Annual Review of Pain & Addiction Medicine: Key Publications from 2020-2021

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Prepared for the Pain & Addiction: Common Threads Course 2021

Presenter & Disclosure Information

William S. Jacobs MD, FASAM-

No Disclosures

Launette M. Rieb, MD, MSc, CCFP(AM), FCFP, FASAM-

Does Disclose: WorkSafeBC, for speaking at workshops and conferences on chronic pain and addiction management

Gregory Rudolf, MD, DFASAM- No Disclosures

Session Overview

Purpose

- New session to be held annually at the Pain & Addiction: Common Threads Course
- Key peer-reviewed manuscripts and notable publications from the last year on pain and addiction topics
- Intended to help busy providers stay on top of new research in the field

Methods

- Articles hand-selected by the ASAM Pain & Addiction Planning Committee
- Discussed and narrowed down from a list of over 50 articles to 12 articles
- Criteria for inclusion:
  - Published in 2020 (1 exception)
  - Intersection of pain & addiction
  - Deemed interesting and/or impactful
- Presented by 3 Committee Members

Consensus and Controversies Between Pain and Addiction Experts on the Prevention, Diagnosis, and Management of Prescription Opioid Use Disorder

Mark Kraus, MD, Nicholas Lintzeris, MBBS, FAChAM, PhD, Arun Bhaskar, MSc, FRCA, FFPMRCA, FFICM, FIPP, Hannu Alho, MD, PhD, Eli Alon, MD, Didier Bouhassira, MD, PhD, Gonzalo Haro, MD, PhD, Oscar D'Agnone, MD, MRCPsych, Maurice Dematteis, MD, PhD, Kai-Uwe Kern, MD, Icro Maremmani, MD, Serge Perrot, MD, Reinhard Sittl, MD, and Kaitlin Pellicano, MD

Objectives: Prescription opioid use disorder (POUD) is an established public health crisis in many countries, and current evidence indicates it is a growing problem in Europe. Many specialists play a role, including pain and addiction medicine specialists, in the diagnosis and management of POUD, but neither group can fully address these patients' needs alone. The purpose of this consensus process was to bring together experts from pain and addiction medicine to examine the positions of both specialties.

Methods: In all, 13 international pain medicine, addiction medicine, and addiction psychiatry experts convened a meeting to formulate a set of consensus statements on the diagnosis and management of POUD. The statements were further refined by a wider group of 22 European expert clinicians. At a second meeting of all 35 participants, a set of controversy statements was also developed to recognize some of the key areas of divergent opinion.

Results/conclusions: There was a high level of agreement between pain and addiction specialists. Key themes that emerged were the need to strengthen interdisciplinary communication, a desire for greater education and training for clinicians in both specialties, and mutual acknowledgment of the importance of

Kraus et al. 2020, J Addict Med

- Highlights & Methods
  - 13 international pain medicine, addiction medicine, and addiction psychiatry experts convened a meeting to formulate a

    set of consensus statements on the diagnosis and management

    of POUD
  - 35 participants, a set of controversy statements was also developed to recognize some of the key areas of divergent opinion.
  - High level of agreement between pain and addiction specialists

Kraus et al. 2020, J Addict Med

- Results
  - There is mounting evidence that, while less established than in the USA, POUD is increasingly problematic in Europe,
  - “Prescription opioid use’’ is referring to medical use as per the intentions of an authorizing prescriber for the treatment of a legitimate health condition
  - ‘‘Nonmedical use’’ is use not prescribed for a medical condition but also not meeting a pattern of use consistent with a use disorder.
  - Efforts are being made in providing clinicians with training and resources for treating this patient population (ie, ‘‘Common Threads’’ as provided by American Society of Addiction Medicine

Kraus et al. 2020, J Addict Med

- Conclusions
  - Modified Delphi approach employed to develop and refine both the consensus and the controversy statements. a process of arriving at group consensus by providing experts with several rounds of questionnaires and feedback, and also the group response before each subsequent round
  - The average level of complete agreement was 87%. The average level of combined complete and partial agreement was 99%. average percentage of complete agreement was 86% for pain. and 87% for addiction clinicians; the median percentage of complete agreement was 89% for both groups
  - First major multinational paper on POUD

Kraus et al. 2020, J Addict Med

- Limitations
  - Only involved specialists, despite evidence that primary care providers are frequent prescribers of opioid analgesics for chronic pain (Blake et al., 2015). The absence of primary care practitioners from this consensus process represents a key omission
  - Identify conceptual issues, rather than to provide specific clinical recommendations
  - It was not possible to find a definition of POUD on which the majority of OPEN participants could agree

Research Paper

PAIN

VIDEO

Receipt of multiple outpatient opioid prescriptions is associated with increased risk of adverse outcomes in youth: opioid prescribing trends, individual characteristics, and outcomes from 2005 to 2016

Melissa Pielech[a,b,*], Eric Kruger[b,c], William Evan Rivers[d], Harry E. Snow[e], Kevin E. Vowles[f]

Abstract

Data on all outpatient opioid prescriptions (N = 71,647) to youth below age 21 (N = 42,020) from 2005 to 2016 were extracted from electronic medical records within a university hospital system in New Mexico (NM) as were demographic details and markers of morbidity/mortality. Relative risk was calculated for markers of morbidity/mortality based on sociodemographic characteristics. The sample was primarily male (55.0%), Hispanic/Latinx (50.1%), English-speaking (88.9%), and publicly insured (50.1%). Mean age was 13.54 (SD = 6.50). From 2005 to 2016, overall frequency of opioid prescriptions increased by 86.6% (from 2470 to 4610) with the largest increase (206.2%) observed from 2005 to 2008 (2470-7562). Patients who were older, white, and non-Hispanic were more likely to receive multiple opioid prescriptions. Large relative increases in morbidity and mortality were documented, although base rates remained low. The percentage of individuals within the sample who experienced an overdose increased steadily from 0 in 2005 to 1.09% in 2016. Incidence of mortality increased from 0.12% of the sample to 1.39% in 2016. The proportion of individuals who received a medication for the treatment of opioid dependence increased from 0.06% in 2005 to 0.44% in 2016. Significantly increased risk of adverse outcomes was observed in patients receiving multiple opioid prescriptions, and in patients who were older, of minority race, received their first prescription in an outpatient clinic, and publicly insured or uninsured. Results add to the growing literature concerning opioid prescription rates over time. They also provide important information on potential additive risks of adverse outcomes when pediatric patients receive multiple opioid prescriptions.

Keywords: Opioids, Pediatric pain, Prescribing, Overdose, Adolescents

Pielech et al. 2020, Pain

- Methods & Results
  - All outpatient opioid prescriptions (N571,647) to youth below age 21 (N542,020) from 2005 to 2016 were extracted from electronic medical records within a university hospital system in New Mexico (NM)
  - From 2005 to 2016, overall frequency of opioid prescriptions increased by 86.6% (from 2470 to 4610) with the largest increase (206.2%) observed from 2005 to 2008 (2470-7562).
  - Patients who were older, white, and non-Hispanic were more likely to receive multiple opioid prescriptions.

Pielech et al. 2020, Pain

- Conclusions
  - Large relative increases in morbidity and mortality were documented, although base rates remained low.
    - The percentage of individuals within the sample who experienced an overdose increased steadily from 0 in 2005 to 1.09% in 2016.
    - Incidence of mortality increased from 0.12% of the sample to 1.39% in 2016.
    - The proportion of individuals who received a medication for the treatment of opioid dependence increased from 0.06% in 2005 to 0.44% in 2016.
    - Significantly increased risk of adverse outcomes was observed in patients receiving multiple opioid prescriptions, and in patients who were older, of minority race, received their first prescription in an outpatient clinic, and publicly insured or uninsured

JAMA Pediatrics | Original Investigation

Association of Opioid Prescription Initiation During Adolescence and Young Adulthood With Subsequent Substance-Related Morbidity

Patrick D. Quinn, PhD; Kimberly L. Fine, PhD; Martin E. Rickert, PhD; Ayesha C. Sujan, MA; Katja Boersma, PhD; Zheng Chang, PhD; Johan Franck, MD, PhD; Paul Lichtenstein, PhD; Henrik Larsson, PhD; Brian M. D'Onofrio, PhD

IMPORTANCE Concerns about adverse outcomes associated with opioid analgesic prescription have led to major guideline and policy changes. Substantial uncertainty remains, however, regarding the association between opioid prescription initiation and increased risk of subsequent substance-related morbidity.

OBJECTIVE To examine the association of opioid initiation among adolescents and young adults with subsequent broadly defined substance-related morbidity.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed population-register data from January 1, 2007, to December 31, 2013, on Swedish individuals aged 13 to 29 years by January 1, 2013, who were naive to opioid prescription. To account for confounding, the analysis compared opioid prescription recipients with recipients of nonsteroidal anti-inflammatory drugs as an active comparator, compared opioid-recipient twins and other multiple birth individuals with their nonrecipient co-multiple birth offspring (co-twin control), examined dental prescription as a specific indication, and included individual, parental, and socioeconomic covariates. Data were analyzed from March 30, 2019, to January 22, 2020.

EXPOSURES Opioid prescription initiation, defined as first dispensed opioid analgesic prescription.

MAIN OUTCOMES AND MEASURES Substance-related morbidity, assessed as clinically diagnosed substance use disorder or overdose identified from inpatient or outpatient specialist records, substance use disorder or overdose cause of death, dispensed pharmacotherapy for alcohol use disorder, or conviction for substance-related crime.

Supplemental content

Quinn et al. 2020, JAMA Pediatrics

- Purpose
  - Cohort study analyzed population-register data from January 1, 2007, to December 31, 2013, on Swedish individuals aged 13 to 29 years by January 1, 2013, who were naive to opioid prescription.
- Method
  - To account for confounding, the analysis compared opioid prescription recipients with recipients of nonsteroidal anti-inflammatory drugs as an active comparator, compared opioid-recipient twins and other multiple birth individuals with their nonrecipient co-multiple birth offspring (co-twin control), examined dental prescription as a specific indication, and included individual, parental, and socioeconomic covariates

Quinn et al. 2020, JAMA Pediatrics

- Methods (Continued)
  - Opioid prescription initiation, defined as first dispensed opioid analgesic prescription.
  - Included cohort (n = 1 541 862; 793 933 male [51.5%]), 193 922 individuals initiated opioid therapy by December 31, 2013 (median age at initiation, 20.9 years [interquartile range, 18.2-23.6 years]).

Quinn et al. 2020, JAMA Pediatrics

- Results
  - The active comparator design included 77 143 opioid recipients without preexisting substance-related morbidity and 229 461 nonsteroidal anti-inflammatory drug recipients.
  - The adjusted cumulative incidence of substance-related morbidity within 5 years was 6.2%(95%CI, 5.9%-6.5%) for opioid recipients and 4.9% (95% CI, 4.8%-5.1%) for nonsteroidal anti-inflammatory drug recipients (hazard ratio, 1.29; 95%CI, 1.23-1.35).
  - The co-twin control design produced comparable results (3013 opioid recipients and 3107 nonrecipients; adjusted hazard ratio, 1.43; 95%CI, 1.02-2.01), as did restriction to analgesics prescribed or dental indications and additional sensitivity analyses.

Quinn et al. 2020, JAMA Pediatrics

- Conclusions
  - Among adolescents and young adults analyzed in this study, initial opioid prescription receipt was associated with an approximately 30% to 40% relative increase in risk of subsequent substance-related morbidity in multiple designs that adjusted for confounding.

Biological Psychiatry

Review

Neurobiology of Opioid Addiction: Opponent Process, Hyperkatifeia, and Negative Reinforcement

George F. Koob

ABSTRACT

Opioids are powerful drugs that usurp and overpower the reward function of endogenous opioids and engage dramatic tolerance and withdrawal via molecular and neurocircuitry neuroadaptations within the same reward system. However, they also engage the brain systems for stress and pain (somatic and emotional) while producing hyperalgesia and hyperkatifeia, which drive pronounced drug-seeking behavior via processes of negative reinforcement. Hyperkatifeia (derived from the Greek "katifeia" for dejection or negative emotional state) is defined as an increase in intensity of the constellation of negative emotional or motivational signs and symptoms of withdrawal from drugs of abuse. In animal models, repeated extended access to drugs or opioids results in negative emotion-like states, reflected by the elevation of reward thresholds, lower pain thresholds, anxiety-like behavior, and dysphoric-like responses. Such negative emotional states that drive negative reinforcement are hypothesized to derive from the within-system dysregulation of key neurochemical circuits that mediate incentive-salience and/or reward systems (dopamine, opioid peptides) in the ventral striatum and from the between-system recruitment of brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors) in the extended amygdala. Hyperkatifeia can extend into protracted abstinence and interact with learning processes in the form of conditioned withdrawal to facilitate relapse to compulsive-like drug seeking. Compelling evidence indicates that plasticity in the brain pain emotional systems is triggered by acute excessive drug intake and becomes sensitized during the development of compulsive drug taking with repeated withdrawal. It then persists into protracted abstinence and contributes to the development and persistence of compulsive opioid-seeking behavior.

Keywords: Addiction, Dysphoria, Hyperkatifeia, Negative reinforcement, Opioids, Stress

https://doi.org/10.1016/j.biopsych.2019.05.023

Koob 2020, Bio Psych

- Highlights
  - Opioids overpower the endogenous opioid system, altering reward pathways (via dopamine, opioid peptides), resulting in tolerance and withdrawal leading to continued drug seeking due to negative reinforcement (relief with use)
  - Opioids sensitize the systems involved with stress (producing hyperkatefeia) and pain (producing hyperalgesia) via corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors in the extended amygdala and elsewhere
  - Excessive drug intake and repeated withdrawal episodes contribute sensitization, protracted abstinence syndrome and compulsive opioid seeking behavior

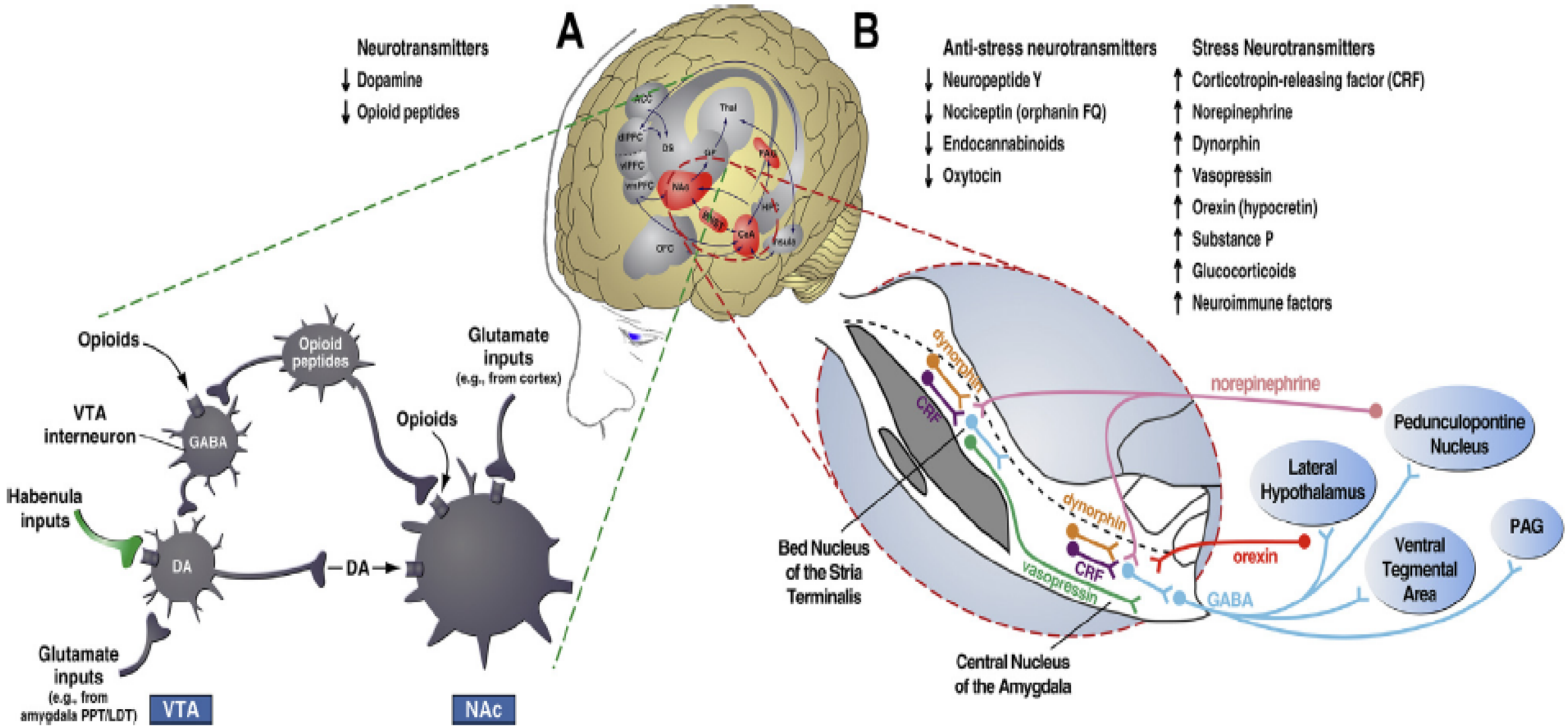

Figure 2. Neural circuitry associated with the negative emotional state of the withdrawal/negative affect stage. **(A)** Extended amygdala and within-system

Koob, 2020

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Withdrawal-associated injury site pain prevalence and correlates among opioid-using people who inject drugs in Vancouver, Canada

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ARTICLE INFO

Keywords:
Pain
Substance withdrawal syndrome
Opioid
Opioid dependence
Hyperalgesia
Observational cohort study

ABSTRACT

Background: Pain can return temporarily to old injury sites during opioid withdrawal. The prevalence and impact of opioid withdrawal-associated injury site pain (WISP) in various groups is unknown.

Methods: Using data from observational cohorts, we estimated the prevalence and correlates of WISP among opioid-using people who inject drugs (PWID). Between June and December 2015, data on WISP and opioid use behaviours were elicited from participants in three ongoing prospective cohort studies in Vancouver, Canada, who were aged 18 years and older and who self-reported at least daily injection of heroin or non-medical prescription opioids.

Results: Among 631 individuals, 276 (43.7 %) had a healed injury (usually pain-free), among whom 112 (40.6 %) experienced WISP, representing 17.7 % of opioid-using PWID interviewed. In a multivariable logistic regression model, WISP was positively associated with having a high school diploma or above (Adjusted Odds Ratio [AOR] = 2.23, 95 % Confidence Interval [CI]: 1.31 – 3.84), any heroin use in the last six months (AOR = 2.00, 95 % CI: 1.14 – 3.57), feeling daily pain that required medication (AOR = 2.06, CI: 1.18 – 3.63), and negatively associated with older age at first drug use (AOR = 0.96, 95 % CI: 0.93 – 0.99). Among 112 individuals with WISP, 79 (70.5 %) said that having this pain affected their opioid use behaviour, of whom 57 (72.2 %) used more opioids, 19 (24.1 %) avoided opioid withdrawal, while 3 (3.8 %) no longer used opioids to avoid WISP.

Conclusions: WISP is prevalent among PWID with a previous injury, and may alter opioid use patterns. Improved care strategies for WISP are warrented.

Rieb et al. 2020, Drug Alc Dep

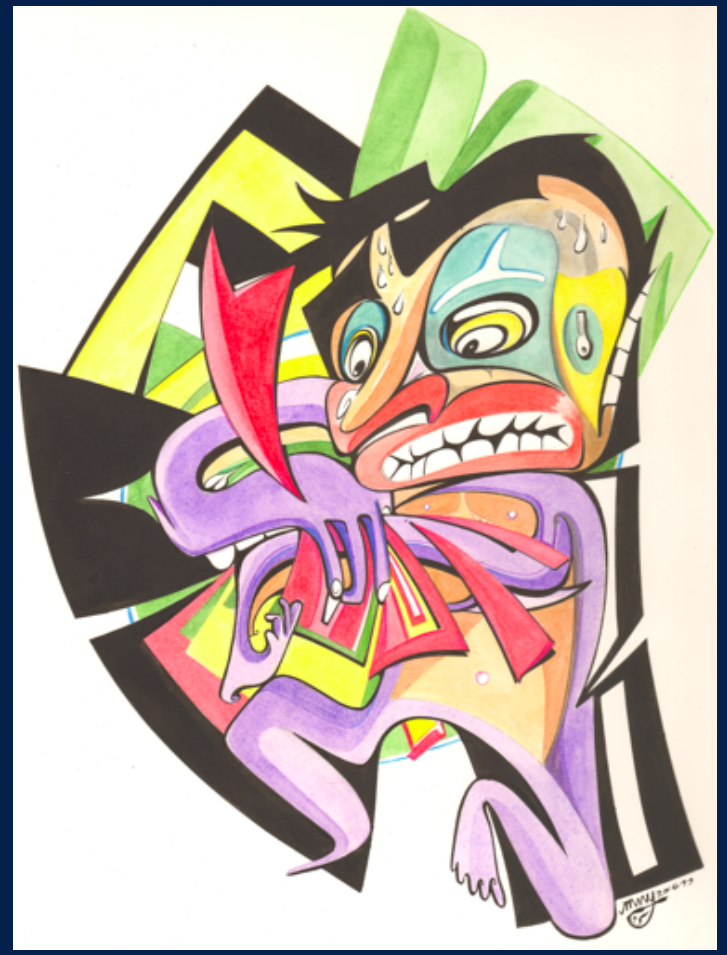
- **Background**
  - In a prior study, a novel physically and emotionally aversive pain phenomenon was identified during opioid withdrawal in which pain can temporarily return to injury sites that were previously healed and pain-free, and resolve after withdrawal is over (Rieb et al., 2016). Withdrawal-associated injury site pain (WISP) may be linked to opioid-induced hyperalgesia, and be due to noradrenaline, neuroimmune, and/or neuroinflammatory mechanisms (Rieb et al. 2018), but prevalence is unknown
- **Purpose**
  - Document the prevalence of withdrawal-associated injury site pain (WISP) among people who inject drugs (PWID); identify associated features; outline the impact of WISP on drug use behavior
- **Methods**
  - For six months in 2015, opioid use behavior and pain experiences were elicited from daily injection opioid users 18 years or older participating in three ongoing questionnaire based cohort studies in Vancouver, Canada

Rieb 2020, Drug Alc Dep

- **Results**
  - Among 631 individuals, 276 (43.7 %) had a healed injury (usually pain-free), among whom 112 (40.6%) experienced WISP, representing 17.7 % of all daily opioid-using PWID interviewed
  - Among 112 individuals with WISP, 79 (70.5 %) said that having this pain affected their opioid use behaviour, of whom 57 (72.2 %) used more opioids, 19 (24.1 %) avoided opioid withdrawal, while 3 (3.8 %) no longer used opioids to avoid WISP
  - WISP was negatively correlated with neuropathic pain, which in turn was correlated with taking NSAIDS and gabapentin which thus may be protective against WISP
- **Limitations**
  - Did not ask about their chronic pain sites and if these too hurt more during withdrawal

Rieb et al. 2020, Drug Alc Dep

- Conclusions
  - WISP Prevalence: 40 % of a community-recruited sample of opioid-using PWID with previously pain-free injury sites
  - WISP was identified as contributing to ongoing opioid use in the vast majority of those with this type of pain experience
  - Thus WISP may be one of the hidden drivers of continued opioid use in PWID
  - Prospective trials needed to test treatments that may mitigate WISP



ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

REVIEW

doi:10.1111/add.15160

Aberrations in peripheral inflammatory cytokine levels in substance use disorders: a meta-analysis of 74 studies

Ze-Xu Wei[1], Lei Chen[1], Jian-Jun Zhang[2,3] & Yong Cheng[1]

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ABSTRACT

Aims To characterize the peripheral inflammatory cytokine profile in people with substance use disorders (SUDs). **Design** Systematic review and meta-analysis. **Setting** Clinical studies that evaluated peripheral blood inflammatory cytokine levels in patients with SUDs and healthy controls **Participants** SUD patients and healthy controls. **Measurements** PubMed and Web of Science were systematically searched for relevant studies. Two investigators independently selected studies and extracted data. A total of 77 articles were included in the meta-analysis, containing 5649 patients with SUDs and 4643 healthy controls. Data were pooled using a random-effects model by the Comprehensive Meta-Analysis version 2 software. **Findings** Concentrations of interleukin (IL)-6) in 32 studies, tumor necrosis factor (TNF)-α in 28 studies, IL-10 in 20 studies, IL-8 in 17 studies, C-reactive protein in 14 studies, IL-4 in 10 studies, IL-12 in seven studies, monocyte chemoattractant protein (MCP)-1 in 6 studies, TNF-receptor 2 (TNF-R2) in four studies and granulocyte–macrophage colony-stimulating factor (GM-CSF) in three studies were significantly higher in patients with SUDs compared with healthy controls, while concentrations of leptin in 14 studies were significantly lower in patients with SUDs compared with healthy controls. The findings were inconclusive for the associations between interferon-γ, IL-1β, IL-2, IL-1 receptor antagonist (IL-1RA), transforming growth factor (TGF)-β1, G-CSF, C-C motif chemokine 11, TGF-α and SUDs. **Conclusions** People with substance use disorders (SUDs) appear to have higher peripheral concentrations of IL-4, IL-6, IL-8, IL-10, IL-12, TNF-α, C-reactive protein, MCP-1, TNF-R2 and GM-CSF and lower peripheral concentrations of leptin than people without SUDs. This strengthens the view that SUD is accompanied by an inflammatory response.

Ze-Xu et al. 2020, SSA

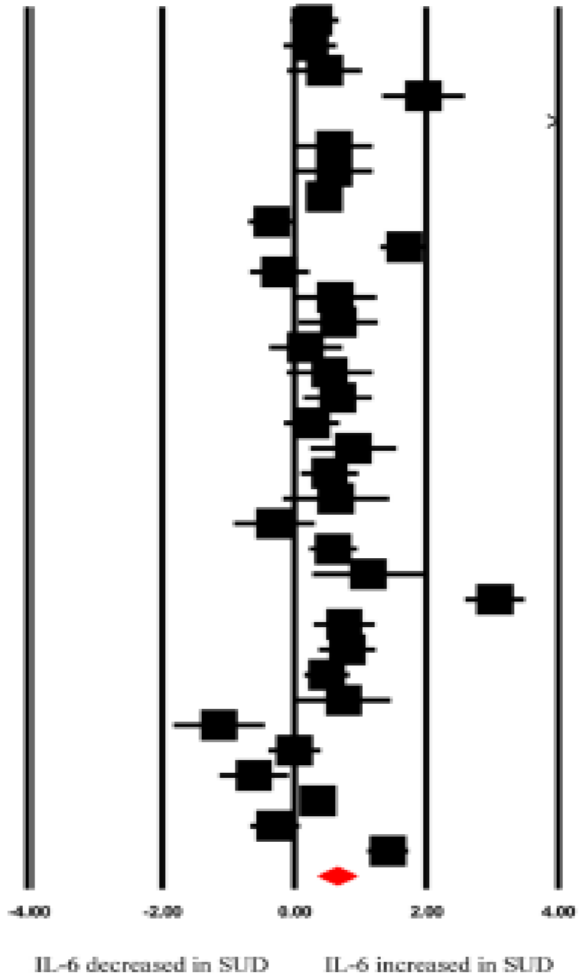
- Background
  - Conflicting data on cytokines association with SUD
  - To characterize the peripheral inflammatory cytokine profile in people with substance use disorders (SUD)
- Methods
  - 1st systematic review and meta-analysis of studies of peripheral blood inflammatory cytokine levels in people with SUD and healthy controls found on PubMed and Web of Science, two independent researcher selected articles and extracted data

Ze-Xu et al. 2020, SSA

- **Results**
  - 77 studies, 5649 patients with SUD (mainly alcohol, opioids and stimulants) and 4643 controls included in the meta-analysis
  - Concentrations of the following cytokines were significantly higher in patients with SUDs compared with healthy controls: interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-10, IL-8, C-reactive protein, IL-4, IL-12, monocyte chemoattractant protein (MCP)-1, TNF-receptor 2 (TNF-R2) and granulocyte–macrophage colony-stimulating factor (GM-CSF); Concentrations of leptin were significantly lower
- **Limitations**
  - directionality/causality; pooled data, other co-morbidities

IL-6 increased in SUD

Study name	Subgroup within study	Hedges's g	Lower limit	Upper limit	p-Value
Wang TY et al. 2018	opioid	0.306	-0.048	0.658	0.091
Lee SY et al. 2015	opioid	0.239	-0.149	0.626	0.228
Chan YY et al. 2015	opioid	0.460	-0.091	1.011	0.102
Nabati S et al. 2013	opioid	1.957	1.347	2.567	0.000
Li JR et al. 2011	opioid	5.277	4.429	6.125	0.000
Rios-Olivares E et al. 2006	cocaine	0.607	0.045	1.169	0.034
Rios-Olivares E et al. 2006	opioid	0.607	0.045	1.169	0.034
Archer M et al. 2018	alcohol	0.450	0.191	0.709	0.001
Zahr NM et al. 2018	alcohol	-0.344	-0.689	0.001	0.051
Yen CH et al. 2017	alcohol	1.670	1.315	2.024	0.000
Wagner N et al. 2016	alcohol	-0.225	-0.664	0.213	0.314
Bailey KL et al. 2015	alcohol	0.621	0.007	1.235	0.047
Heberlein A et al. 2014	alcohol	0.665	0.075	1.255	0.027
González-Reimers E et al. 2012	alcohol	0.169	-0.368	0.707	0.537
González-Reimers E et al. 2011	alcohol	0.534	-0.101	1.169	0.099
Vidali M et al. 2008	alcohol	0.656	0.153	1.158	0.011
González-Reimers E et al. 2007	alcohol	0.261	-0.144	0.666	0.207
Nicolaou C et al. 2004	alcohol	0.890	0.252	1.528	0.006
Santolaria F et al. 2003	alcohol	0.535	0.117	0.954	0.012
De Vos N et al. 1999	alcohol	0.631	-0.161	1.424	0.119
Khoruts A et al. 1991	alcohol	-0.304	-0.908	0.300	0.324
González-Quintela A et al. 1999	alcohol	0.587	0.238	0.937	0.001
Maes M et al. 1999	alcohol	1.118	0.283	1.952	0.009
Pianca TG et al. 2017	cocaine	3.036	2.597	3.475	0.000
Lewandowski ML et al. 2016	cocaine	0.755	0.306	1.205	0.001
Lewandowski ML 2 et al. 2016	cocaine	0.802	0.383	1.221	0.000
Mardini V et al. 2016	cocaine	0.490	0.161	0.819	0.003
Moreira FP et al. 2015	cocaine	0.751	0.051	1.450	0.035
Pedraz M et al. 2015	cocaine	-1.141	-1.817	-0.466	0.001
Narvaez JC et al. 2013	cocaine	0.000	-0.384	0.384	1.000
Halpern JH et al. 2003	cocaine	-0.615	-1.126	-0.103	0.018
Ugur MG et al. 2018	nicotine	0.354	0.143	0.565	0.001
Keen L nd et al. 2014	marijuana	-0.297	-0.661	0.067	0.110
Fan N et al. 2015	ketamine	1.420	1.122	1.718	0.000
		0.653	0.372	0.934	0.000



Ze-Xu, 2020

Ze-Xu et al. 2020, SSA

- Conclusions
  - The authors discuss literature indicating that inflammation can play a role in SUD pathogenesis (i.e. inflammation may play a role in developing SUD), as well as SUD inducing inflammation both directly (e.g. dopamine oxidative effects) and via impact on other organs (e.g. gut in binge drinkers)
  - This study strengthening the view that SUD is accompanied by an inflammatory response
  - Prospective longitudinal studies are needed on risk and protective factors, as well as mitigation of inflammation in those with SUD

Research Paper

PAIN

VIDEO

Impact of opioid dose escalation on pain intensity: a retrospective cohort study

Corey J. Hayes[a,b], Erin E. Krebs[c,d], Teresa Hudson[a,b], Joshua Brown[e], Chenghui Li[f], Bradley C. Martin[f,*]

Abstract

Prescribers are often confronted with the decision to escalate opioid doses to achieve adequate analgesia. Understanding the impact of dose escalation on pain intensity is warranted. Using a retrospective cohort study design, Veterans with chronic pain and chronic opioid therapy were identified. Opioid dose escalators (>20% increase in average morphine milligram equivalent daily dose) were compared with dose maintainers (±20% change in average morphine milligram equivalent daily dose) assessed over 2 consecutive 6-month windows. Pain intensity was measured by the Numeric Rating Scale. The primary analyses used linear repeated-measures models among a 1:1 matched sample of escalators and maintainers matched on propensity score and within ±180 days of the index date. Sensitivity analyses were conducted using adjusted linear repeated-measures models with and without incorporating stabilized inverse probability of treatment weighting. There were 32,420 dose maintainers and 20,767 dose escalators identified with 19,358 (93%) matched pairs. Pain scores were persistently higher among dose escalators at each 90-day period after the index date (0-90 days after index date: dose escalators: 4.68, 95% confidence interval [CI]: 4.64-4.72 dose maintainers: 4.32, 95% CI: 4.28-4.36, $P < 0.0001$; 91-180 days after index date: dose escalators: 4.53, 95% CI: 4.49-4.57; dose maintainers: 4.25, 95% CI: 4.22-4.29, $P < 0.0001$) but were not different in the 90 days before the index date (dose escalators: 4.64, 95% CI: 4.61-4.68; dose maintainers: 4.59, 95% CI: 4.55-4.63, $P = 0.0551$). Sensitivity analyses provided similar results as the primary analyses. Opioid dose escalation among patients with chronic pain is not associated with improvements in Numeric Rating Scale pain scores.

Keywords: Opioids, Dose escalation, Pain intensity, Numeric Rating Scale, Pain scores

Hayes et al. 2020, Pain

- **Background**
  - Clinicians are often asked to increase opioid doses to achieve adequate analgesia
  - To understand the effect of opioid dose escalation on self-reported chronic noncancer pain intensity
- **Methods**
  - Retrospective cohort design spanning 2008-2018 investigating US veterans 18 years and older with chronic non-cancer pain on long-term opioid therapy for at least a year.
  - Dose escalators (>=20% dose elevation) and dose maintainers (<20% dose change) were compared using Numeric Rating Scale (0-10) recorded in electronic medical records.
  - Matched pairs were created controlling for covarients (age, race, urban/rural, physical and mental health status, meds, etc.) Excluded vets with over 20% drop in morphine milligram equivalent (MME), those on over 1000 mg MME, and those with SUD

Hayes et al. 2020, Pain

- **Results**
  - 32,420 dose maintainers and 20,767 dose escalators identified with 19,358 (93%) matched pairs, mainly urban men between 50-60 yrs
  - In the 90 days before the index date (dose change) there was no difference in MME, nor pain scoring between dose escalators (4.64, 95% CI: 4.61-4.68) and dose maintainers (4.59, 95% CI: 4.55-4.63, P5 0.0551)
  - Pain scores were persistently higher among dose escalators at each 90-day period after the index date (MME 45 vs 28):
    - Day 0-90: dose escalators: 4.68, 95% CI: 4.64-4.72 dose maintainers: 4.32, 95% CI: 4.28-4.36, P , 0.0001
    - Day 91-180: dose escalators: 4.53, 95% CI: 4.49-4.57; dose maintainers: 4.25, 95% CI: 4.22-4.29, P,0.0001)
  - Pain dropped significantly in opioid maintainers
- **Limitations**
  - Quality of life and adverse side effects not measured, changes in the underlying pain condition or later medication changes are not accounted for

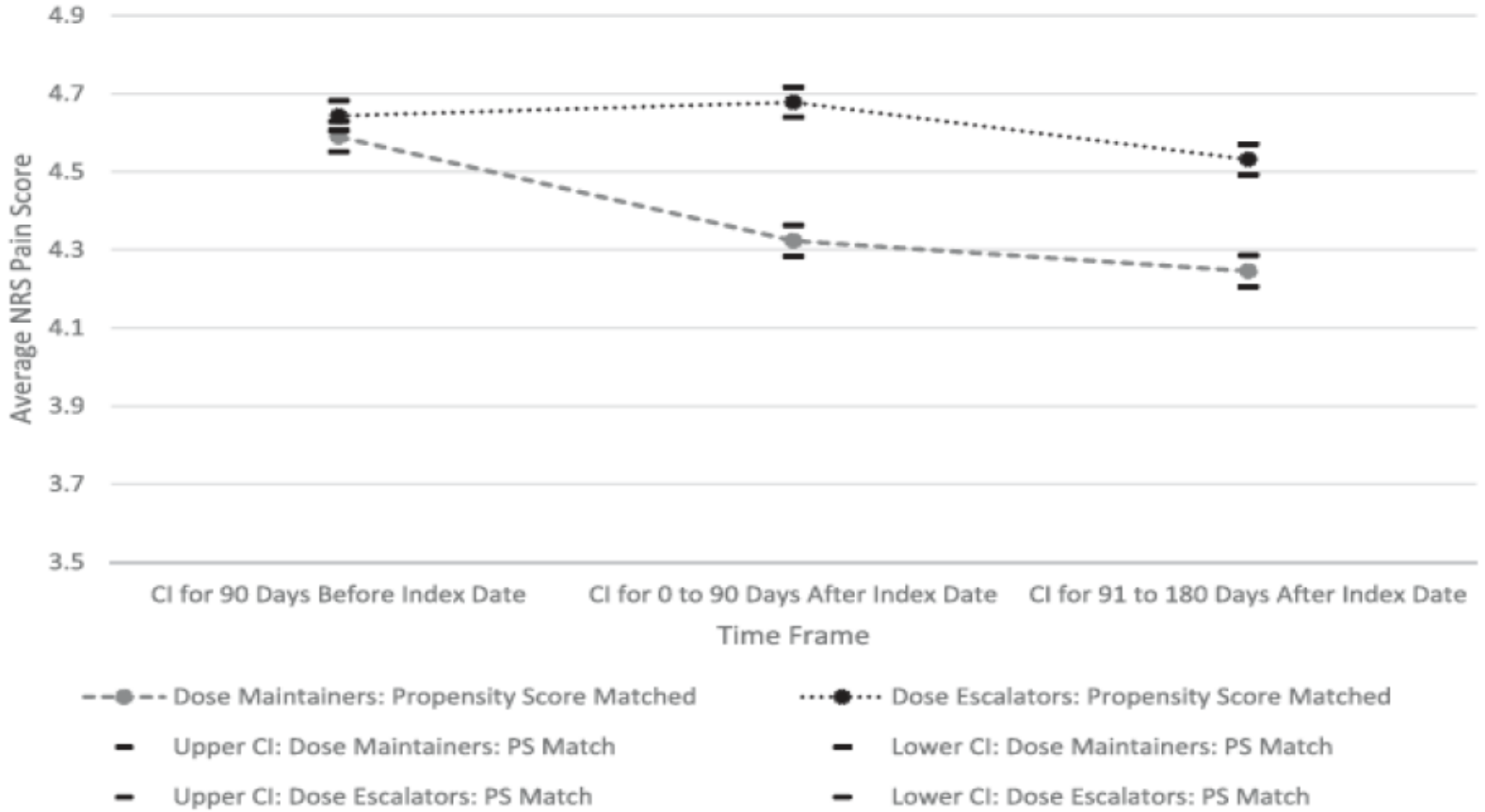


Figure 2. Average pain scores over time between opioid dose escalators and maintainers among the propensity score-matched samples.

Hayes et al. 2020, Pain

- Conclusions
  - Opioid dose escalation among patients with chronic non-cancer pain is not associated with improvements in Numeric Rating Scale pain scores.
  - “Clinicians should exercise extreme caution when embarking on a path of increasing opioid doses to manage noncancer pain”
  - 40840567
  - Prospective studies are needed to understand the effect of opioid dose escalation (as well as controlled dose tapering) on chronic noncancer pain in those on opioid agonist therapy for an opioid use disorder

Research Paper

PAIN

OPEN

Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain

Danilo De Gregorio[a], Ryan J. McLaughlin[b], Luca Posa[a,c], Rafael Ochoa-Sanchez[a], Justine Enns[a], Martha Lopez-Canul[a], Matthew Aboud[a], Sabatino Maione[d], Stefano Comai[a,e], Gabriella Gobbi[a,c,*]

Abstract

Clinical studies indicate that cannabidiol (CBD), the primary nonaddictive component of cannabis that interacts with the serotonin $(5\text{-HT})_{1A}$ receptor, may possess analgesic and anxiolytic effects. However, its effects on 5-HT neuronal activity, as well as its impact on models of neuropathic pain are unknown. First, using in vivo single-unit extracellular recordings in rats, we demonstrated that acute intravenous (i.v.) increasing doses of CBD (0.1-1.0 mg/kg) decreased the firing rate of 5-HT neurons in the dorsal raphe nucleus, which was prevented by administration of the 5-HT_{1A} antagonist WAY 100635 (0.3 mg/kg, i.v.) and the $TRPV_1$ antagonist capsazepine (1 mg/kg, i.v.) but not by the CB_1 receptor antagonist AM 251 (1 mg/kg, i.v.). Repeated treatment with CBD (5 mg/kg/day, subcutaneously [s.c.], for 7 days) increased 5-HT firing through desensitization of 5-HT_{1A} receptors. Rats subjected to the spared nerve injury model for 24 days showed decreased 5-HT firing activity, mechanical allodynia, and increased anxiety-like behavior in the elevated plus maze test, open-field test, and novelty-suppressed feeding test. Seven days of treatment with CBD reduced mechanical allodynia, decreased anxiety-like behavior, and normalized 5-HT activity. Antiallodynic effects of CBD were fully prevented by capsazepine (10 mg/kg/day, s.c., for 7 days) and partially prevented by WAY 100635 (2 mg/kg/day, s.c., for 7 days), whereas the anxiolytic effect was blocked only by WAY. Overall, repeated treatment with low-dose CBD induces analgesia predominantly through $TRPV_1$ activation, reduces anxiety through 5-HT_{1A} receptor activation, and rescues impaired 5-HT neurotransmission under neuropathic pain conditions.

Keywords: Cannabidiol, Pain, Dorsal raphe, Electrophysiology, Anxiety

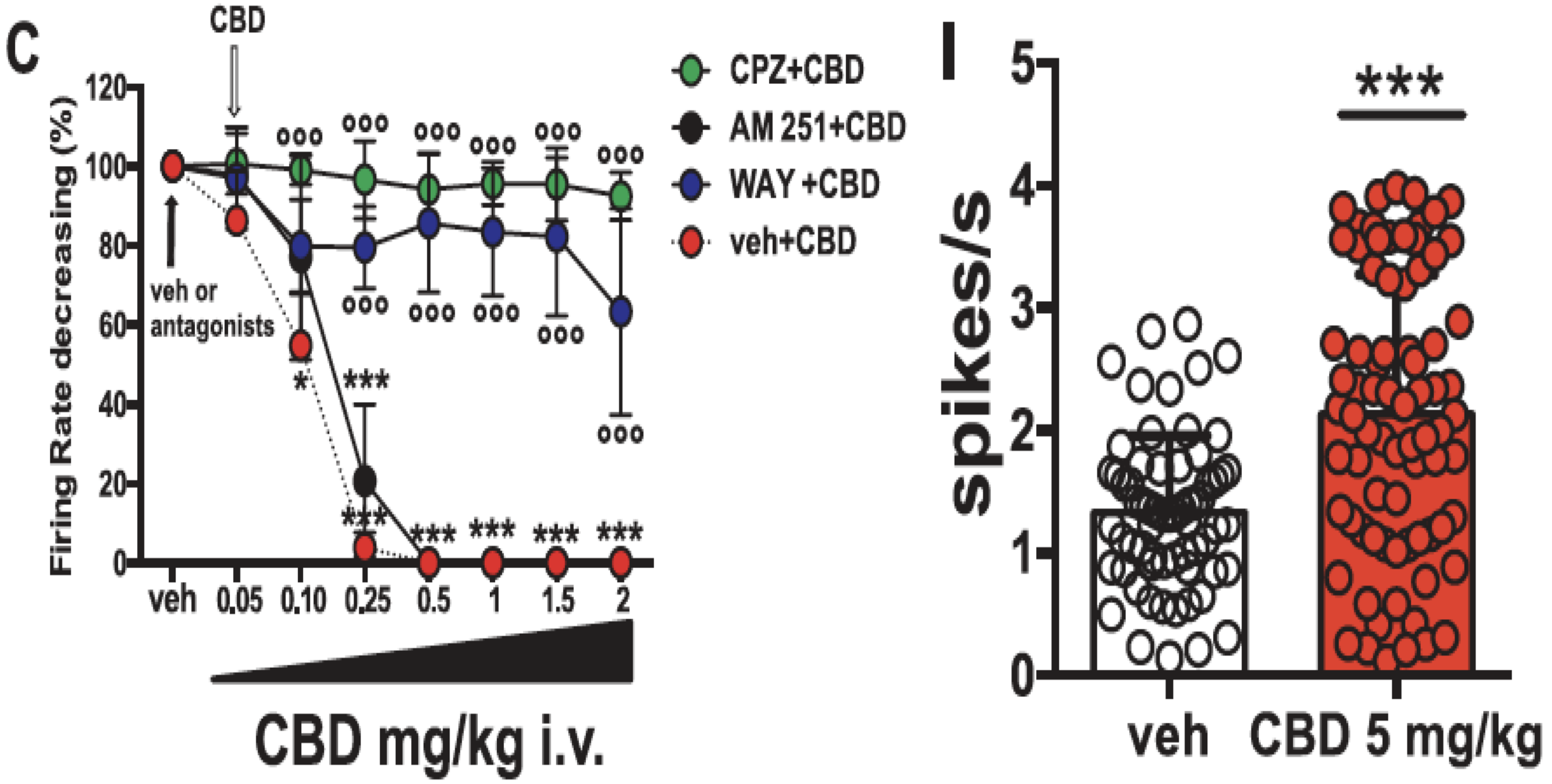
De Gregorio et al. 2019, Pain

- **Background**
  - Human clinical trials have suggested that cannabidiol (CBD), a non-addictive component of cannabis, may provide anxiolytic and analgesic effects among those with neuropathic pain. However, not much is known about CBDs effect on neuronal activity
  - To determine whether acute administration of CBD modulates DRN 5-HT neuronal activity in naive animals through 5-HT1A, CB1, or TRPV1 receptor–mediated mechanisms; examine the effect of repeated low-dose CBD treatment on mechanical allodynia, anxiety-like behaviors, and DRN 5-HT neuronal activity in the spared nerve injury (SNI) model of neuropathic pain in rats

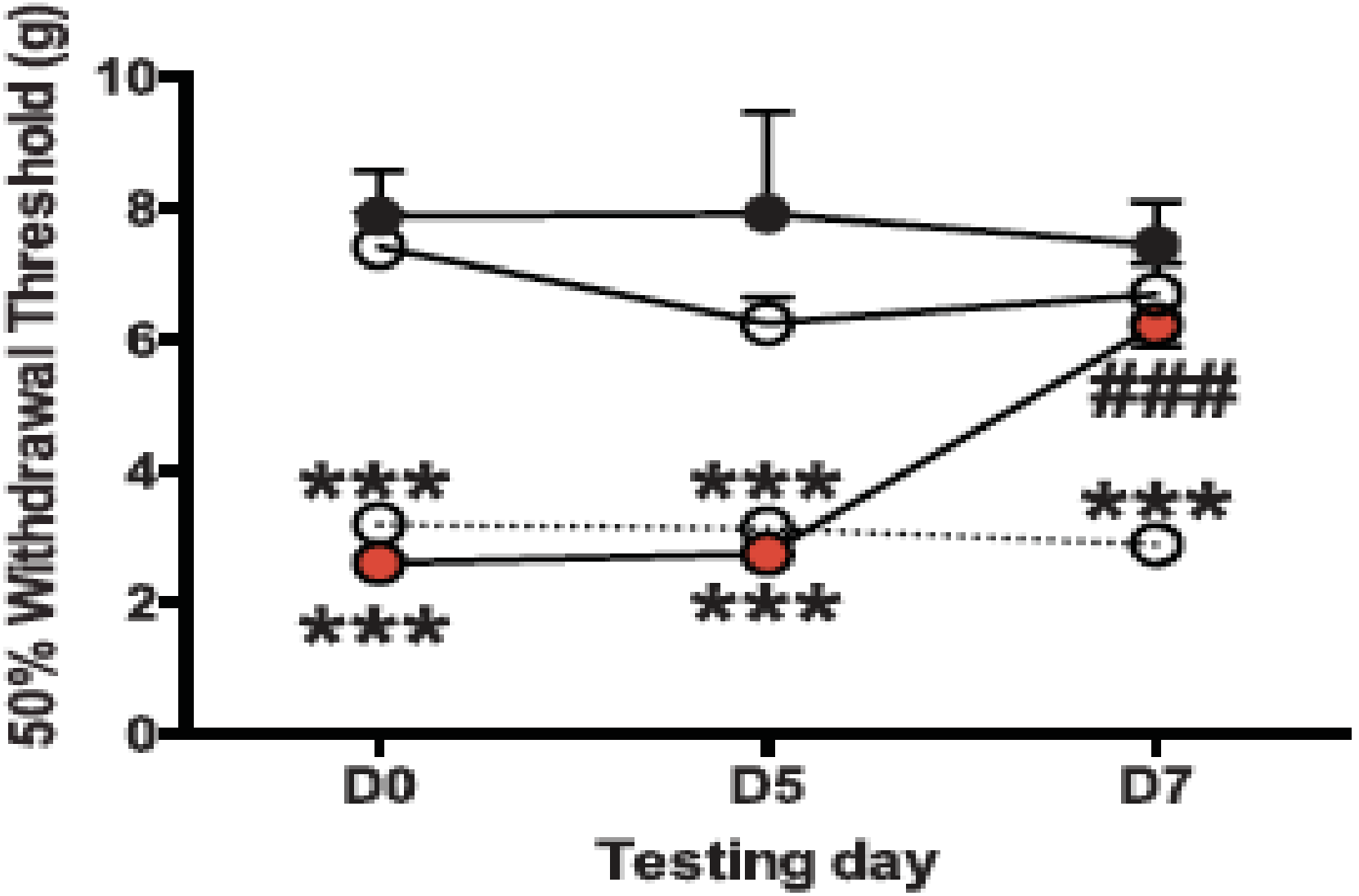
- **Methods**
  - In vivo single-unit extracellular recordings and behavioral experiments in 229 rats.
  - Measured the effect of increasing doses of CBD 0.1 -1.0 mg/kg on 5-HT neurons in the dorsal raphe nucleus before and after partial severing of sciatic nerve (SNI model), and before and after administration of a 5-HT antagonist and a TRPV1 antagonist

De Gregorio et al. 2019, Pain

- **Results**
  - In non-injured rats acute CBD i.v. administration decreased firing activity of DRN 5HT neurons (0.25mg/kg shut it down completely), whereas repeated CBD treatment (total of 5 mg/kg/d for 7 days) increased firing activity in DRN 5-HT neurons by making the 5-HT receptors less sensitive
  - Rats subjected to the SNI, over 24 days showed decreased 5-HT firing activity, mechanical allodynia, and increased anxiety-like behavior. But seven days of treatment with CBD reversed these effects
  - Antiallodynic effects of CBD were fully prevented by capsazepine – a TRPV1 anatagonist) and partially prevented by WAY 100635 – a 5-HT antagonist, whereas the anxiolytic effect was blocked only by WAY
- **Limitations**
  - routes of administration, animal study



De Gregorio, 2019


50% Withdrawal Threshold (g)
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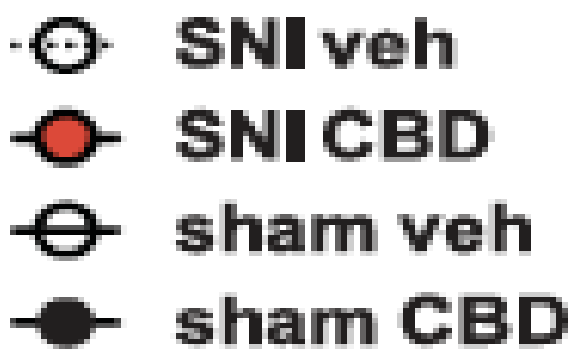
SNI veh
SNI CBD
sham veh
sham CBD


Von Frey test

De Gregorio et al. 2019, Pain

- **Conclusions:**
  - "Repeated treatment with low-dose CBD induces analgesia predominantly through TRPV1 activation, reduces anxiety through 5-HT1A receptor activation, and rescues impaired 5-HT neurotransmission under neuropathic pain conditions"
  - This study could inform clinical trials using CBD for neuropathic pain and related anxiety

40840567

Takeaways

- Opioids and some other addictive substances have been shown to alter elements of the nervous, inflammatory and immune systems to become more sensitive to pain and emotional states, particularly during withdrawal and early abstinence
- Pain can return temporarily to old injury sites during opioid withdrawal
- Escalating opioid dosing is unlikely to provide long-term pain benefit
- Prospective medication trials are needed (e.g. CBD, alpha-blockers, NSAIDS and immune modulators like ibudilast, gabapentinoids, naltrexone, buprenorphine, etc.) to assess their role in mitigation of symptoms of substance induced hyperalgesia and neuroinflammation

MAYO CLINIC

CONSENSUS RECOMMENDATION

Ensuring Patient Protections When Tapering Opioids: Consensus Panel Recommendations

Edward C. Covington, MD; Charles E. Argoff, MD; Jane C. Ballantyne, MD; Penney Cowan; Halena M. Gazelka, MD; W. Michael Hooten, MD; Stefan G. Kertesz, MD, MSc; Ajay Manhapra, MD; Jennifer L. Murphy, PhD; Steven P. Stanos, Jr, DO; and Mark D. Sullivan, MD, PhD

Abstract

Long-term opioid therapy has the potential for serious adverse outcomes and is often used in a vulnerable population. Because adverse effects or failure to maintain benefits is common with long-term use, opioid taper or discontinuation may be indicated in certain patients. Concerns about the adverse individual and population effects of opioids have led to numerous strategies aimed at reductions in prescribing. Although opioid reduction efforts have had generally beneficial effects, there have been unintended consequences. Abrupt reduction or discontinuation has been associated with harms that include serious withdrawal symptoms, psychological distress, self-medicating with illicit substances, uncontrolled pain, and suicide. Key questions remain about when and how to safely reduce or discontinue opioids in different patient populations. Thus, health care professionals who reduce or discontinue long-term opioid therapy require a clear understanding of the associated benefits and risks as well as guidance on the best practices for safe and effective opioid reduction. An interdisciplinary panel of pain clinicians and one patient advocate formulated recommendations on tapering methods and ongoing pain management in primary care with emphasis on patient-centered, integrated, comprehensive treatment models employing a biopsychosocial perspective.

 ■ Mayo Clin Proc. 2020;95(10):2155-2171

AMERICAN SOCIETY OF ADDICTION MEDICINE FOUNDED 1954 ASAM

Covington et al. 2020, Mayo

- Background
  - Follows from 2019 HHS opioid tapering guideline
  - Aimed at primary care in dealing with “legacy” higher dose long term opioid therapy (LTOT) patients
  - Expert consensus, with one pt advocate/participant
  - used existing literature (scant) and multiple draft revisions after 1-day mtg 4/16/19

Covington et al. 2020, Mayo

- Highlights
  - Clear, concise presentation of risks of LTOT, indications for tapering LTOT, common opioid WD sx, ensuring pt safety during taper
  - Provides “checklists” for before taper initiated, and for initiation/active tapering
  - Underscores harms of abrupt taper (physical and psych distress, illicit drug use, uncontrolled pain, suicide)
  - Refers to buprenorphine as a treatment option
    - Suggested if OUD present or taper fails (consistent with HHS 2019 guideline)

Covington et al. 2020, Mayo

- Limitations
  - Non-randomized assessment regarding opioid reduction/discontinuation vs LTOT maintenance vs transition to buprenorphine
  - No comment on larger debate/controversy over question of benefit of LTOT for chronic non-cancer pain (CNCP)

- Conclusions
  - Don’t stop opioids abruptly
  - Don’t abandon the pt or make “cold” referrals
  - Seek pt consent/collaboration with plan to taper
  - Consider buprenorphine
  - Monitor pt, provide support and make appropriate referrals
  - Diagnose and tx OUD
  - Document treatment response and adjust plan as needed

DISCUSSION PAPER

Best Practices, Research Gaps, and Future Priorities to Support Tapering Patients on Long-Term Opioid Therapy for Chronic Non-Cancer Pain in Outpatient Settings

Robert "Chuck" Rich, Jr., MD, FAAFP, Bladen Medical Associates and Campbell University; **Roger Chou, MD,** Oregon Health and Science University; **Edward R. Mariano, MD, MAS,** American Society of Anesthesiologists; **Anna Legreid Dopp, PharmD,** American Society of Health-System Pharmacists; **Rebecca Sullenger,** National Academy of Medicine; **Helen Burstin, MD, MPH,** Council of Medical Specialty Societies; and the **Pain Management Guidelines and Evidence Standards Working Group** of the Action Collaborative on Countering the U.S. Opioid Epidemic

August 10, 2020

Disclaimer: The views expressed in this paper are those of the authors and not necessarily of the authors' organizations, the National Academy of Medicine (NAM), or the National Academies of Sciences, Engineering, and Medicine (the National Academies). This paper is intended to inform and stimulate discussion. It is not a report of the NAM or the National Academies.

Rich et al. 2020, Nat'l Acad Medicine

- Background
  - Another expert consensus paper regarding tapering LTOT
  - Acknowledges that "evidence supporting use of opioids in managing CNCP is weak" and "strong evidence that LTOT among CNCP pts can be detrimental, esp high doses"
  - Balanced view of decision to taper
    - Advise "as much pt buy-in as possible"; mentions use of MI, CBT
    - "authors support sustaining pts on existing medication at current level if pt benefiting from use, no adverse effects, and pt declines taper"
    - Refers to 2019 HHS opioid tapering guideline, seeks to "build on it"

Rich et al. 2020, Nat'l Acad Medicine

- Limitations
  - No mention of buprenorphine except as treatment for withdrawal or OUD
  - Mostly narrative format, lots of uninterrupted text

- Conclusions
  - Tapering should generally be consensual with appropriate planning and support measures in place
  - Suggests areas of future research for improved approaches/outcomes

Secondary Analysis of Pain Outcomes in a Large Pragmatic Randomized Trial of Buprenorphine/Naloxone Versus Methadone for Opioid Use Disorder

Matisyahu Shulman, MD, Sean X. Luo, MD, Aimee N. C. Campbell, PhD, Jennifer Scodes, MS, Martina Pavlicova, PhD, Andi Broffman, MS, Andrew J. Saxon, MD, and Edward V. Nunes, MD

Objective: Opioid use disorder (OUD) is associated with chronic pain. We investigated the association between medication treatments for OUD and pain in a post-hoc secondary analysis of a randomized trial of methadone versus buprenorphine/naloxone.

Methods: 1241 individuals with OUD participated in an open label, pragmatic randomized trial of methadone versus buprenorphine/naloxone in nine treatment programs licensed to dispense agonist medication for OUD between 2006 to 2009. In this post-hoc analysis, pain was dichotomized (present or not present) using responses from the Short Form-36. Logistic regression models were fit to test the effect of (1) having baseline pain on week 24 retention, (2) treatment assignment on improvement in pain among those reporting pain at baseline, and (3) pain improvement at week 4 on week 24 retention among those reporting pain at baseline.

Results: Almost half (48.2%) of the sample reported pain at baseline. Participants with baseline pain did not significantly differ in week 24 retention compared to those without baseline pain. Among those reporting pain at baseline, there was no significant difference between treatment arms in improvement of pain at week 4, but improvement in pain at week 4 was associated with significantly greater odds of being retained at week 24 (OR [95% CI] = 1.76 [1.10, 2.82], $P = 0.020$).

Conclusion and Relevance: In this large multisite randomized trial of medication treatments for OUD, nearly half of the participants reported pain at baseline, and improvement in pain early in treatment was associated with increased likelihood of retention in treatment.

Key Words: buprenorphine, opioid use disorder, pain

(*J Addict Med* 2020;14: e188–e194)

Comorbid pain and opioid use disorder (OUD) are common; about 1 in 3 individuals requiring chronic opioids for pain also meet criteria for OUD (Boscarino et al., 2011). However, few studies of people with OUD consider pain as a moderator of treatment success.

Of the trials that have been conducted, there are mixed findings with regards to the association between pain and OUD outcomes. Trials of comorbid pain and OUD show that individuals with persistent pain after detoxification are at increased risk of continued opioid use when compared to those without persistent pain (Larson et al., 2007; Potter et al., 2010). Several trials show that addressing chronic pain improves cravings and other OUD outcomes (Garland et al., 2014; Ilgen et al., 2011), others found no evidence that pain is associated with differential retention or illicit drug use outcomes (Barry et al., 2009; Weiss et al., 2011). Considering the potential for pain to result in poorer OUD outcomes, additional research is needed to understand the relationship and improve treatment.

Shulman et al. 2020, JAM

- Background & Methods
  - Randomized 1241 pts from 9 OTPs 2006-2009 to either bup/nx or methadone, assessing dichotomized pain response (present or not present) before/during early phase of treatment (0-24 wks)
    - About ½ of pts reported pain at baseline
  - Compared retention in treatment, presence/absence of ongoing pain between pts on bup/nx and methadone
    - Both agents were dosed once daily

Shulman et al. 2020, JAM

- Highlights
  - No significant difference between bup/nx arm and methadone arm in # of pts reporting improvement in pain by week 4
    - Younger age, higher maximum dose were associated with improved pain
  - Presence of baseline pain not predictive of retention at week 24
  - High prevalence of baseline pain
  - Improvement in pain at week 4 was associated with greater retention
  - Pts on methadone arm had 2.78x greater odds of retention at week 24 compared to bup/nx

Shulman et al. 2020, JAM

- Limitations
  - Once daily dosing
  - No differentiation in type or duration of pain symptoms
  - Use of Short form-36 (non-specific)
  - No accounting for role of withdrawal-mediated pain/hyperalgesia from opioid used before treatment as influence on pain
  - *Mischaracterization of buprenorphine pharmacology which influenced entire premise of this study*
    - "bup/nx is a partial opioid agonist and has a CEILING EFFECT on the opioid receptor…is generally assumed to be less efficacious than methadone at alleviating chronic pain in clinical practice"
      - Richardson, M "Lack of Evidence for Ceiling Effect for Buprenorphine Analgesia in Humans"". Anesthesia and Analgesia. July 2018; 127 (1): 310-311.

Pain Medicine, 21(9), 2020, 1955–1960
doi: 10.1093/pm/pnaa020
Advance Access Publication Date: 13 March 2020
Preliminary Research Article

Perioperative Continuation of Buprenorphine at Low–Moderate Doses Was Associated with Lower Postoperative Pain Scores and Decreased Outpatient Opioid Dispensing Compared with Buprenorphine Discontinuation

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Funding sources: None.

Conflicts of interest: None.

Abstract

Objective. An increasing number of individuals are prescribed buprenorphine as medication-assisted treatment for opioid use disorder. Our institution developed guidelines for perioperative buprenorphine continuation with an algorithm for dose reduction based upon the surgical procedure and patient's maintenance dose. The objective of this study was to compare the effects of buprenorphine continuation with those of discontinuation on postoperative pain scores and outpatient opioid dispensing. **Design.** Retrospective observational study. **Subjects.** Surgical patients on buprenorphine from March 2018 to October 2018. Patients on buprenorphine for chronic pain and those with minor procedures were excluded from analysis. **Methods.** We compared postoperative outpatient opioid dispensing and postanesthesia care unit (PACU) pain scores in patients where buprenorphine was continued compared with held perioperatively, collecting single surgical subspecialty prescriber data on outpatient full mu-opioid agonist prescriptions dispensed, converted into mean morphine equivalents. Buprenorphine formulations were not included in our morphine milligram equivalents (MME) total. **Results.** There were 55 patients total (38 cont. vs 17 held). There was no difference in postoperative buprenorphine treatment adherence (91% cont. vs 88% held, $P = 0.324$). The number of opioid prescriptions dispensed was significantly higher with buprenorphine discontinuation (53% cont. vs 82% held, $P = 0.011$), as was MME dispensed (mean of 229 cont. vs mean of 521 held, $P = 0.033$). PACU pain scores were higher with buprenorphine discontinuation (mean 2.9 cont. vs mean 7.6 held, $P < 0.001$). **Conclusions.** There was a significant reduction in opioid prescriptions filled, MME dispensed, and PACU pain scores in patients where buprenorphine was continued vs held perioperatively. We provide evidence to support that buprenorphine can be continued perioperatively and that continuation is associated with decreased postoperative pain and decreased outpatient opioid dispensing. These results contribute to the existing literature supporting the perioperative continuation of buprenorphine.

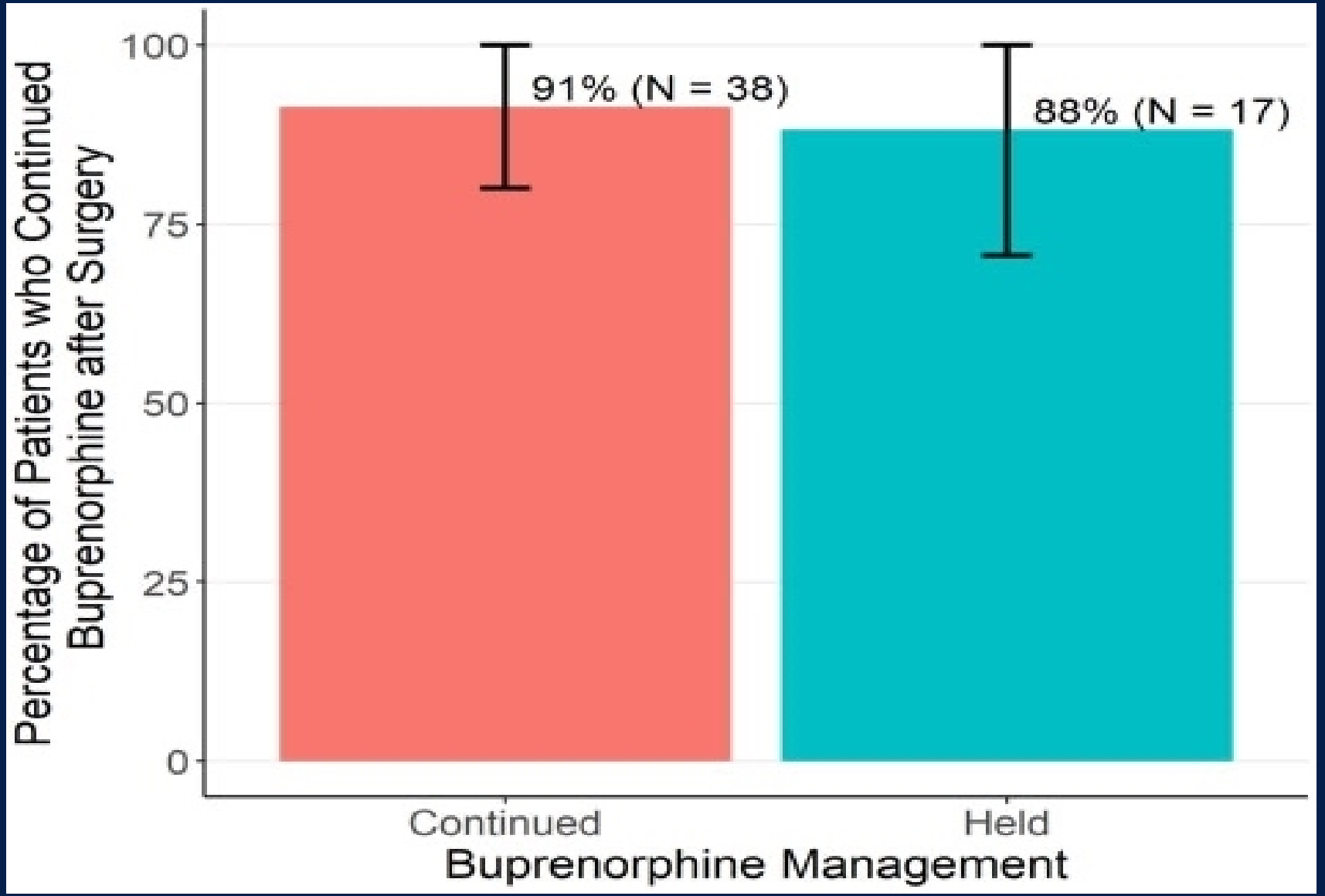
Quaye et al. 2020, Pain Medicine

- Background
  - "Perioperative Continuation of Buprenorphine at Low–Moderate Doses Was Associated with Lower Postoperative Pain Scores and Decreased Outpatient Opioid Dispensing Compared with Buprenorphine Discontinuation"
    - TITLE SAYS IT ALL
    - Goal of study was to help establish "standard of care" for perioperative opioid management for pts maintained on buprenorphine for OUD
      - Retrospective analysis of electronic chart records of 55 pts from March-Oct 2018, and use of PMP database to track outpatient opioid Rxs
        - 38 pts continued bup, 17 held bup
      - Excluded those Rx'd buprenorphine for chronic pain management
      - Excluded emergent surgeries (so buprenorphine could be stopped in planned fashion)

Quaye et al. 2020, Pain Medicine

- Results
  - Patients were significantly more likely to have an opioid prescription dispensed as an outpatient when buprenorphine was held perioperatively
  - MMEs of full mu opioid agonists dispensed were significantly higher in the buprenorphine discontinuation group
  - PACU pain scores were significantly higher in the buprenorphine discontinuation group
  - Both groups had excellent rates of buprenorphine retention following surgery/recovery

Quaye 2020, Pain Medicine



Quaye et al. 2020, Pain Medicine

- Limitations
  - Retrospective study
  - Looked at multiple types of common surgeries
  - No accounting for intraoperative regional anesthetic
    - This is why PACU opioid administration was not examined
  - Study assumes opioids dispensed per PMP were taken as Rx'd

- Conclusions
  - Beautifully simple and clear study showing that standard of care should be to continue buprenorphine through perioperative period for better pain control, less reliance on post-op opioids, less risk to OUD treatment stability

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