Current Controversies in Addiction Medicine

Julie Kmiec, DO
Assistant Professor of Psychiatry
Addiction Psychiatrist
University of Pittsburgh School of Medicine

Disclosures

- I have no financial conflicts of interest
- I will discuss off-label use of medications: gabapentin

Objectives

- At the conclusion of this activity participants should be able to:
  - discuss controversy surrounding the use of medical marijuana for treatment of OUD
  - discuss the potential harms and benefits of the use of benzodiazepines for treatment of anxiety in individuals with a substance use disorder
  - explain the potential harms and benefits of off-label use of gabapentin for pain, anxiety, sleep, cravings in persons with a substance use disorder
  - describe the evidence for syringe service programs

Controversy with medical marijuana for treatment of OUD

State Medical Marijuana (MM) Laws

- States which have OUD as an improved indication for medical marijuana
  - Pennsylvania
  - New Jersey
  - Nevada
  - Rejected in OH
- Can recommend medical marijuana for any condition for which they would prescribe an opioid
  - New York
  - Illinois
  - Colorado

What is the rationale for medical marijuana for OUD?

Rationale for Cannabis for OUD

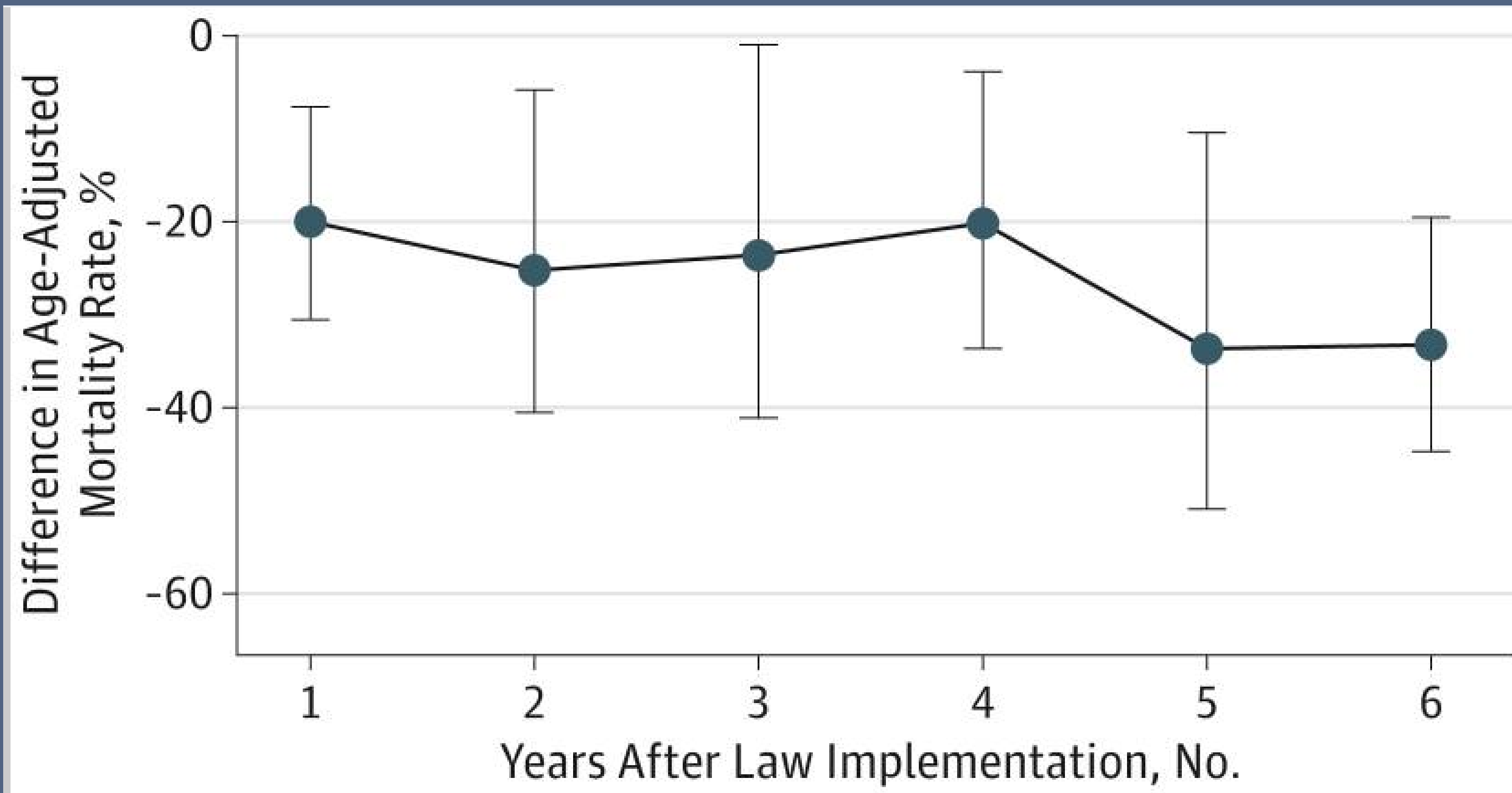
- Commonly cited reasons
  - Association with reduced opioid pain relievers prescriptions in Medicare and Medicaid populations
  - Associated with reduced opioid overdoses
  - Treats symptoms of opioid withdrawal
  - Treats pain, anxiety, insomnia

- By having OUD as an indication for medical marijuana, does this
  - Undermine evidence-based treatments for OUD?
  - Are we harming patients (do they go on to use opioids?)

Does medical marijuana affect mortality from OUD? Part I

- Time-series analysis looking at medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010 from all 50 states
- **Main Outcome:** Age-adjusted opioid analgesic overdose death rate per 100,000 in each state
- **Results**
  - 3 states (California, Oregon, and Washington) had medical cannabis laws effective prior to 1999
  - 10 states enacted medical cannabis laws between 1999 and 2010
  - States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; *P* = .003) compared with states without medical cannabis laws.

Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668–1673. doi:10.1001/jamainternmed.2014.4005



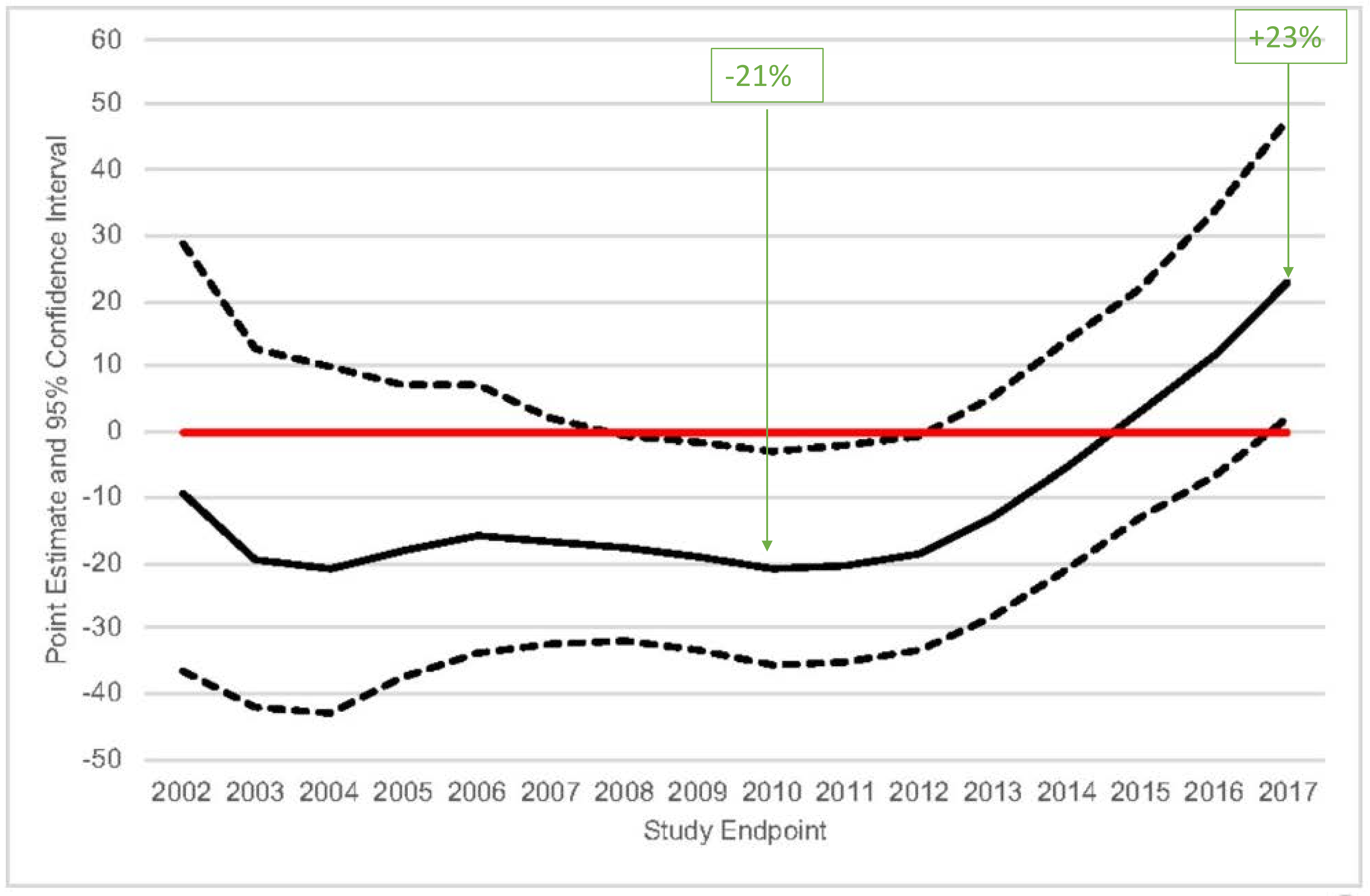
Examination of the association between medical cannabis laws and opioid analgesic overdose mortality were associated with a lower rate of overdose mortality that generally strengthened over time

Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010. *JAMA Intern Med.* 2014;174(10):1668–1673. doi:10.1001/jamainternmed.2014.4005

Does medical marijuana affect mortality from OUD? Part II

- Used the same methods to extend Bachhuber et al.'s analysis through 2017
- The findings from the original analysis did not hold over the longer period
- The association between state medical cannabis laws and opioid **overdose mortality reversed direction from −21% to +23%**

Association between medical cannabis laws and opioid overdose mortality has reversed over time. Chelsea L. Shover, Corey S. Davis, Sanford C. Gordon, Keith Humphreys. *Proceedings of the National Academy of Sciences* Jun 2019, 116 (26) 12624-12626; DOI:10.1073/pnas.1903434116



Association between medical cannabis laws and opioid overdose mortality has reversed over time. Chelsea L. Shover, Corey S. Davis, Sanford C. Gordon, Keith Humphreys. *Proceedings of the National Academy of Sciences* Jun 2019, 116 (26) 12624-12626; DOI:10.1073/pnas.1903434116

Does medical marijuana affect mortality from OUD? Part II

- Authors believed it to be unlikely that medical marijuana—used by about 2.5% of the US population—exerted large conflicting effects on opioid overdose mortality

- Things that correlate in the aggregate do not at the individual level
    - Regions of France with the highest rates of smoking have the lower rates of esophageal cancer (Cohen, 1990)
    - US counties with the highest levels of radon exposure have the lowest rates of lung cancer (Richardson et al., 1987)
- Unmeasured and/or confounding variables likely explain relationship

Association between medical cannabis laws and opioid overdose mortality has reversed over time. Chelsea L. Shover, Corey S. Davis, Sanford C. Gordon, Keith Humphreys. *Proceedings of the National Academy of Sciences* Jun 2019, 116 (26) 12624-12626; DOI:10.1073/pnas.1903434116

Does Medical Marijuana (MM) reduce prescription drug use?

- Medicare Part D drug claims from 2010 to 2013.
- They found reductions of the following drugs in states with medical marijuana

5.7% in pain prescriptions	4.8% in sleep disorder prescriptions
5.4% in nausea prescriptions	4.5% in psychosis prescriptions
5.2% in seizure prescriptions	2.8% in depression prescriptions
5.0% in anxiety prescriptions	1.5% in spasticity prescriptions

- Forecasted Medicare Part D would be $468.1 million less if all states had MM

Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661. PubMed PMID: 27385238.

Does Medical Marijuana (MM) reduce prescription drug use?

- Based on individual-level data (NSDUH) approximately 2% to 3% of Medicare recipients in states with legalized medical marijuana used medical marijuana
- While technically possible, it seems unlikely that 2% to 3% of Medicare recipients could account for all of the medication reductions in Bradford and Bradford's analysis

Bradford AC, Bradford WD. Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D. Health Aff (Millwood). 2016 Jul 1;35(7):1230-6. doi: 10.1377/hlthaff.2015.1661. PubMed PMID: 27385238.
Caputi TL, Humphreys K. Medicare Recipients' Use Of Medical Marijuana. Health Aff (Millwood). 2016 Oct 1;35(10):1936. PubMed PMID: 27702976.

What's the relationship between use of medical marijuana and prescription drugs?

- Examined individual-level data from the NSDUH to determine whether medical marijuana users are at lower or higher risk for medical and nonmedical prescription drug use
- Performed logistic regression analyses of data from the 2015 NSDUH
- 2015 NSDUH: 57,146 US household residents aged 12 and older to a computer-assisted personal interview

Caputi TL, Humphreys K. Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically. *J Addict Med*. 2018 Jul/Aug;12(4):295-299. doi: 10.1097/ADM.0000000000000405. PubMed PMID: 29664895.

What’s the relationship between use of medical marijuana and prescription drugs?

- Participants were asked about using prescription drugs in aggregate and about the following: pain relievers, sedatives, stimulants, tranquilizers
  - Asked about any use (i.e., medical or nonmedical use) and strictly nonmedical use
- If used marijuana in the past 12 months, asked if any of their marijuana use was recommended by a healthcare professional; if so, coded as medical marijuana users

Caputi TL, Humphreys K. Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically. *J Addict Med*. 2018 Jul/Aug;12(4):295-299. doi: 10.1097/ADM.0000000000000405. PubMed PMID: 29664895.

TABLE 1. Risk Ratios of Medical Marijuana Users Relative to Medical Marijuana Nonusers

	Unadjusted RR	95% CI	Adjusted RR	95% CI
Use (medical and/or nonmedical)				
All prescription drugs	1.64*	(1.51–1.76)	1.62*	(1.50–1.74)
Pain relievers	1.69*	(1.51–1.87)	1.66*	(1.49–1.83)
Sedatives	1.70*	(1.23–2.29)	1.82*	(1.26–2.51)
Stimulants	2.50*	(2.03–3.04)	2.23*	(1.71–2.86)
Tranquilizers	2.33*	(1.98–2.69)	2.46*	(2.00–2.98)
Nonmedical use				
All prescription drugs	2.76*	(2.23–3.36)	2.12*	(1.67–2.62)
Pain relievers	2.67*	(1.99–3.49)	1.95*	(1.41–2.62)
Sedatives	2.87	(0.96–6.69)	2.45	(0.72–6.06)
Stimulants	2.62*	(1.71–3.82)	1.86*	(1.09–3.02)
Tranquilizers	2.97*	(2.00–4.24)	2.18*	(1.45–3.16)
Nonmedical use (among users)				
All prescription drugs	1.68*	(1.36–2.04)	1.38*	(1.09–1.70)
Pain relievers	1.57*	(1.19–2.02)	1.25	(0.92–1.66)
Sedatives	1.66	(0.56–3.56)	1.61	(0.43–3.96)
Stimulants	1.04	(0.68–1.47)	0.99	(0.66–1.39)
Tranquilizers	1.28	(0.87–1.78)	0.99	(0.66–1.42)

Data are drawn from the 2015 National Survey for Drug Use and Health. Each result represents a model where prescription drug use/nonmedical use in the past 12 months is the independent variable, medical marijuana use in the past 12 months is the dependent variable, and controls are added for age, sex, race, health status, family income, and living in a state with legalized medical marijuana. Estimates and confidence intervals were calculated based upon 10,000 bootstrapped simulations from random draws of the variance–covariance matrix of the logistic regression model, with covariates set at their mean. Results are presented as risk ratios, that is, the estimated probability among medical marijuana users divided by the estimated probability among medical marijuana nonusers. All estimates are adjusted for the NSDUH complex survey design.

CI, confidence interval; RR, risk ratio.

*Represents statistical significance ($P < 0.05$).

Caputi TL, Humphreys K. Medical Marijuana Users are More Likely to Use Prescription Drugs Medically and Nonmedically. *J Addict Med*. 2018 Jul/Aug;12(4):295-299. doi: 10.1097/ADM.0000000000000405. PubMed PMID: 29664895.

Is medical marijuana associated with less nonmedical use of prescription opioids (NMUPO) and reduced prescription opioid use disorder (POUD)?

- Between 1997 and 2017, there were increases in nonmedical prescription opioid use, as well as changes in marijuana policies in the U.S.
- Study investigated the association of the enactment of state-level medical marijuana laws with individual-level nonmedical prescription opioid use and prescription opioid use disorder

Segura LE, Mauro CM, Levy NS, et al. Association of US Medical Marijuana Laws With Nonmedical Prescription Opioid Use and Prescription Opioid Use Disorder. *JAMA Netw Open.* Published online July 17, 20192(7):e197216. doi:10.1001/jamanetworkopen.2019.7216

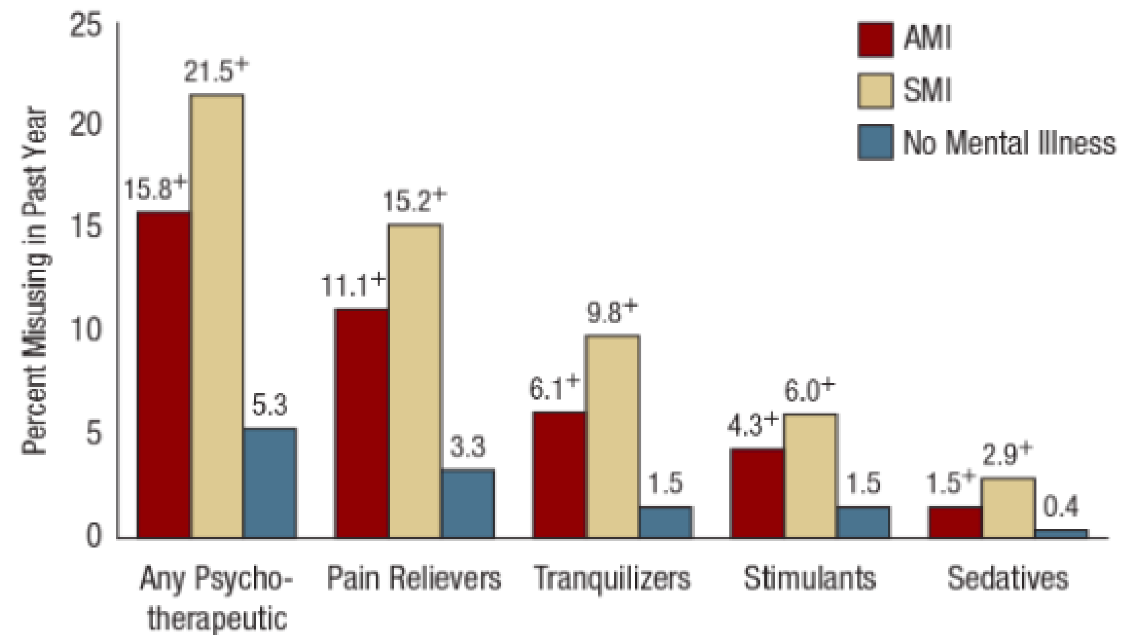
Is MM associated with less NMUPO and reduced POUD?

- Cross-sectional study used data from 627,000 individuals aged ≥12 from the 2004 to 2014 NSDUH
- Looked at state MM law enactment (early [before 2004], late [after 2004], never enacted)
- Outcomes were
  - past-year NMUPO
  - past-year POUD
- comparing the period before and after MM law enactment

Segura LE, Mauro CM, Levy NS, et al. Association of US Medical Marijuana Laws With Nonmedical Prescription Opioid Use and Prescription Opioid Use Disorder. *JAMA Netw Open.* Published online July 17, 20192(7):e197216. doi:10.1001/jamanetworkopen.2019.7216

Mental Illness in Past Year and Tranquilizer Misuse

- 3.4% 12-17 yo who misused tranquilizers had MDE
- 7.9% of those 18+ yrs who misused tranquilizers had MDE
- 10% who misused tranquilizers had suicidal thoughts



Of those misusing tranquilizers, ~3-10% are struggling with mental illness or suicidal thoughts

Experiences & Perceptions of BZD Prescribing

- Prescribing influenced by
  - Practitioner attitudes towards benzodiazepines (personal use, quick fix)
  - Practitioner attitudes towards other interventions (psychotherapy not available or not effective, too time consuming to discuss alternatives or tapering, other tx not fast enough relief)
  - Perceived patient expectations (unmotivated patients want quick fix, pt not going to go to therapy, will find another doc if no rx)
  - Perceived role of GP (responsibility for past rx, need to treat anxiety/insomnia, need to make pts feel better)
  - Deserving patients (elderly, bereavement, incurable problems)
  - Difficulty managing withdrawal

Sirdifield C, Anthierens S, Creupelandt H, Chipchase SY, Christiaens T, Siriwardena AN. General practitioners' experiences and perceptions of benzodiazepine prescribing: systematic review and meta-synthesis. BMC Fam Pract. 2013 Dec 13;14:191. doi: 10.1186/1471-2296-14-191. Review. PubMed PMID: 24330388

Anxiety Disorders and Treatments

- In gen population, 19% with AUD and 28% with drug use disorder had an anxiety disorder
- In treatment seeking, 33% with AUD and 43% with drug use disorder had an anxiety disorder

- Untreated anxiety can lead to worse SUD outcomes

Wolitzky-Taylor K, Operskalski JT, Ries R, Craske MG, Roy-Byrne P. Understanding and treating comorbid anxiety disorders in substance users: review and future directions. J Addict Med. 2011 Dec;5(4):233-47. doi: 10.1097/ADM.0b013e31823276d7. Review. PubMed PMID: 22042216.

Common Reasons Agst Using BZD in Pts with SUD

- Puts patient’s recovery in jeopardy
- Evidence-based psychotherapies for anxiety and insomnia
- Nonaddictive meds available
- Few studies of BZD in people with co-occurring anxiety and SUD
- BZD misused for their effects (sleep, relax)
- BZD misused for intoxicating effect, boost other substances, or to combat effects of other substances
- Potential adverse effects: accidents, falls, memory problems, dependence
- Risk of overdose, toxicity, death when mixed with other substances

Park TW. Debate: Are Benzodiazepines Appropriate Treatments for Patients with Substance Use Disorders? Yes. J Addict Med. 2017 Mar/Apr;11(2):87-89. PubMed PMID: 28301370.
DuPont RL. "Should Patients With Substance Use Disorders Be Prescribed Benzodiazepines?" No. J Addict Med. 2017 Mar/Apr;11(2):84-86. PubMed PMID: 28301369.

AUD and BZD: Some Studies

- Alcohol withdrawal with carbamazepine vs. lorazepam: those exposed to lorazepam were 3x more likely to have drink after withdrawal and had more drinks on average

- Open-label 16 wk trial of lorazepam plus disulfiram for 41 people with anxiety and AUD, lorazepam was associated with reduced anxiety, and no evidence for loss of control of BZD

Malcolm R, Myrick H, Roberts J, Wang W, Anton RF, Ballenger JC. The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. *J Gen Intern Med*. 2002;17(5):349–355. doi:10.1046/j.1525-1497.2002.10201.x
Bogenschutz MP, Bhatt S, Bohan J, et al. Coadministration of disulfiram and lorazepam in the treatment of alcohol dependence and co-occurring anxiety disorder: an open-label pilot study. *Am J Drug Alcohol Abuse*. 2016;42(5):490–499. doi:10.3109/00952990.2016.1168430

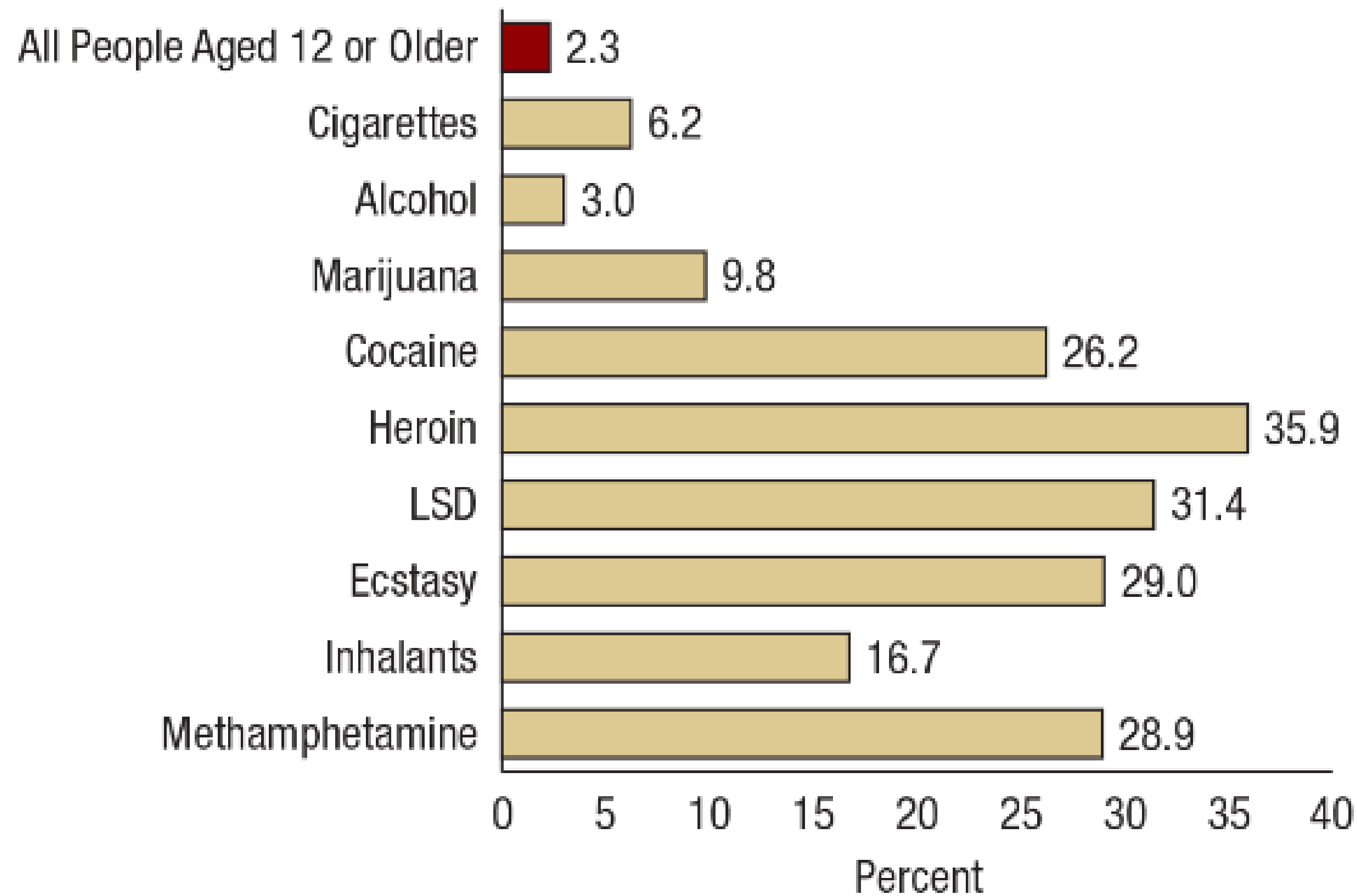
Benzodiazepine Maintenance for AUD

- Indian case series
- 10 patients, all men, 30-59 yo, married and employed
- Maintaining abstinence from alcohol in addiction clinic
- Rx diazepam (avg dose 7.5 mg) for 3-13 mos, avg 7.8 mos

	n (%)
Craving for alcohol: Present	5 (50)
Adverse effects: Present (memory-2+drowsiness-1)	3 (30)
Patient has negative attitude toward: Yes	5 (50)
Negative remark by medical/paramedical staff: Yes	0
Negative remark by family member: Yes	
Negative remark by friend: Yes	3 (30)
Current–harmful use/dependence symptoms	0
Intended duration	
As per doctors' advice	5 (50)
For 1 year	2 (20)
For sleep	1 (10)
Presence of anxiety disorder	0
Confident of staying sober without benzodiazepine: Low	5 (50)

Kattimani S, Bharadwaj B, Arun AB. Benzodiazepine maintenance for alcohol dependence: A case series. *J Family Med Prim Care*. 2017;6(2):431–433. doi:10.4103/2249-4863.220038

Figure 13. Past Year Misuse of Prescription Tranquilizers among People Aged 12 or Older Who Were Past Year Users of Other Substances, by Substance: Percentages, 2015



Be sure buprenorphine or methadone dose is adequate in patients using benzodiazepines

Inadequate Dose of Opioid-agonist Medication is Related to Misuse of Benzodiazepines

Heikman, Pertti Kalevi PhD*; Ojanperä, Ilkka Antero PhD†

Addictive Disorders & Their Treatment: September 2009 - Volume 8 - Issue 3 - p 145-153
doi: 10.1097/ADT.0b013e31817ea8b8
Original Articles

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Abstract | Author Information | Article Metrics

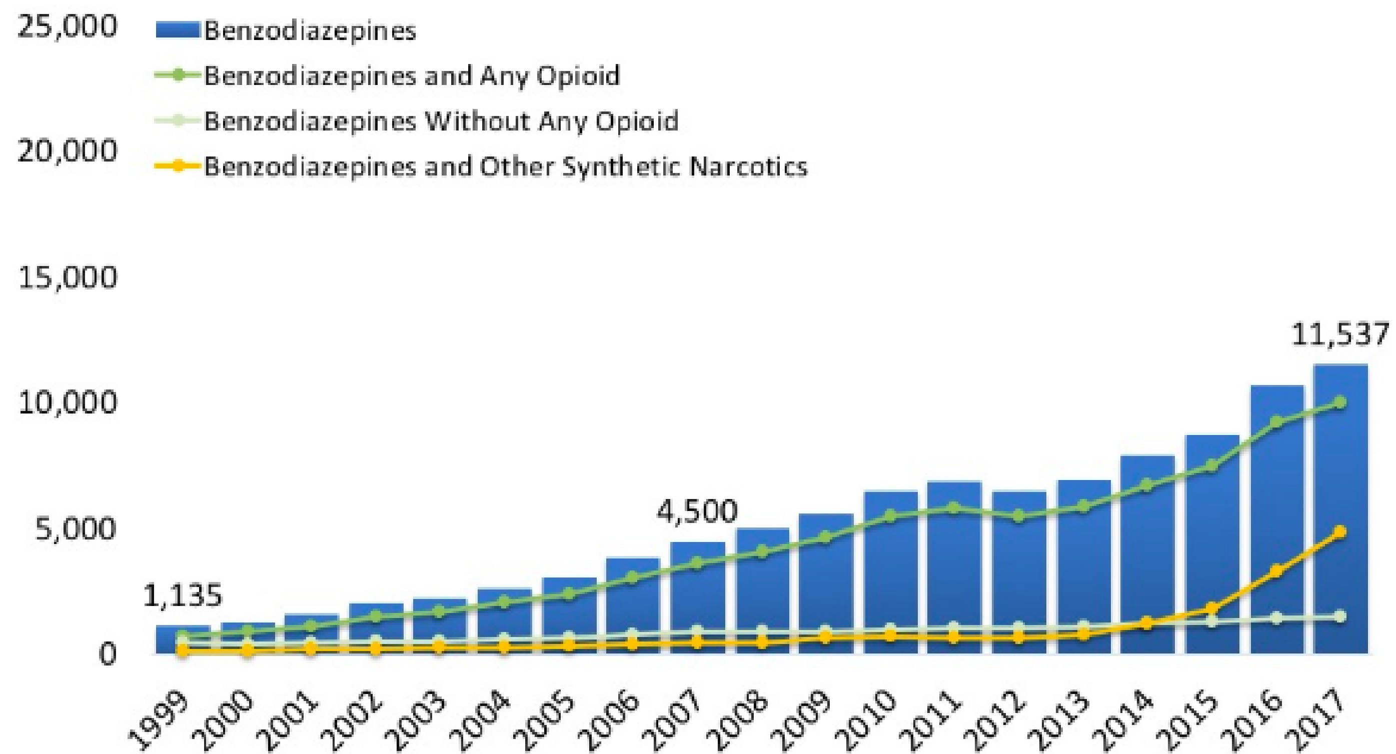
Objectives To evaluate whether misuse of nonprescribed substances is related to dose-adequacy of opioid-agonist medication (OAM) in opioid substitution treatment.

Methods Opioid-dependent patients undergoing a substitution treatment program of the Helsinki University Central Hospital. Opioid-dependent patients evaluated their dose of OAM (methadone or buprenorphine combined with naloxone) as either too low (group 1) or adequate (group 2). Instead of being limited to the main drug classes detectable by standard immunoassay techniques, this study systematically investigated the incidental use of a very broad spectrum of therapeutic and illicit drugs both from blood and urine samples.

Results Of the 65 participating patients 21 (32%) completed the study. Their doses and blood concentrations of OAM showed no differences between the 2 groups. The group 1 patients, however, showed more positive laboratory findings for nonprescribed benzodiazepines (7/10 vs. 1/11, P=0.008). Diazepam was present in all positive samples of nonprescribed benzodiazepines, alprazolam in 4, clonazepam in 3, and midazolam in 2 samples. There was no difference in misuse of opiates, amphetamine, cannabis, barbiturates, designer drugs, or psychotropic drugs between groups 1 and 2.

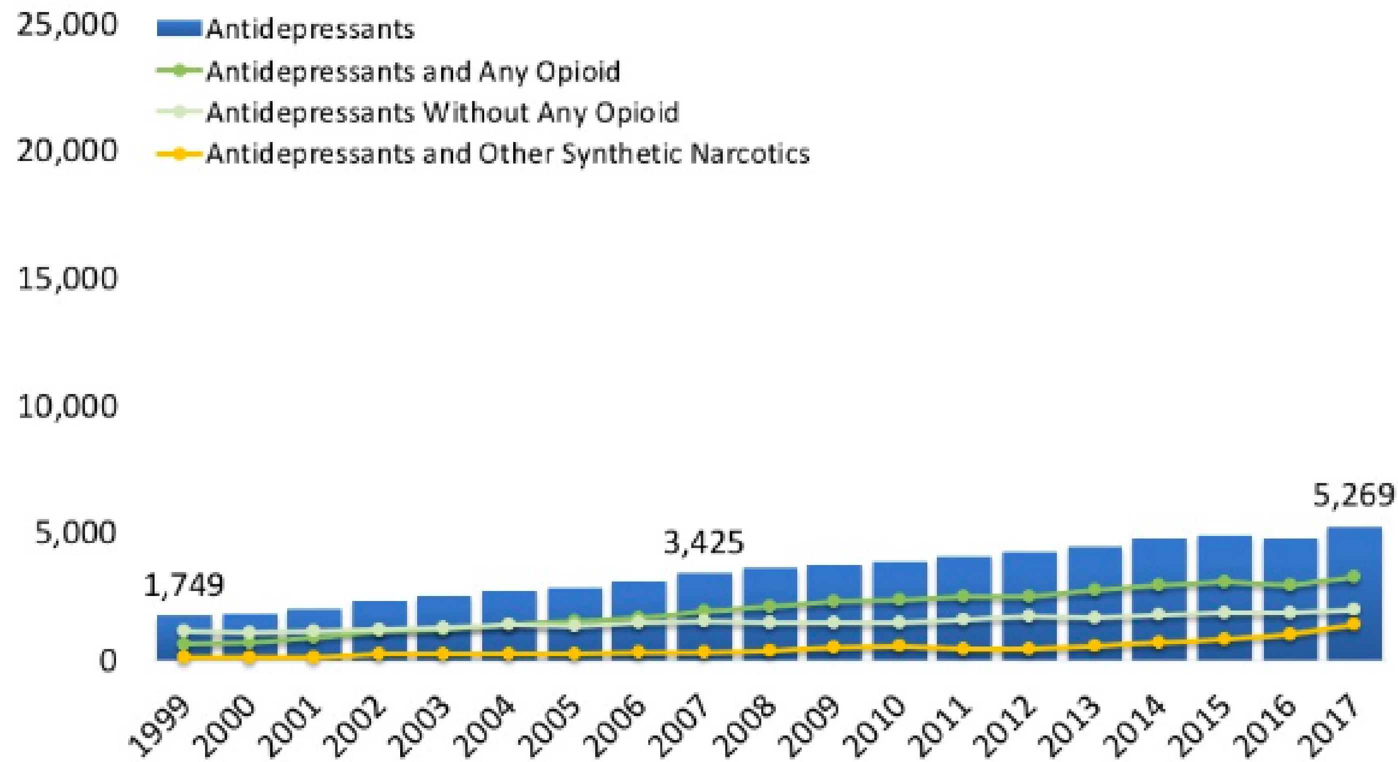
Conclusions The inadequate dose of OAM in opioid substitution treatment for opioid-dependent patients seems to be related to the misuse of benzodiazepines.

Figure 8. **National Drug Overdose Deaths Involving Benzodiazepines, by Opioid Involvement,** Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Figure 9. **National Drug Overdose Deaths Involving Antidepressants, by Opioid Involvement,** Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Gabapentin

Gabapentin History

- Approved by FDA in 1993 for use as an adjunctive medication to control partial seizures
  - currently the smallest market for gabapentin
- 2004 approved for treatment of postherpetic neuralgia
- European Medicines Agency approvals
  - Epilepsy
  - Neuropathic pain

Allegations in Whistleblower Lawsuit

- Parke-Davis undertook an elaborate program to distribute information about unapproved uses to increase sales since going off patent
- They made payments to doctors for “consultations” and “studies”
  - Comments by “consultants” were not recorded at some of the events
  - “Studies” supporting unapproved uses ranged from
    - case reports falsely labelled as studies
    - non-existent data (e.g., for bipolar disorder there was no study)
    - Ghost writers but doctors were "authors," published about 20 articles
- Doctors served as a “surrogate sales force” violating anti-kickback laws

Lenzer J. Whistleblower charges drug company with deceptive practices. *BMJ*. 2003;326(7390):620. doi:10.1136/bmj.326.7390.620

Court Settlements

- Settlement of $430 million in criminal and civil liability charges in 2004
  - However, there was tremendous growth in gabapentin prescriptions for off-label use from the early 1990s to early 2000s
  - Prescribers still have access to industry-funded literature that promotes gabapentin for off-label use
- Pfizer, who bought Parke-Davis in 2000, agreed to pay $190 million in April 2014 as part of a settlement that alleged the company took steps to delay market entry of generic versions of gabapentin
- Pfizer also agreed to pay $325 million for defrauding insurers and health care benefit providers via off-label marketing of gabapentin

Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?. *Subst Abuse*. 2018;12:1178221818801311. Published 2018 Sep 23. doi:10.1177/1178221818801311

Reported Off-Label Uses of Gabapentin

- bipolar disorder
- neuropathic pain
- diabetic neuropathy
- complex regional pain syndrome
- attention deficit disorder
- restless legs syndrome
- trigeminal neuralgia
- insomnia
- periodic limb movement disorders of sleep
- premenstrual syndrome
- migraine headache
- drug and alcohol withdrawal seizures
- alcohol use disorder and withdrawal
- anxiety

Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?. *Subst Abuse*. 2018;12:1178221818801311. Published 2018 Sep 23. doi:10.1177/1178221818801311

Off-Label Use

- Up to 95% of gabapentin today prescribed for off-label indications
- Prescribing in the United States increased 64% from 2012 to 2016
- In 2016, gabapentin was the 10th most commonly prescribed medication in the United States with 64 million prescriptions dispensed, an increase from 39 million in 2012
- In a majority of cases when gabapentin is prescribed for off-label use, it is not the optimal treatment
- Reviews of off-label indications such as migraine, fibromyalgia, mental illness, and substance dependence have found modest to no effect on relevant clinical outcomes

Mack, A. (2003). Examination of the evidence for off-label use of gabapentin. *J Manag Care Pharm, 9*(6), 559-568. doi:10.18553/jmcp.2003.9.6.559
Peckham AM, Evoy KE, Ochs L, Covvey JR. Gabapentin for Off-Label Use: Evidence-Based or Cause for Concern?. *Subst Abuse*. 2018;12:1178221818801311. Published 2018 Sep 23. doi:10.1177/1178221818801311

Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD;
Mark Kyle, MD; Adnan Begovic, MD

IMPORTANCE Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics.

OBJECTIVE To determine if gabapentin, a widely prescribed generic calcium channel/γ-aminobutyric acid–modulating medication, increases rates of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria, and craving, in a dose-dependent manner.

DESIGN, PARTICIPANTS AND SETTING A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women older than 18 years with current alcohol dependence, conducted from 2004 through 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital.

INTERVENTIONS Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

MAIN OUTCOMES AND MEASURES Rates of complete abstinence and no heavy drinking (coprimary) and changes in mood, sleep, and craving (secondary) over the 12-week study.

RESULTS Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group ($P = .04$ for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group ($P = .02$ for linear dose effect; NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood ($F_2 = 7.37$; $P = .001$), sleep ($F_2 = 136$; $P < .001$), and craving ($F_2 = 3.56$; $P = .03$). There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among groups.

CONCLUSIONS AND RELEVANCE Gabapentin (particularly the 1800-mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving, with a favorable safety profile. Increased implementation of pharmacological treatment of alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

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A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal

Hugh Myrick, Robert Malcolm, Patrick K. Randall, Elizabeth Boyle, Raymond F. Anton, Howard C. Becker, and Carrie L. Randall

Introduction: Some anticonvulsants ameliorate signs and symptoms of alcohol withdrawal, but have an unacceptable side effect burden. Among the advantages of using anticonvulsant agents in this capacity is their purported lack of interaction with alcohol that could increase psychomotor deficits, increase cognitive impairment, or increase intoxication. The aim of this study was to evaluate alcohol use and symptom reduction of gabapentin when compared with lorazepam in the treatment of alcohol withdrawal in a double-blinded randomized clinical trial.

Methods: One hundred individuals seeking outpatient treatment of alcohol withdrawal with Clinical Institute Withdrawal Assessment for Alcohol–Revised (CIWA-Ar) ratings ≥10 were randomized to double-blind treatment with 2 doses of gabapentin (900 mg tapering to 600 mg or 1200 tapering to 800 mg) or lorazepam (6 mg tapering to 4 mg) for 4 days. Severity of alcohol withdrawal was measured by the CIWA-Ar on days 1 to 4 of treatment and on days 5, 7, and 12 post-treatment and alcohol use monitored by verbal report and breath alcohol levels.

Results: CIWA-Ar scores decreased over time in all groups; high-dose gabapentin was statistically superior but clinically similar to lorazepam ($p = 0.009$). During treatment, lorazepam-treated participants had higher probabilities of drinking on the first day of dose decrease (day 2) and the second day off medication (day 6) compared to gabapentin-treated participants ($p = 0.0002$). Post-treatment, gabapentin-treated participants had less probability of drinking during the follow-up post-treatment period ($p = 0.2$ for 900 mg and $p = 0.3$ for 1200 mg) compared to the lorazepam-treated participants ($p = 0.55$). The gabapentin groups also had less craving, anxiety, and sedation compared to lorazepam.

Conclusions: Gabapentin was well tolerated and effectively diminished the symptoms of alcohol withdrawal in our population especially at the higher target dose (1200 mg) used in this study. Gabapentin reduced the probability of drinking during alcohol withdrawal and in the immediate postwithdrawal week compared to lorazepam.

Key Words: Gabapentin, Alcohol Dependence, Alcohol Withdrawal, Lorazepam.

Importance of Gabapentin Dose in Treatment of Opioid Withdrawal

Mehrdad Salehi, MD, Gholam Reza Kheirabadi, MD,* Mohammad Reza Maracy, PhD,† and Mansour Ranjkesh, MD**

Aim: The aim of the study was to evaluate the efficacy of gabapentin (1600 mg/d) as an adjunctive to methadone-assisted detoxification in the treatment of opioid withdrawal symptoms.

Design: This was a 3-week open-label study (as second phase) following a double-blind, placebo-controlled study with 900 mg/d of gabapentin (as first phase of this study).

Setting: The study was conducted at a specialized outpatient clinic for the treatment of patients with addictive disorders.

Participants: The study subjects were composed of 27 patients addicted to opiate who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for opioid dependency, randomly selected among outpatients referred to our clinic.

Intervention: Subjects received adjunctive treatment with gabapentin (1600 mg/d) in addition to methadone-assisted detoxification for 3 weeks.

Measurements: Subjective Opiate Withdrawal Scale (SOWS) with a total score of 0 to 64 was administered at 6 time points during the study.

Findings: The total SOWS score was significantly decreased after the intervention. Compared to our previous trial, an almost significant difference was observed in total SOWS scores between groups treated with gabapentin 1600 and 900 mg/d at the end of the intervention period ($P = 0.06$). Gabapentin with a dose of 1600 mg/d was significantly superior to a dose of 900 mg/d in decreasing severity of coldness, diarrhea, dysphoria, yawing, and muscle tension.

Conclusions: Add-on gabapentin with a dose of 1600 mg/d is effective in reducing some of the withdrawal symptoms in patients addicted to opiate undergoing methadone-assisted detoxification.

Key Words: opium dependence, opioid withdrawal, gabapentin

(*J Clin Psychopharmacol* 2011;31: 593–596)

without medical interventions. Therefore, controlling withdrawal symptoms is the first and very important step in any detoxification and rehabilitation program for patients addicted to opiate.[1]

Strategies found to be effective for the treatment of opioid dependency include switching to methadone or buprenorphine followed by gradual tapering and use of nonopioid drugs at the final stages of methadone or buprenorphine tapering and transition to perhaps nonopiate maintenance methods such as naltrexone. Clonidine has for some time become the main nonopiate alternative for withdrawal treatment. However, it is not effective in the alleviation of muscle aches, insomnia, or drug craving. Moreover, it is associated with high rates of adverse effects such as sedation and hypotension that limit its use in outpatient setting. Lofexidine, in some countries, has replaced clonidine because of its fewer adverse effects. However, this drug is still not available in many countries.[1] The limited number of pharmacological options available for the maintenance treatment of opioid dependency led to an increasing interest in alternative pharmacological strategies.

Anticonvulsant drugs have been evaluated for the treatment of substance-abuse patients because of their lack of addiction potential and their efficacy in comorbid psychiatric disorders and pain conditions.[2] The role of kindling mechanisms in withdrawal syndromes is another rationale for using antiepileptic drugs in this case.[3] Preliminarily evidence is available on the efficacy of carbamazepine, valproate, lamotrigine, and gabapentin for detoxification from benzodiazepines, alcohol, and opiates, yet to be confirmed by further well-designed controlled trials.[3] In the first phase of this study, a dose of 900 mg/d of gabapentin for 3 weeks was not significantly superior to

Gabapentin Misuse

- ~1% prevalence rate in general population
- 40-65% misuse among those with prescriptions
- 15-22% misuse in those who misuse opioids

Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse and diversion: a systematic review. Addiction. 2016 Jul;111(7):1160-74. doi: 10.1111/add.13324. Epub 2016 Mar 18. Review. PubMed PMID: 27265421; PubMed Central PMCID: PMC5573873.

Gabapentinoids and Substance Use

- Questionnaire distributed to individuals in substance use clinics in Scotland
- 129 questionnaires were completed
- 8% (11/129) were using prescribed gabapentinoids - all for chronic pain conditions
- 22% (29/129) admitted to using non-prescribed gabapentinoids
  - 100% (29/29) were on prescribed methadone for OUD
  - 76% (22/29) stated they took gabapentinoids in order to become intoxicated
  - 38% (11/29) stated they took them in order to potentiate the effect of methadone

Baird, C. R., Fox, P., & Colvin, L. A. (2014). Gabapentinoid abuse in order to potentiate the effect of methadone: a survey among substance misusers. *Eur Addict Res, 20*(3), 115-118. doi:10.1159/000355268

Gabapentin Misuse

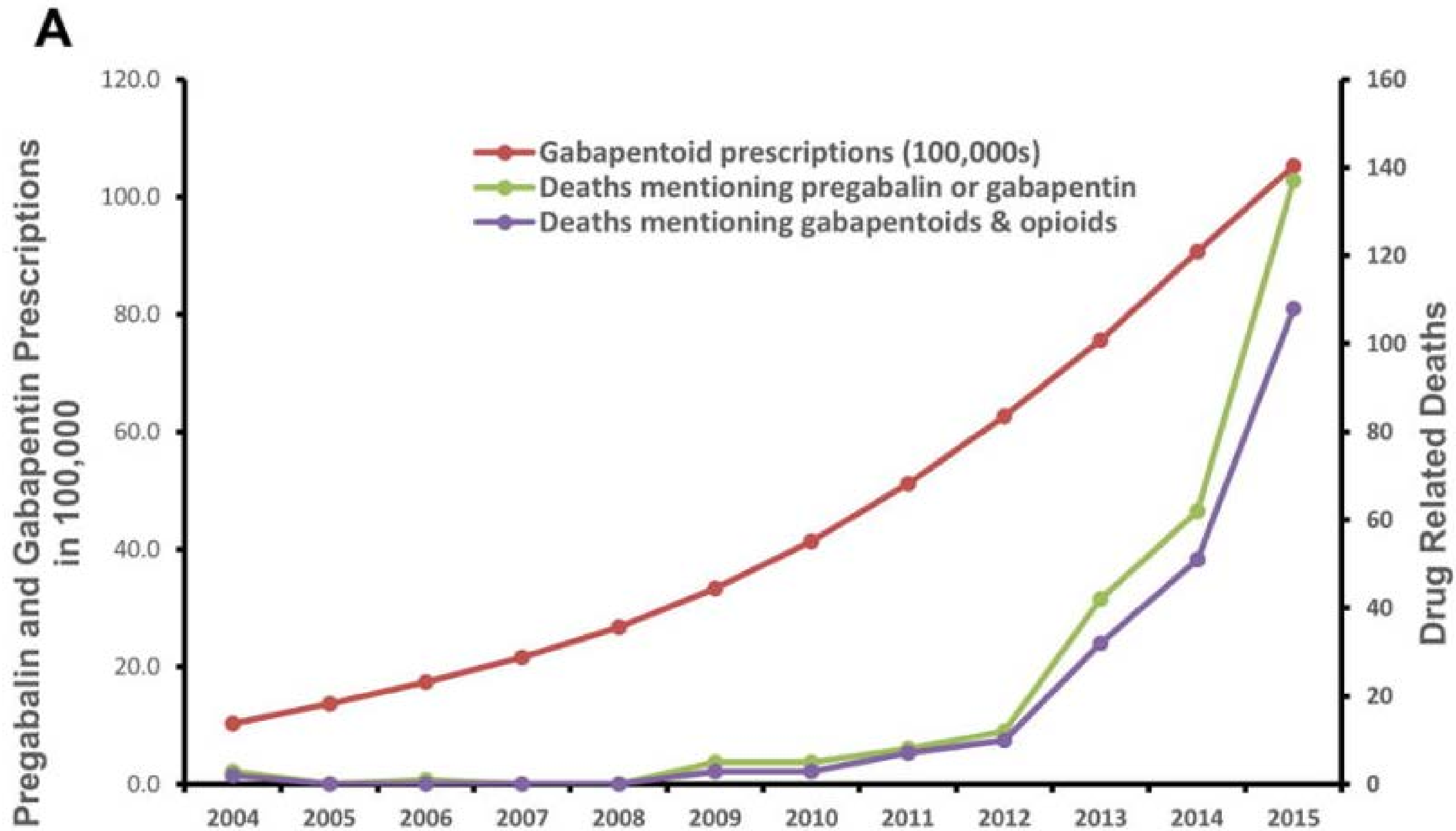
- Qualitative study of 33 people who use drugs in Appalachian Kentucky (4 focus groups)
- Majority started gabapentin more than 10 years earlier (~2005).
- Effects of misusing gabapentin:
  - Several said similar to an opioid high
  - 1 used gabapentin intranasally and thought it was like a "shot of cocaine"
  - Others described increased energy, increased appetite, "mellow" feeling, and "nodding"
- Few negative effects, except a considerable number complained of gabapentin withdrawal

Vickers Smith, R., Boland, E. M., Young, A. M., Lofwall, M. R., Quiroz, A., Staton, M., & Havens, J. R. (2018). A qualitative analysis of gabapentin misuse and diversion among people who use drugs in Appalachian Kentucky. *Psychol Addict Behav*, 32(1), 115-121. doi:10.1037/adb0000337

Opioids and Gabapentinoids

- Multi-disciplinary study examining combination of opioids with gabapentin or pregabalin in England and Wales
- Pregabalin and gabapentin prescriptions increased
  - ~24% per year
  - From 1 million in 2004 → 10.5 million in 2015
- The number of deaths involving gabapentinoids increased from
  - <1 per year prior to 2009 to 137 in 2015
  - 79% of these deaths also involved opioids

Lyndon, A., Audrey, S., Wells, C., Burnell, E. S., Ingle, S., Hill, R., . . . Henderson, G. (2017). Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction, 112*(9), 1580-1589. doi:10.1111/add.13843



Lyndon, A., Audrey, S., Wells, C., Burnell, E. S., Ingle, S., Hill, R., . . . Henderson, G. (2017). Risk to heroin users of polydrug use of pregabalin or gabapentin. *Addiction, 112*(9), 1580-1589. doi:10.1111/add.13843

Gabapentin and Overdose Deaths

- Death certificates and postmortem tox reports from 5 jurisdictions were used to identify residents who died from drug overdoses in 2015 and to calculate prevalence rates of gabapentin in postmortem toxicology by jurisdiction
- 22% of all drug overdose decedents tested positive for gabapentin
- Gabapentin-positive OD deaths varied significantly among jurisdictions:
  - 4% in Northeast Tennessee
  - 7% in Maricopa County
  - 15% in West Virginia
  - 20% in North Carolina
  - 41% in Kentucky

Slavova S, Miller A, Bunn TL, White JR, Kirschke D, Light T, Christy D, Thompson G, Winecker R. Prevalence of gabapentin in drug overdose postmortem toxicology testing results. Drug Alcohol Depend. 2018 May 1;186:80-85. doi: 10.1016/j.drugalcdep.2018.01.018. Epub 2018 Mar 10. PubMed PMID: 29554591.

Syringe Service Programs

Scott County, IN
HIV & HCV outbreak

- January 23, 2015, the Indiana State Department of Health (ISDH) began an ongoing investigation of an outbreak of HIV infection, after there were 11 confirmed HIV cases traced to a rural county in southeastern Indiana
- Historically, 5 cases of HIV infection were diagnosed from 2004 to 2013
- The majority of cases were residents of the same community and linked to syringe-sharing partners injecting the prescription opioid oxymorphone
- ISDH diagnosed HIV infection in 135 persons in a community of 4,200 persons
- By November 2015, there were 181 cases of HIV and 92.3% were co-infected with HCV

Conrad C, Bradley HM, Broz D, et al. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(16):443–444.
Peters PJ, Pontones P, Hoover KW, Patel MR, Galang RR, Shields J, Blosser SJ, Spiller MW, Combs B, Switzer WM, Conrad C, Gentry J, Khudyakov Y, Waterhouse D, Owen SM, Chapman E, Roseberry JC, McCants V, Weidle PJ, Broz D, Samandari T, Mermin J, Walthall J, Brooks JT, Duwve JM; Indiana HIV Outbreak Investigation Team. HIV Infection Linked to Injection Use of Oxymorphone in Indiana, 2014-2015. *N Engl J Med*. 2016 Jul 21;375(3):229-39. PubMed PMID: 27468059.

Scott County, IN
HIV & HCV outbreak

- IDU in the community was a multi-generational activity, with as many as three generations of a family and multiple community members injecting together.
- IDU practices include crushing and cooking extended-release oxymorphone, most frequently 40 mg tablets not designed to resist crushing or dissolving.
- Syringes and drug preparation equipment were frequently shared
- The reported daily numbers of injections ranged from 4 to 15, with the reported number of injection partners ranging from 1 to 6 per injection event

Conrad C, Bradley HM, Broz D, et al. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(16):443–444.

Scott County, IN
HIV & HCV outbreak

- Public health emergency was declared by governor on March 26 by executive order, the response included:
  - a public education campaign
  - establishment of an incident command center and a community outreach center
  - short-term authorization of syringe exchange
  - support for comprehensive medical care including HIV and hepatitis C virus care and treatment
  - substance abuse counseling and treatment.

Conrad C, Bradley HM, Broz D, et al. Community Outbreak of HIV Infection Linked to Injection Drug Use of Oxymorphone--Indiana, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(16):443–444.

Harms of IDU

- Risk for transmission of viral hepatitis and HIV
  - Sharing of needles, syringes, water, cotton, cookers, straws
  - Studies have found little to no protection against HIV and HCV in people who use bleach decontamination strategies (WHO, 2004)
- Majority of new hepatitis C virus (HCV) infections are due to IDU
- From 2010 to 2016, there has been a 3.5-fold increase in reported cases of HCV
  - New HCV virus infections are increasing most rapidly in individuals under 30
- From 2014 to 2015, new HIV infections among white PWID increased 10%
- Over 2,500 new HIV infections occur each year among people who inject drugs

Centers for Disease Control. (2018). Surveillance for Viral Hepatitis — United States, 2016.
Centers for Disease Control and Prevention. HIV Surveillance Report, 2016; vol. 28. Published November 2017. Accessed 7/30/2018.
Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2010–2015. HIV Surveillance Supplemental Report. 2018;23(No. 1). Published March 2018.

Costs of IDU

- The estimated lifetime cost of treating one person living with HIV is near $450,000
- Hospitalization in the US due to substance-use related infections alone costs over $700 million annually
- In the United States, the estimated cost of providing health care services for people living with chronic HCV is $15 billion annually

Farnham PG et al. Updates of lifetime costs of care and quality of life estimates for HIV-infected persons in the United States: Late versus early diagnosis and entry into care. JAIDS 2013; 64: 183-189. Estimates updated to 2017
Ronan, M., & Herzig, S. (2016). Hospitalizations related to opioid abuse/ dependence and associated serious infections increased sharply, 2002–12. Health Affairs, 35(5), 832-837.
Chahal, H. S., Marseille, E. A., Tice, J. A., Pearson, S. D., Ollendorf, D. A., Fox, R. K., et al. (2016, January). Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a U.S. treatment-naive population. The Journal of the American Medical Association, 176(1), 65–73. Retrieved October 25, 2017.

Syringe Service Programs

- First organized programs in US late 1980s in Tacoma, San Francisco, Portland, New York
- In addition to providing access to sterile syringes and disposal of syringes and injection equipment, SSPs offer
  - HIV/AIDS education and counseling, on-site HIV testing
  - Overdose education, safer injection practices, distribution of naloxone
  - Condom distribution to prevent sexual transmission of HIV and other sexually transmitted infections
  - Referrals to substance use disorder treatment
  - Referral to medical, mental health, and social services
  - Testing for tuberculosis (TB), hepatitis B, hepatitis C, and other infections and linkage to treatment
  - Vaccinations
  - Abscess and wound care

International Journal of Drug Policy 55 (2018) 95–104

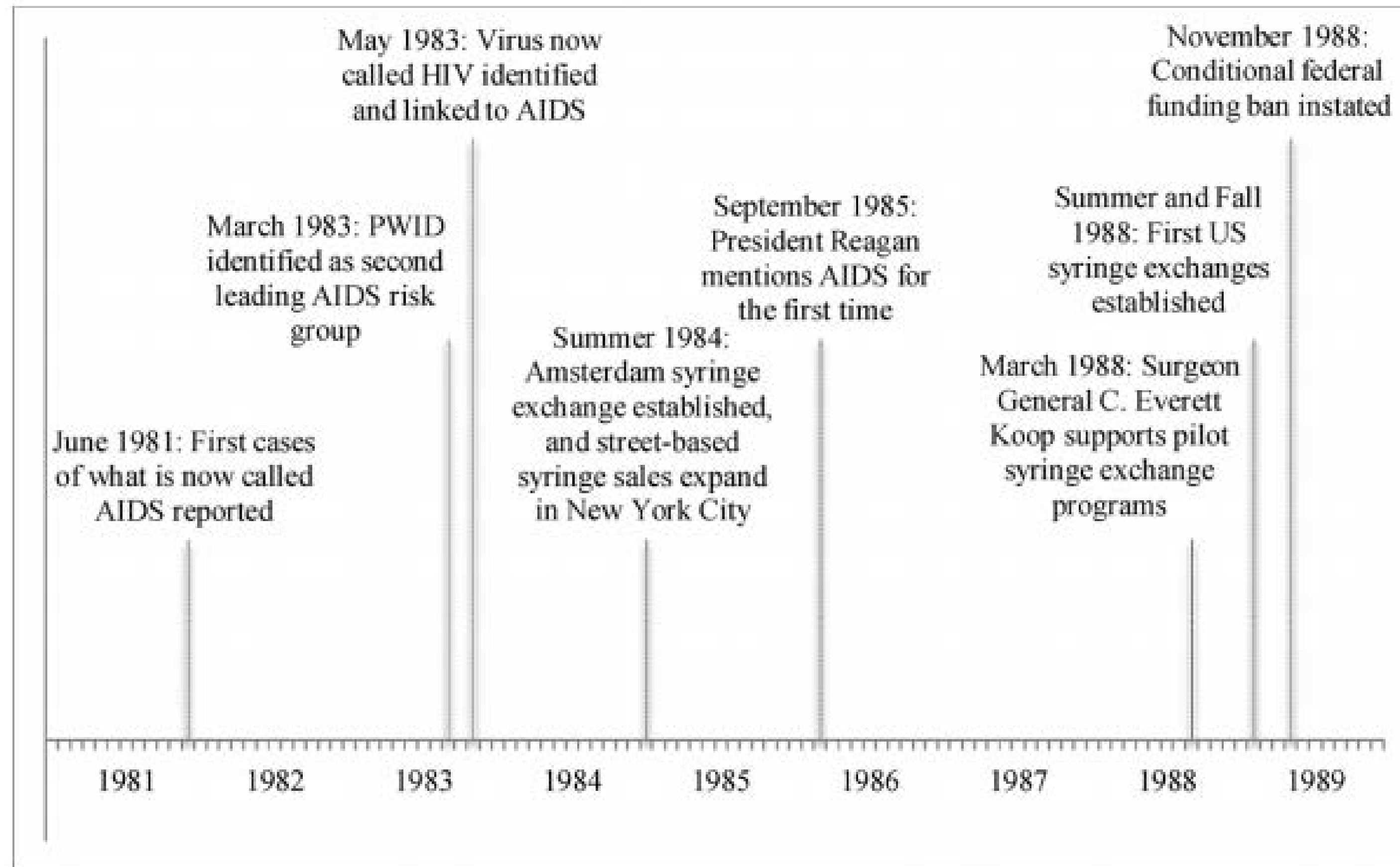


Fig. 1. Milestones in the US Syringe Exchange Debate, 1981 to 1988.

Showalter D. Federal funding for syringe exchange in the US: Explaining a long-term policy failure. Int J Drug Policy. 2018 May;55:95-104. doi: 10.1016/j.drugpo.2018.02.006. Epub 2018 Mar 20. PubMed PMID: 29525361.

International Journal of Drug Policy 55 (2018) 95–104

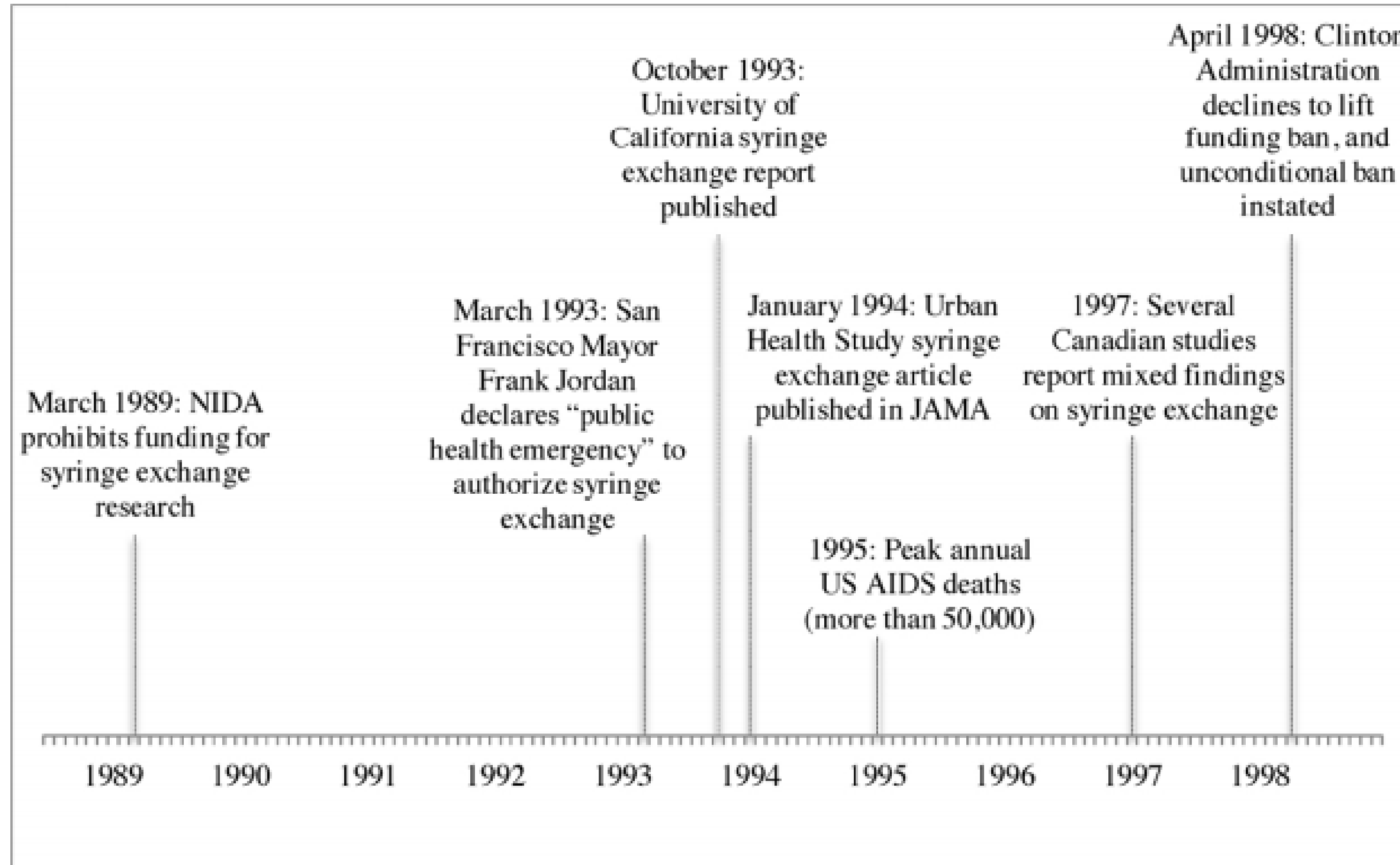


Fig. 2. Milestones in the US Syringe Exchange Debate, 1989 to 1998.

Showalter D. Federal funding for syringe exchange in the US: Explaining a long-term policy failure. Int J Drug Policy. 2018 May;55:95-104. doi: 10.1016/j.drugpo.2018.02.006. Epub 2018 Mar 20. PubMed PMID: 29525361.

International Journal of Drug Policy 55 (2018) 95–104

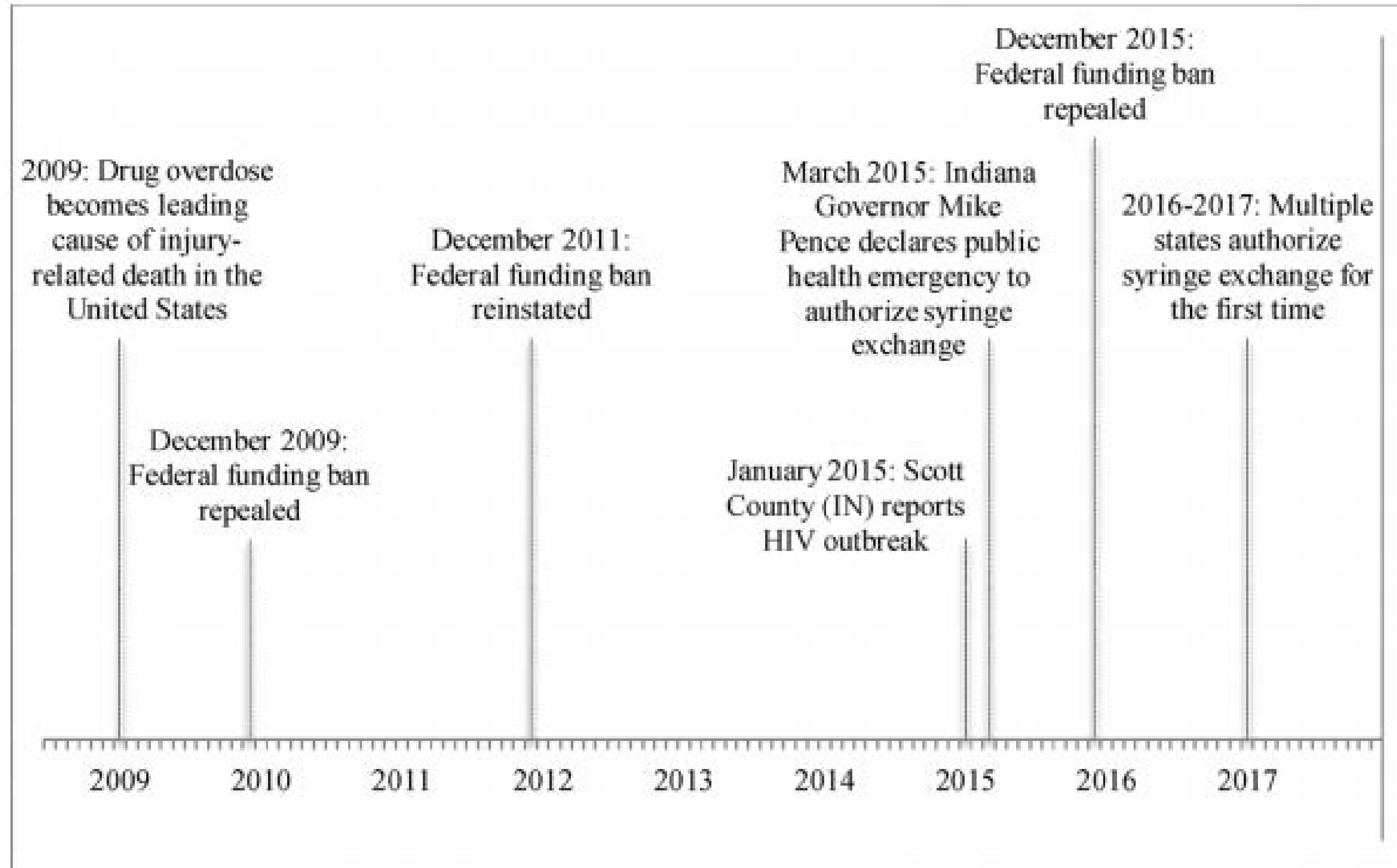


Fig. 3. Milestones in the US Syringe Exchange Debate, 2009 to 2017.

Showalter D. Federal funding for syringe exchange in the US: Explaining a long-term policy failure. Int J Drug Policy. 2018 May;55:95-104. doi: 10.1016/j.drugpo.2018.02.006. Epub 2018 Mar 20. PubMed PMID: 29525361.

Stigma and PWID

- Self-stigma among PWID is associated with lower utilization of pharmacies and Syringe Service Programs (SSPs) to obtain sterile syringes
- Drug use stigma is associated with higher risk injection behaviors (e.g., sharing syringes and other injection supplies)

Luoma JB, Twohig MP, Waltz T, Hayes SC, Roget N, Padilla M, Fisher G. An investigation of stigma in individuals receiving treatment for substance abuse. Addict Behav. 2007 Jul;32(7):1331-46.
Paquette CE, Syvertsen JL, Pollini RA. Stigma at every turn: Health services experiences among people who inject drugs. *Int J Drug Policy*. 2018;57:104–110. doi:10.1016/j.drugpo.2018.04.004

Purchasing syringes at a pharmacy

- California study involved a syringe purchase trial, followed by a pharmacy survey, followed by interviews of 46 PWID regarding their experiences
  - California Senate Bill 41 (SB41) went into effect to expand sterile syringe access across the state by allowing pharmacies to sell syringes without a prescription in 2012
  - Any California pharmacy may voluntarily sell syringes to customers at least 18 years old without a prescription
  - Law allows possession of syringes for personal use if acquired from a physician, pharmacist, SSP, or other legally authorized sterile syringe distribution source

Pollini RA, Rudolph AE, Case P. Nonprescription syringe sales: a missed opportunity for HIV prevention in California. *J Am Pharm Assoc (2003)*. 2015;55(1):31–40. doi:10.1331/JAPhA.2015.14148
Pollini RA. Self-reported participation in voluntary nonprescription syringe sales in California's Central Valley. *J Am Pharm Assoc (2003)*. 2017;57(6):677–685. doi:10.1016/j.japh.2017.06.017
Paquette CE, Syvertsen JL, Pollini RA. Stigma at every turn: Health services experiences among people who inject drugs. *Int J Drug Policy*. 2018;57:104–110. doi:10.1016/j.drugpo.2018.04.004

Purchasing syringes at a pharmacy

- Only 21% of purchase attempts at pharmacies across two counties were successful
- Only 29% of pharmacists and other pharmacy staff were willing to sell nonprescription syringes to PWID compared to 79% for people with diabetes
- More than half said their pharmacy required people purchasing syringes without prescription to enter name and sign logbook (not required by law)
- 61.1% knew it was legal to sell nonprescribed syringes to PWID
- Negatively correlated with syringe sales were
  - Working at an independent pharmacy
  - Agreeing that only people with "medical conditions" like diabetes should be able to buy syringes
  - Viewing syringe sales to PWID as "not good business"

Pollini RA, Rudolph AE, Case P. Nonprescription syringe sales: a missed opportunity for HIV prevention in California. *J Am Pharm Assoc (2003)*. 2015;55(1):31–40. doi:10.1331/JAPhA.2015.14148
Pollini RA. Self-reported participation in voluntary nonprescription syringe sales in California's Central Valley. *J Am Pharm Assoc (2003)*. 2017;57(6):677–685. doi:10.1016/j.japh.2017.06.017

Scientists, including those at the Centers for Disease Control and Prevention (CDC), have studied SSPs for more than 30 years and found that comprehensive SSPs benefit communities.

SSPs save lives by lowering the likelihood of deaths from overdoses.

Providing testing, counseling, and sterile injection supplies helps prevent outbreaks of other diseases. For example, SSPs are associated with a **50% decline** in the risk of HIV transmission.

Users of SSPs were **three times more likely** to stop injecting drugs.

Law enforcement benefits from reduced risk of needlesticks, **no increase in crime**, and the ability to save lives by preventing overdoses.

When two similar cities were compared, the one with an SSP had **86% fewer syringes** in places like parks and sidewalks.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS300156-D March 22, 2019

Bridge To treatment

- SSPs serve as a bridge to other health services including, HCV and HIV diagnosis and treatment and MAT for substance use.[24]
  - Attending a SSP was associated with entering detoxification for both people who inject drugs with and without HIV
  - People who inject drugs who regularly use an SSP are >5x as likely to enter treatment for SUD and nearly 3x as likely to report reducing or discontinuing injection as those who have never used an SSP

HIV and Injection Drug Use: Syringe Services Programs for HIV Prevention. (2016). CDC Vital Signs.
Strathdee, S.A., Celentano, D.D., Shah, N., Lyles, C., Stambolis, V.A., Macal, G., Nelson, K., Vlahov, D., "Needle-exchange attendance and health care utilization promote entry into detoxification", J Urban Health 1999; 76(4):448-60.
Heimer, R. (1998). Can syringe exchange serve as a conduit to substance abuse treatment? Journal of Substance Abuse Treatment 15:183–191.

Preventing Transmission of HIV, HBV, HCV

- Studies have found that
  - Not using syringe exchange was associated with a **hazard ratio of 3.35** (95% CI 1.29, 8.65) for **incident HIV infection** compared with using the exchanges
  - **Non-use** of syringe exchange was associated with almost **6x greater increase** of **hepatitis B** (OR = 5.5) and a **7x greater risk of hepatitis C** (OR = 7.3)

Hagan H, Jarlais DC, Friedman SR, Purchase D, Alter MJ. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health*. 1995;85(11):1531–1537. doi:10.2105/ajph.85.11.1531

Des Jarlais, D. C., Marmor, M., Paone, D., Titus, S., Shi, Q., Perlis, T., . . . Friedman, S. R. (1996). HIV incidence among injecting drug users in New York City syringe-exchange programmes. *Lancet, 348*(9033), 987-991. doi:10.1016/s0140-6736(96)02536-6

Fears about Negative Consequences of SSP

- Studies have found <u>no convincing evidence</u> of the following unintended complications :
  - Greater injection frequency (Hartgers et al. 1989; Watters et al., 1994)
  - Increased illicit drug use (Wolk et al., 1990; Guydish et al., 1993)
  - Rise in syringe lending to other IDUs (Schechter et al. 1999; Hartgers et al. 1989)
  - Recruitment of new IDU (Heimer et al, 1993; Watters et al., 1994, van Ameijden et al., 2001)
  - Greater numbers of discarded used needles (Broadhead et al., 1999, Oliver et al, 1992; Doherty et al., 2000)
  - Less motivation to change, i.e. reduce drug use (Bluthenthal et al., 2001)
  - Increased transition from non-injecting drug use to IDU (Guydish et al., 1993)