tobacco, cocaine, and amphetamine use
- Methylphenidate appeared to minimize cocaine and amphetamine use
- Craving for alcohol, tobacco, amphetamine, and cocaine seemed slightly diminished.
- Moderate reduction in the severity of ADHD symptoms in cocaine, alcohol, cannabis, and tobacco use, and the frequency of ADHD symptoms for tobacco, amphetamine, and cocaine use.
- ADHD symptoms' improvement did not seem to correlate with a decrease in substance use
- Small advantage of medication over placebo for tobacco and cocaine abstinence

Strengths & Limitations

STRENGTHS:

- **Thirteen out of seventeen trials combined behavioral therapies with medications**
- **Active drugs in the trials are common medications to treat ADHD, except varenicline**

LIMITATIONS:

- **Racial and Sex differences in SUD and ADHD were hard to determine.**
- **Medications were blended under the umbrella of pharmacological interventions**
- **Gaps in identifying specific and individualized outcome measures for SUD treatment from the RCTs reviewed may limit the reproducibility of the results of the meta-analysis**
- **Pharmacological approach to treat SUD might specifically aim to manage acute withdrawal syndrome, attenuate craving, decrease the urge to use illicit drugs, prevent relapse, and decrease compulsive drug use**

Discussion

IMPACT ON PRACTICE:

- Favor stimulants and nonstimulants over placebo to treat SUD in ADHD patients
- Stimulants and nonstimulants may be clinically practical to treat both disorders
- Stimulants can be misused or abused, thus perpetuating the circle of addiction

RESEARCH IMPLICATIONS:

- Patients are unable to describe recent periods of abstinence from substance use, making the distinction between primary and substance-induced symptoms difficult
- Difficulty in differentiating SUD from ADHD symptoms can render treatment of substance use difficult
- Newly controlled clinical trials may include a study design that covers specific criteria of ADHD and SUD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as the primary diagnostic tool
- Newly controlled trials that incorporate only stimulants or nonstimulants with no additional therapy may be difficult to undertake due to ethical limitations but may be needed to reduce the potentiality of bias

Our Discussion

RESEARCH Open Access

A call for consensus in defining efficacy in clinical trials for opioid addiction: combined results from a systematic review and qualitative study in patients receiving pharmacological assisted therapy for opioid use disorder

Brittany B. Dennis[1,2], Nitika Sanger[2], Monica Bawor[1], Leen Naji[3], Carolyn Plater[4], Andrew Worster[2,5], Julia Woo[6], Anuja Bhalerao[6], Natasha Baptist-Mohseni[4], Alannah Hillmer[4], Danielle Rice[7,8], Kim Corace[9,10], Brian Hutton[11,12], Peter Tugwell[13], Lehana Thabane[2,14,15] and Zainab Samaan[2,4,16*]

Background

- **Decisions regarding “significant” treatment targets, the research community exerts a strong influence on the generation of evidence.**
- **Value of many pharmacological interventions is commonly evaluated on their observed effect across different biochemical and surrogate measurements**
- **No “gold standard” measure of treatment effect**
- **Commonly included endpoints comprise attrition rates, illicit substance use, presence of medical and psychiatric comorbidity, social function as measured by current housing arrangements, collective neighborhood income, educational achievement, employment, and involvement in criminal activity.**

Methods

- **Phase 1 Systematic Review to Establish Outcomes Commonly used in literature Adheres to PRISM guidelines and registered in PROSPERO.**
- **Any studies in special populations, including prison, were excluded.**
- **Methodological quality assessment was conducted using the Cochrane Risk of Bias Tool for RCTs.**
- **PRIMAY AIM: summarize all outcome domains and subdomains and their definitions and outcomes measurements/instruments used for each outcome in trials of OSAT for OUD.**
- **EXTRACTION: abstracted the sample size, mean age, eligibility criteria, intervention description, dose, approaches to missing data, outcome definition, outcome measurement, covariates included in regression models if adjusted analyses were per- formed, and the statistical association reported (e.g., odds ratio (OR), relative risk (RR)).**
- **Addiction Severity Index and (ASI) [9] and Maudsley Addiction Profile (MAP) used to determine structured outcomes.**

Methods Continued

PHASE 2: qualitative interviewing of patients on pharmacological treatment for OUD

- **Participants patients ≥ 18 years, currently receiving an opioid substitution therapy including methadone maintenance treatment or buprenorphine, able to understand and speak English, and able to provide informed consent**
- **Structured open-ended interviews were conducted to explore each patient's end-goals of therapy.**
- **interviews were transcribed and analyzed for themes, clarifications, and deeper understanding of the topics outlined above**
- **Convenience sampling was utilized between two addiction treatment clinics.**
- **Patients were given a demographic questionnaire and interviewed by two investigators using structured questions and open ended questions.**

Methods Continued

- **Provided patients a list of commonly anticipated treatment goals and asked them to rank which aspect of recovery meant the most to their addiction treatment.**
- **Data coded by the interviewers using broader domains established from ASI and MAP**

Results

- **6077 articles. We identified 60 trials with a combined participant sample of 13,341 patients eligible for full text extraction**
- **Retention was the most commonly reported measure.**
- **Second was illicit opioid use measured in 1) Frequency of use 2) Mean time individuals are abstinent 3)Predefined criteria for success 4) Global severity of opioid use.**

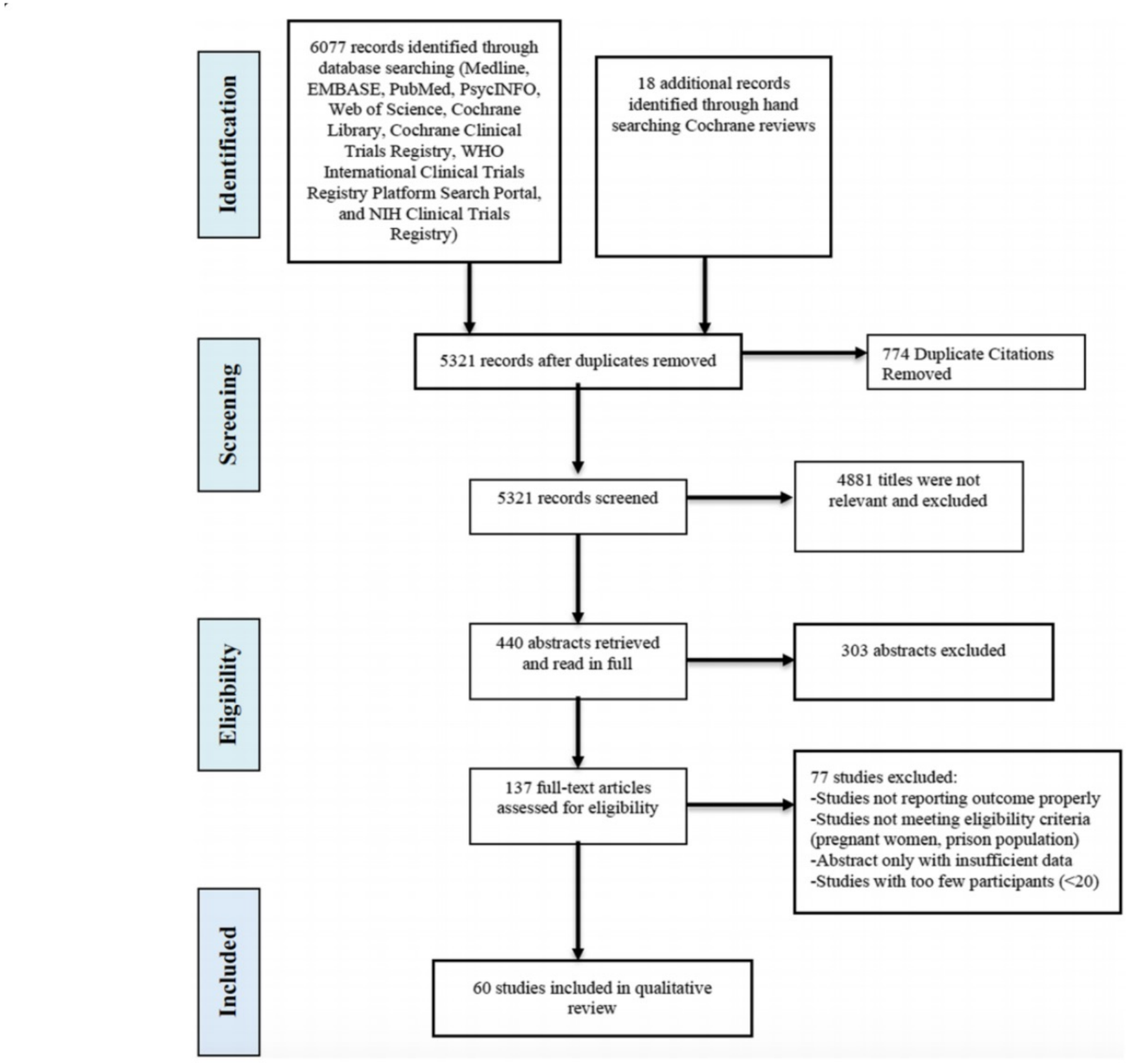

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Results

Qualitative Analysis

- **18 Individuals interviewed. 16 received MMT in the last year. 2 Buprenorphine.**
- **61% main goal for methadone was being abstinent from substances.**
- **1/3 had a goal of being off methadone completely. Others had no desire.**
- **Getting back to normal life.**

Table 2 Verbatim answers to qualitative interview to understand goals of therapy

Participant	Verbal answer
1	Remain abstinent from drugs
2	I don't want to use drugs
3	Not use street drugs
4	Get off opioids completely
5	Maintain my job
6	Just get my life back; I'm still an addict a nd I don't want that to sneak back on me
7	To not be sick anymore
8	Being completely off drugs. To never touch drugs again
9	Being able to control my addiction. Just living a life without having to take medication every day
10	Not to use drugs
11	Being independent from methadone and drugs
12	Pain control
13	To get off methadone and never look back at any opioids
14	Managing my addictive personality, whether it is a drug addiction or not
15	Get clean; not going back on opioid and not go back on Suboxone
16	Become drug free
17	Get off methadone; be done with this all
18	Get off it (methadone) completely

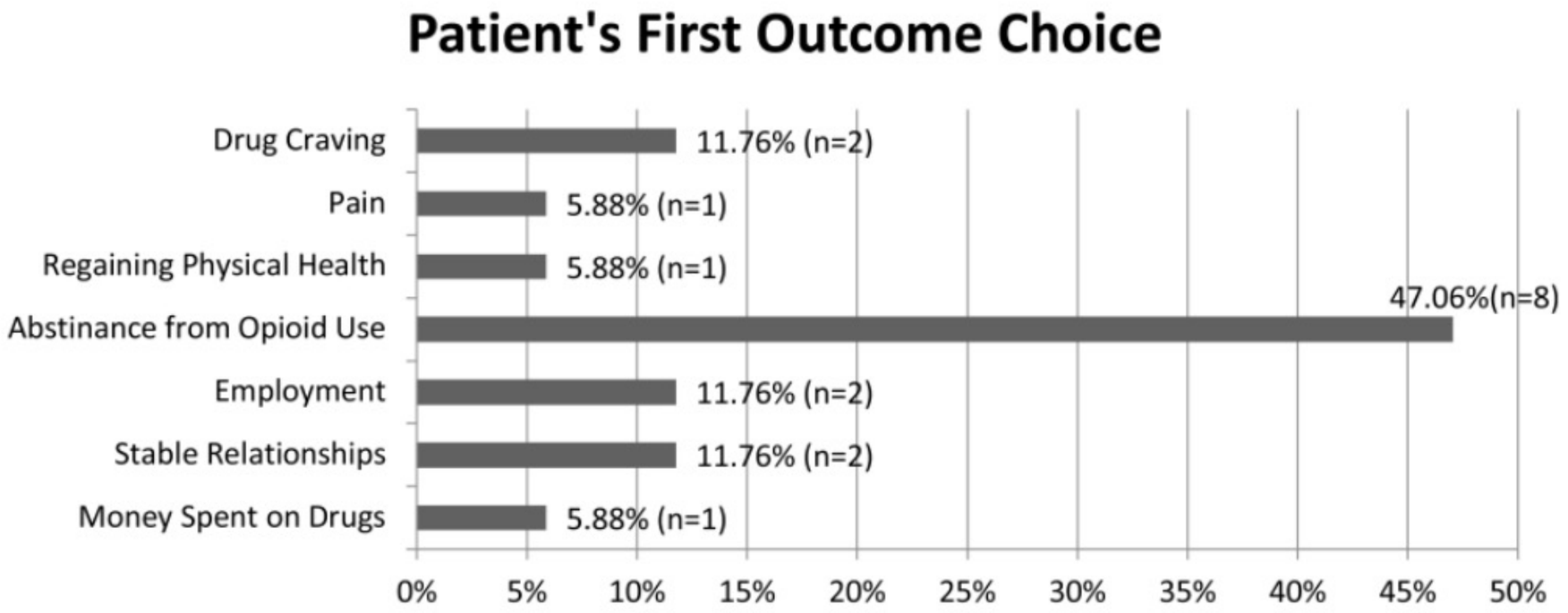

Fig. 2 First ranked treatment goals among patients receiving OSAT. Patients ranking of treatment goals from a "pre-determined" list provided during the qualitative interview. Patients were asked to rank which aspect of recovery was most important to their addiction treatment goals. Patients were allowed to rank up to four items. The figure illustrates the first ranked items

Discussion

- **Compared literature outcome measures with perceptions of people of lived experience about what outcomes matter.**
- **High variation on what are meaningful outcomes to clinicians.**
- **Treatment retention was most important to researchers**
- **Trialists seldom explored pharmacological effect on personal and social functioning outcomes such as criminal behavior, employment, relationships, and personal stability endpoints, including type of accommodation**

Table 3 Patients' responses to predetermined treatment goals

Participant	Outcome 1	Outcome 2	Outcome 3	Outcome 4
1	Money spent on drugs	Overdose	Injecting	NA
2	Stable relationships	Coping	NA	NA
3	Employment	Housing	Depression	
4	Stable relationships	Money spent on drugs	Sexual function	Money spent on drugs
5	Employment	Stable relationships	Housing	NA
6	Abstinence from opioid use	Employment	NA	NA
7	Regaining physical health	Abstinence from opioid use	NA	NA
8	Abstinence from opioid us	Regaining physical health	Coping	NA
9	Missing data			
10	Abstinence from opioid use	Depression	Coping	NA
11	Abstinence from opioid use	Drug craving	Money spent on drugs	Regaining physical health
12	Pain	Employment	NA	NA
13	Abstinence from opioid use	Money spent on drugs	Drug craving	Stable relationships
14	Drug craving	Stable relationship	Money spent on drugs	NA
15	Drug craving	Pain		
16	Abstinence from opioid use	Pain	Stable relationships	Drug craving
17	Abstinence from opioid use	Money spent on drugs	Depression	Anxiety
18	Abstinence from opioid use	Drug craving	Stable relationships	NA

NA not available

Discussion

- **Concerns about interpretation of results of clinical trials.**
- **New assessment strategies needed to for studies.**
- **Trials evaluating OSATs suffer from poor methodological quality**
- **Need for more consensus in the field and understanding of what treatment outcomes are most important to addiction patients.**

Limitations

LIMITATIONS:

- **Study was not updated and lacked studies from the opioid crisis paradigm.**
- **Group consensus was not determined.**

Our Discussion

Thank You For Joining Us!

Next session is April 8 , 2021 @ 6:00pm MST via Zoom

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