TREATMENT OF OPIOID USE DISORDER IN THE FENTANYL ERA

William Trautman, MD

Emergency Medicine and Medical Toxicology Attending

OUTLINE

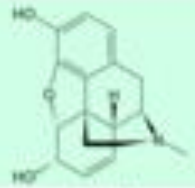
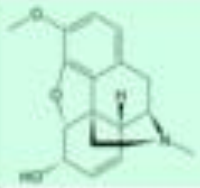
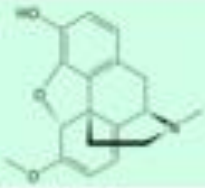
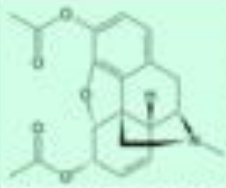
- Fentanyl vs OpiaTes
- Scope of the opioid epidemic
- The fentanyl epidemic?
- Meeting People Where They Are, Addressing Stigma and Language
- Reminders of the medical condition
- Appropriate Definitions
- Stigmatizing Language
- Inpatient treatment of opioid use disorder and opioid withdrawal

Methadone, buprenorphine

Unique Challenges In the Fentanyl Era

- *Macrodose strategy*
- *Microdose strategy*

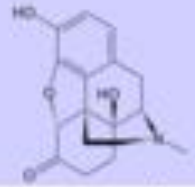
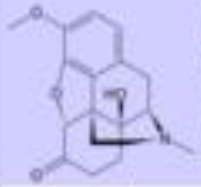
FENTANYL VS OPIATES

3,6 Diol	3-Methoxy	6-Methoxy	3,6 Diester
			
morphine	codeine	thebaine	diacetyl morphine (heroin)

Natural Products Opiates

	
hydromorphone (Dilaudid)	hydrocodone (Vicodin)

Hydroketone Semi-Synthetic Opioids

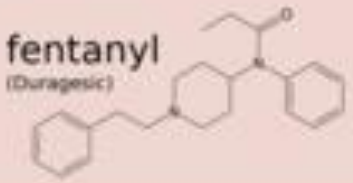
	
oxymorphone	oxycodone (Percocet, Oxycontin)

Oxyketone Semi-Synthetics Opioids

Fully Synthetic Opioids

methadone (Dolophine)

fentanyl (Duragesic)



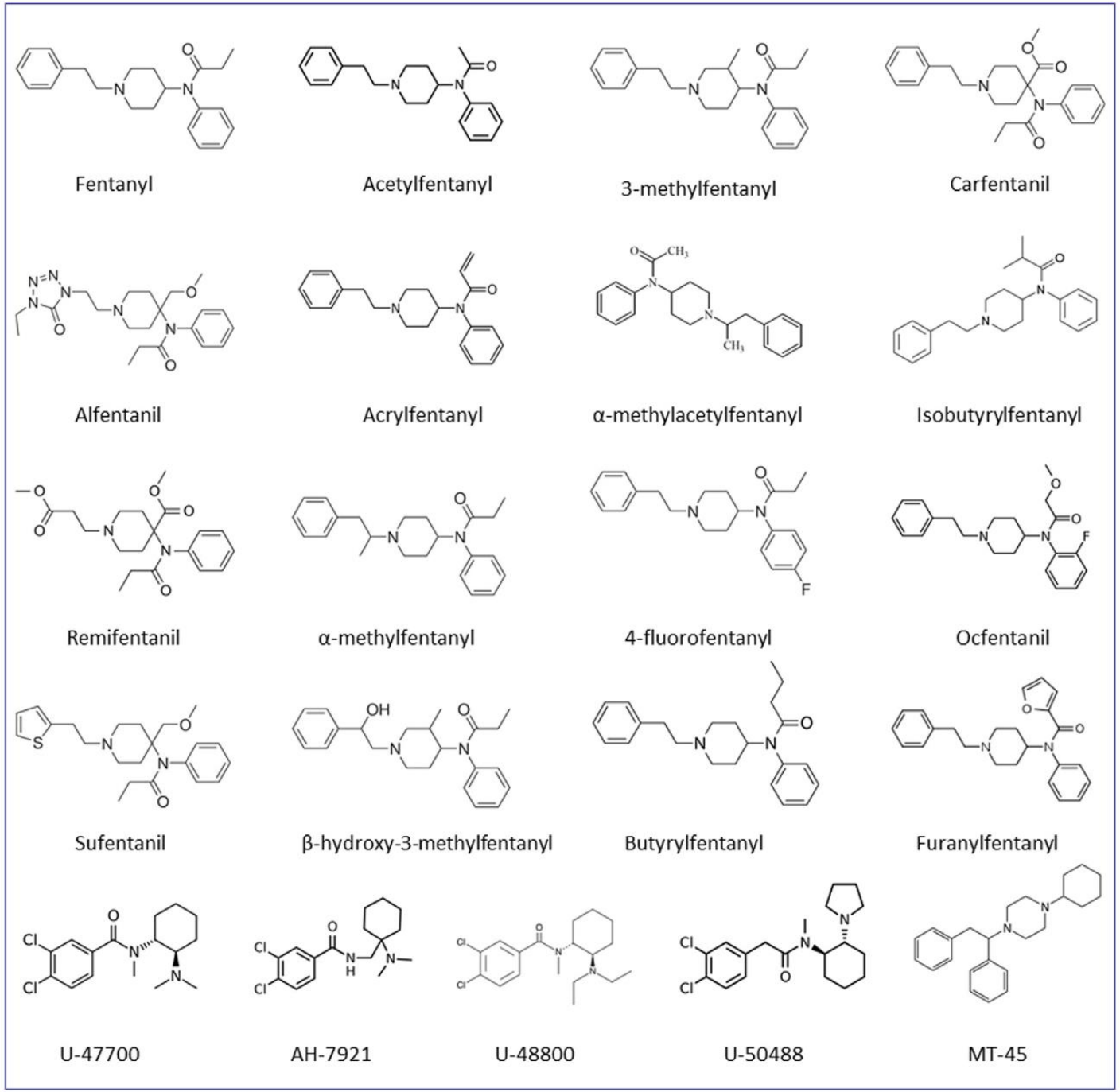


Figure 1. Chemical structures of fentanyl and some NSO.

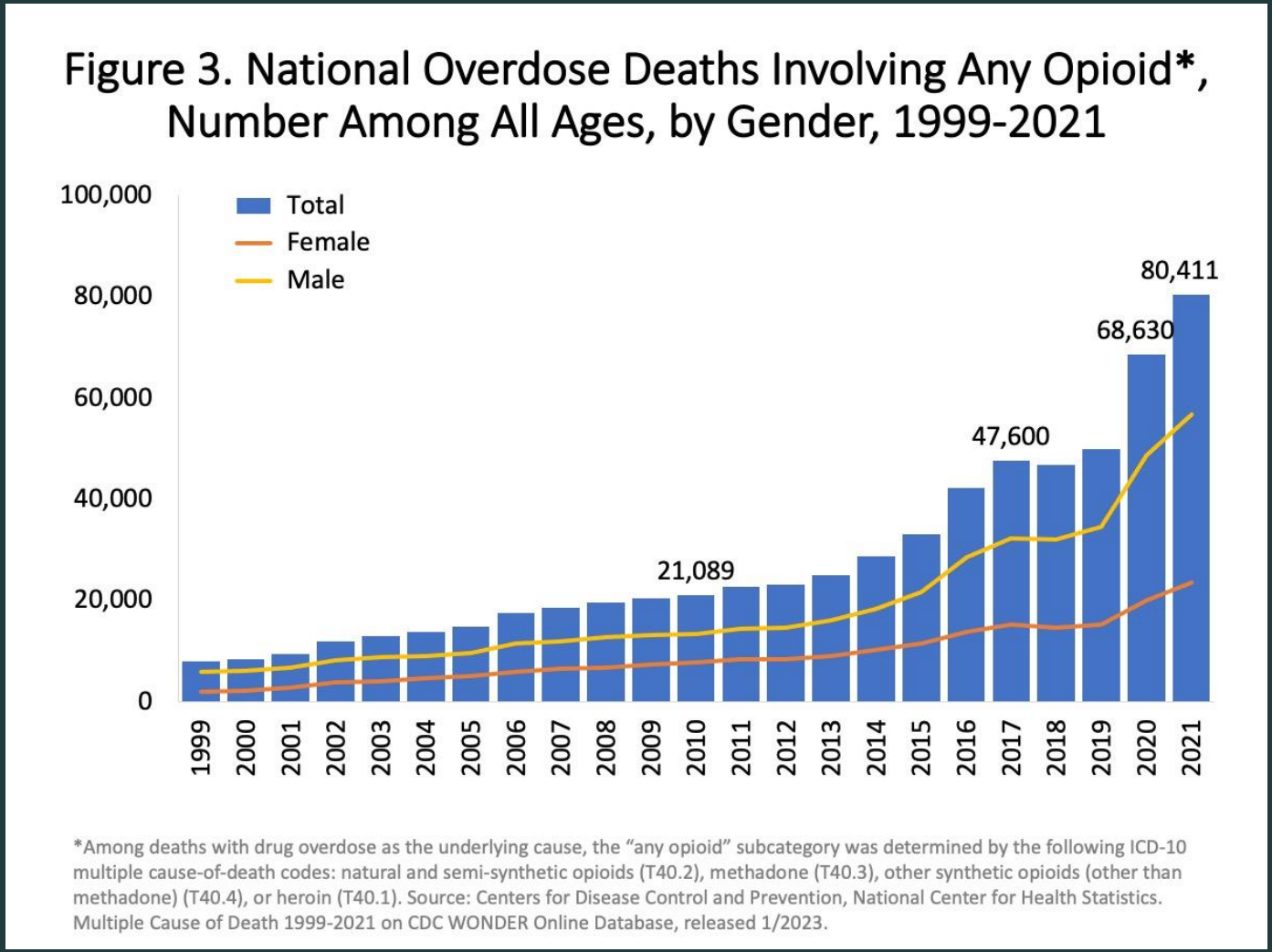
Salle, S., Bodeau, S., Dhersin, A., Ferdonnet, M., Goncalves, R., Lenski, M., … Fabresse, N. (2019). *Novel synthetic opioids: A review of the literature. Toxicologie Analytique et Clinique.*

Table 1 Relative potencies of fentanyl and its pharmaceuticals derivatives, non-pharmaceutical fentanyl derivatives and NSOs compared to morphine and fentanyl (NA: not available).

Compounds	Opioid receptor selectivity			Analgesic potency related to morphine	Analgesic potency related to fentanyl	References
	μ	κ	σ			
Fentanyl and pharmaceutical derivatives						
Fentanyl	+++			50–100	1	[53,8]
Sufentanil	+++	+	+	(500–) 1000 to 4000	5–10	[53,8,61,66]
Alfentanil	+++			72	0.1–0.2	[8,57,67,68]
Remifentanil	+++			220	2–20	[8,57,69]
Illicit fentanyl analogs						
Acetylfentanyl	+++			15.7	0.29	[8,70]
Acrylfentanyl	+++			170	NA	[57,71]
3-methyl-fentanyl	+++			48.5–569	(0.9–)10.5	[8,70,72]
β-hydroxy-3-methyl-fentanyl	+++			6300	28	[8,73]
α-methyl-fentanyl	+++			56.9	1.1	[8,70,72]
α-methyl-acetyl-fentanyl	+++			3.1	0.06	[8,70]
4-fluoro-fentanyl	+++			15.7	0.29	[8,70]
Butyr-fentanyl	+++			(1.5–) 7	0.03–0.13	[21,8,70,30]
Carfentanil	+++			10,000	100	[21,57,61,74]
Isobutyrylfentanyl	+++			NA	1.3–6.9	[57,70]
Ocfentanil	+++			90	1.7	[21,75]
Furanyl-fentanyl	+++			7	NA	[57,70]
Benzamide derivatives						
U-47700	+++			7.5	0.1	[7,21,57,72,76–78]
AH-7921	+++	+		1–1.7	NA	[17,7,57,79,80]
U-48800	+++	++		7.5	NA	[7]
U-50488	-	++		NA	NA	[7,81]
Piperazine derivatives						
MT-45	+++	+	+	≈1	NA	[7,57,74,81–83]

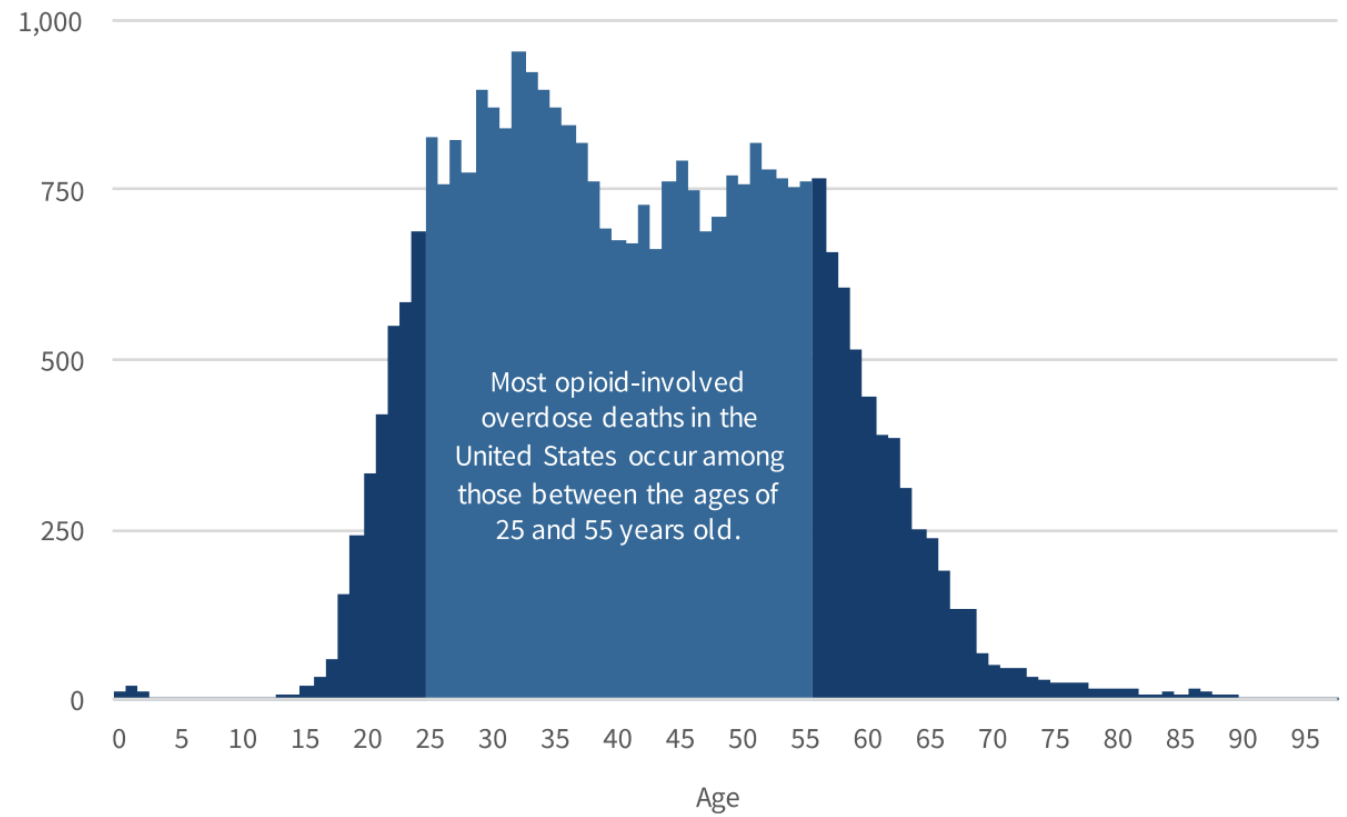
THE OPIOID EPIDEMIC BY THE NUMBERS

THE OPIOID EPIDEMIC BY THE NUMBERS



THE OPIOID EPIDEMIC BY THE NUMBERS

Figure 2. Opioid-involved Overdose Deaths by Age in 2015
(Number of deaths)



Source: CDC Wonder database, multiple cause of death files

THE OPIOID EPIDEMIC BY THE NUMBERS

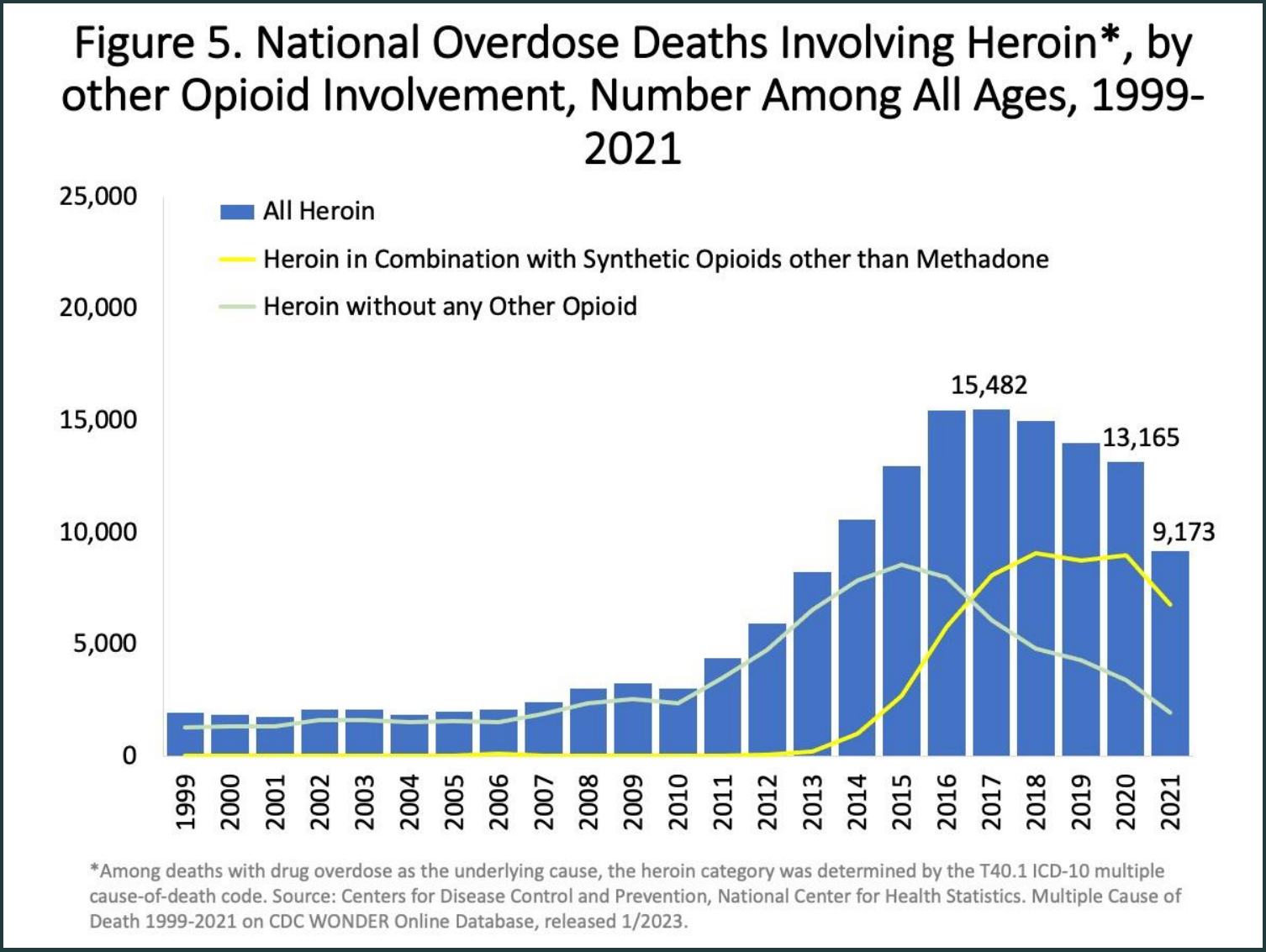
Table 2: Estimated Cost of the Opioid Crisis in 2015 (2015 $)

VSL Assumption	Fatality Costs	Non-fatality Costs	Total Costs
Age-dependent	$431.7 billion	$72.3 billion	$504.0 billion
Low	$221.6 billion	$72.3 billion	$293.9 billion
Middle	$393.9 billion	$72.3 billion	$466.2 billion
High	$549.8 billion	$72.3 billion	$622.1 billion

Note: We assign the VSL of 18 to 24 year-olds for fatalities in the 0 to 17 year-old group, and we assign the VSL of 55 to 62 year-olds for fatalities in the over-62 year-old group. Two fatalities had no reported age; they were assigned the average VSL over all other fatalities. We also adjust Aldy and Viscusi's figures for the effects of inflation and real income growth, following the procedure described in the U.S. DOT (2016), p. 8.

Source: Aldy and Viscusi (2008); U.S. Department of Transportation (2016); CDC WONDER database, multiple cause of death files; Substance Abuse and Mental Health Services Administration (2016); Ruhm (2017); CEA calculations.

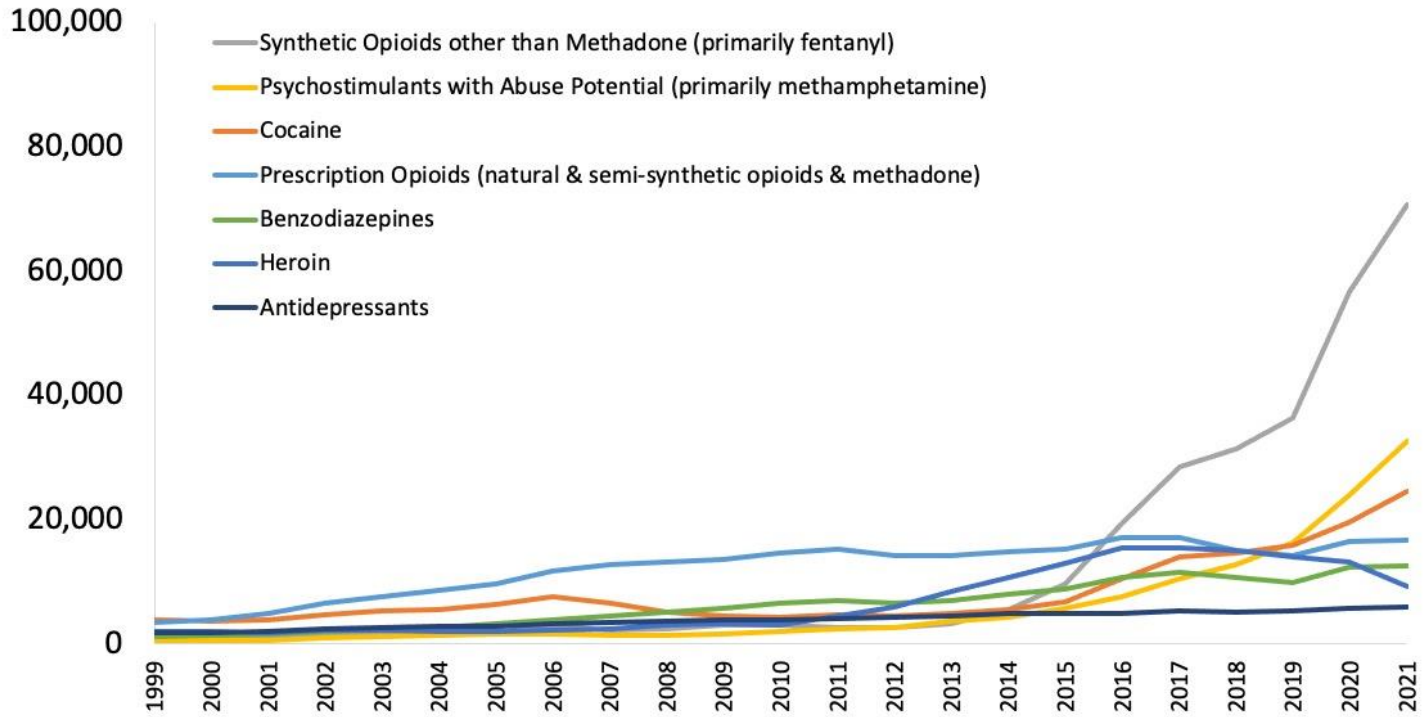
THE OPIOID EPIDEMIC BY THE NUMBERS



Fentanyl

THE OPIOID EPIDEMIC BY THE NUMBERS

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

REMINDERS OF THE MEDICAL CONDITION,

MEETING PEOPLE WHERE THEY ARE

LANGUAGE AND STIGMA

- Stigma origins:
  1. *"Understanding of opioid use disorder as a medical illness is still overshadowed by its misconception as a moral weakness or a willful choice"*
  2. *"Separation of opioid use disorder treatment from the rest of health care has meant that clinicians who treat these patients have not always paid sufficient attention to other substance use, mental health, and physical health conditions"*
  3. *"Language mirrors and perpetuates the stigma related to treatment of opioid use disorder with medications"*
  4. *"Criminal justice system often fails to defer to medical judgment in the treatment of opioid use disorders"*

Olsen, Y., & Sharfstein, J. M. (2014). *Confronting the Stigma of Opioid Use Disorder—and Its Treatment. JAMA, 311(14), 1393.* doi:10.1001/jama.2014.2147

Table 1. Diagnostic Criteria for an Opioid-Use Disorder.*

Use of an opioid in increased amounts or longer than intended
Persistent wish or unsuccessful effort to cut down or control opioid use
Excessive time spent to obtain, use, or recover from opioid use
Strong desire or urge to use an opioid
Interference of opioid use with important obligations
Continued opioid use despite resulting interpersonal problems, social problems (e.g., interference with work), or both
Elimination or reduction of important activities because of opioid use
Use of an opioid in physically hazardous situations (e.g., while driving)
Continued opioid use despite resulting physical problems, psychological problems, or both
Need for increased doses of an opioid for effects, diminished effect per dose, or both†
Withdrawal when dose of an opioid is decreased, use of drug to relieve withdrawal, or both†

* If two or three items cluster together in the same 12 months, the disorder is mild; if four or five items cluster, the disorder is moderate; and if six or more items cluster, the disorder is severe. Criteria are from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.[8]

† If the opioid is taken only as prescribed, this item does not count toward a diagnosis of an opioid-use disorder.

OKAY THAT SOUNDS EASY BUT REAL LIFE…

5/05	[Meds] & Comments/Nursing Notes
8:15 a	pt seen leaving with security guard walking beside him, pt yelling while walking. pt's mom and dad at bedside. went to the nurses' station and spoke with the unit director. unit director walked them to get help from security.
8:07 a	assisted parents with parking validation and security escort to car
8:03 a	security dispatched to review behavioral expectations with patient - pt continues with vulgarities to staff and his own mother. Said he was done and he weas leaving. No IV to remove. pt ambulated without difficulty, yelling the entire way out - security professional and escorted offf premisis.
7:55 a	patient in hallway yelling '[redacted]' - no mask - with middle finger waving in the air. pateint asked to replace mask and asked what was needed. pateint states he has been here all night without any pain medications,[redacted] discussed that she has been here and knew he had been medicated, but she would readress his pain with the MD. pt again continued to yell obsenities frightening some of the staff/CM. Security will be asked to speak with patient.
7:20 a	pt in the bathroom when attempted to round after report.
6:42 a	IV team consulted, IV team states that Pt is very well known to IV team and Pt can be very demanding with US, IF no IV site is able to be obtained then re consult after 7 am. Will pass on to oncoming nurse.

MEDIAN NUMBER OF ATTEMPTS: 5.35

Methods: Cross-sectional, nationally representative survey of U.S. adults (N = 39,809) who reported resolving a significant AOD problem (n = 2,002) and assessed on number of prior serious recovery attempts, demographic variables, primary substance, clinical histories, and indices of psychological distress and well-being.

How Many Recovery Attempts Does it Take to Successfully Resolve an Alcohol or Drug Problem? Estimates and Correlates From a National Study of Recovering U.S. Adults

John F. Kelly, Martha Claire Greene, Brandon G. Bergman, William L. White, and Bettina B. Hoeppner

LANGUAGE ADJUSTMENTS

Instead of	Use	Because…
Addict	Person with substance use disorder	Person-first language. The change shows that a person "has" a problem, rather than "is" the problem. The terms avoid eliciting negative associations, punitive attitudes, and individual blame.
User	Person with substance use disorder	
Substance or drug abuser	Patient	
Junkie	Patient with active use	
Alcoholic	Person with alcohol use disorder	
Drunk	Person who misuses alcohol/engages in unhealthy/hazardous alcohol use	
Former addict	Person who previously used drugs	

https://nida.nih.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction

LANGUAGE ADJUSTMENTS

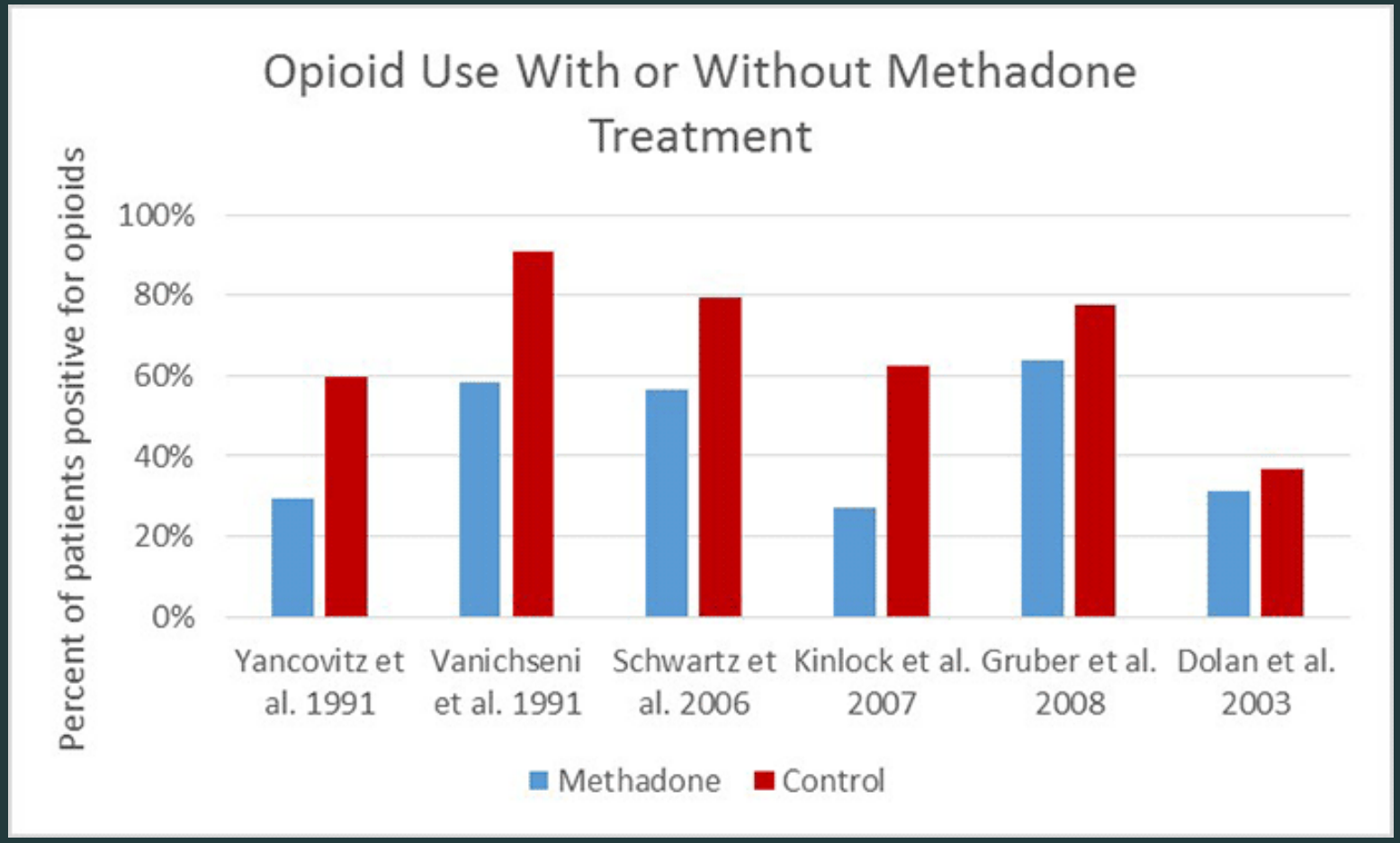
Instead of	Use	Because…
Clean	**For toxicology screen results:** Testing negative **For non-toxicology purposes:** Being in remission or recovery Abstinent from drugs Not drinking or taking drugs Not currently or actively using drugs	Use clinically accurate, non-stigmatizing terminology the same way it would be used for other medical conditions.[10] Set an example with your own language when treating patients who might use stigmatizing slang. Use of such terms may evoke negative and punitive implicit cognitions.[7]
Dirty	•**For toxicology screen results:** Testing positive •**For non-toxicology purposes:** Person who uses drugs	Use clinically accurate, non-stigmatizing terminology the same way it would be used for other medical conditions.[9] May decrease patients' sense of hope and self-efficacy for change.

https://nida.nih.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction

TREATMENT OPTIONS

TREATMENT OF OUD: METHADONE

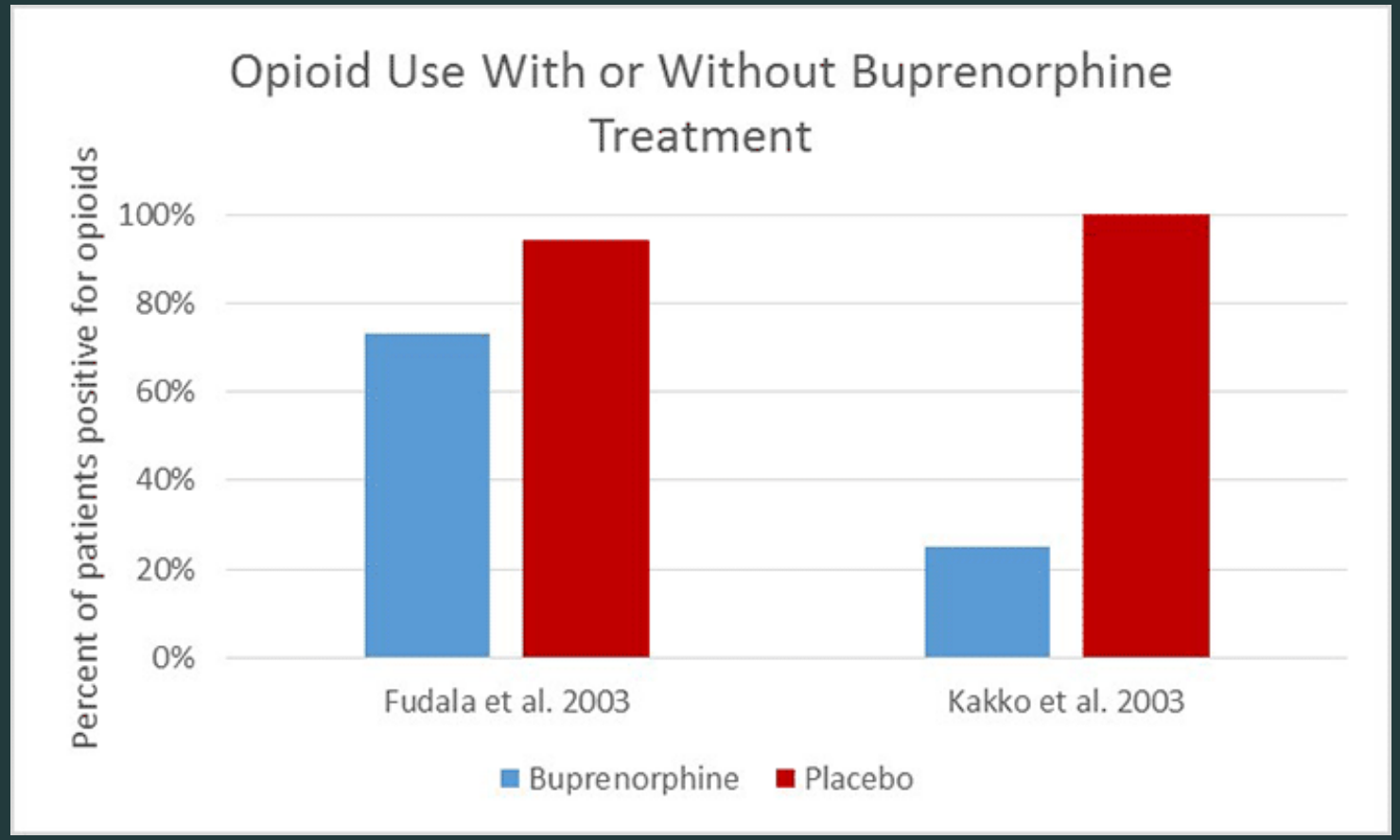
- 33 percent fewer opioid-positive drug tests
- 4.44 times more likely to stay in treatment compared to controls.
- Methadone treatment long-term (beyond 6 months) outcomes are better in groups receiving methadone, regardless of the frequency of counseling received.



NIDA. 2021, December 3. How effective are medications to treat opioid use disorder?. Retrieved from https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder on 2023, August 20

TREATMENT OF OUD: BUPRENORPHINE

- Meta-analysis determined that patients on doses of buprenorphine of 16 mg per day or more were 1.82 times more likely to stay in treatment than placebo-treated patients,
- Buprenorphine decreased the number of opioid-positive drug tests by 14.2 percent



NIDA. 2021, December 3. How effective are medications to treat opioid use disorder?. Retrieved from https://nida.nih.gov/publications/research-reports/medications-to-treat-opioid-addiction/efficacy-medications-opioid-use-disorder on 2023, August 20

CHALLENGES RELATED TO FENTANYL/ANALOGS

SAMHSA
Substance Abuse and Mental Health Services Administration

BUPRENORPHINE

QUICK START GUIDE

Induction Considerations

The dose of buprenorphine depends on the severity of withdrawal symptoms, and the history of last opioid use (see flowchart in appendix for dosing advice).

- Long acting opioids, such as methadone, require at least 48-72 hours since last use before initiating buprenorphine.
- Short acting opioids (for example, heroin) require approximately 12 hours since last use for sufficient withdrawal to occur in order to safely initiate treatment. Some opioid such as fentanyl may require greater than 12 hours.
- Clinical presentation should guide this decision as individual presentations will vary.

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

"Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl

Sydney M. Silverstein[a,*], Raminta Daniulaityte[a], Silvia S. Martins[b], Shannon C. Miller[c,d], Robert G. Carlson[a]

Meeting Patient's Where They Are: Start by Listening

"You have to be clean four or five days before you can even take the Suboxone. So you're sick four or five days and it's like, it's not, no. It's like you can't do it…, I tried it a couple of times and I just couldn't do it."

"I was almost 72 hours into withdrawal…and I took it [Suboxone] and it made me… I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever…But immediately—Bam! Not even five minutes after I took it I was dripping sweat. It felt like water had just gotten dumped all over me, I'm puking and it's coming ou every end"

Silverstein SM, Daniulaityte R, Martins SS, Miller SC, Carlson RG. "Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl. Int J Drug Policy. 2019 Dec;74:76-83.

MEETING PATIENT'S WHERE THEY ARE: START BY LISTENING

SMS: *"Do you notice any differences in how well the Suboxone works for heroin versus how it works for fentanyl?"*

A: *"Yes, for me it sends me into precipitated withdrawals every* [redacted] *time that I try to get off of fentanyl. Then I have these Sub doctors telling me that it's not real and it's like, go* [redacted] *ask the people that are buying it off the streets. It is real! I waited 80 hours. I was in a detox and after 80 hours they gave me a Suboxone and it still put me into precipitated"*

Silverstein SM, Daniulaityte R, Martins SS, Miller SC, Carlson RG. "Everything is not right anymore": Buprenorphine experiences in an era of illicit fentanyl. Int J Drug Policy. 2019 Dec;74:76-83.

FENTANYL PHARMACOKINETICS

- Absorption: Oral – 30%, IN 89%, IV 100%
- 86% to 89% protein bound in blood, with approximately

  78% bound to albumin and 12% bound to α-1 acid glycoprotein,
- pKa = 8.43 (weakly basic)
- Half life – highly variable dependent on use:

  Mean fentanyl clearance in urine was 2 weeks, with a range of 4–26 days.[1]

1. Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend. 2020 Sep 1;214:108147

SO WHAT CAN WE DO?

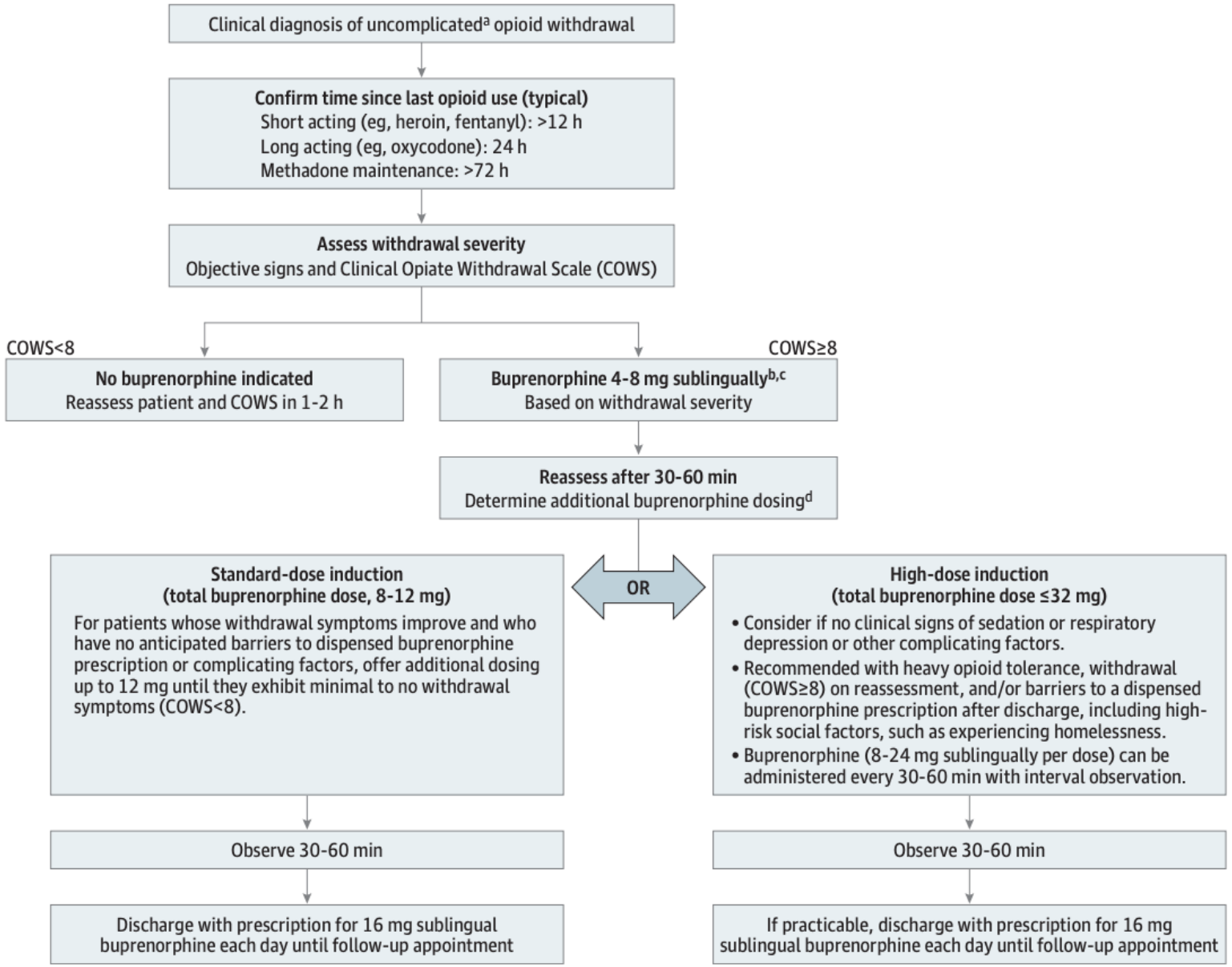
JAMA Network | Open™

Original Investigation | Substance Use and Addiction

High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS

Figure 1. High-Dose Buprenorphine Treatment Pathway



Buprenorphine Macro-Dosing Induction for OUD in the Inpatient Setting

Authors: Cheryl Monteiro, MD; Ryan Golden, MD; Lewis S. Nelson, MD

Population: 15 patients with Opioid Use Disorder who were macro-dosed with buprenorphine while inpatient

Inclusion: clinical opioid withdrawal scores of >8
or had at least 4 hours since full opioid agonist administration prior to induction. Fourteen patients were inducted with 16 mg and 1 received 20 mg.

Outcome: 10/15 patients had complete resolution of opioid withdrawal and none experienced precipitated withdrawal.

5 patients with persistent withdrawal, 2 improved with additional 8 mg (one of whom reported non-pharmaceutical fentanyl use). The remaining 3 patients had persistent withdrawal despite total doses of 32-40 mg on induction (one of whom also reported non-pharmaceutical fentanyl use)

Monteiro C., Golden R., Nelson L Buprenorphine macro-dosing induction for OUD in the inpatient setting: a case series. 2021 poster abstracts. J Addict Med. 2021; 15: E1-E58

WHAT'S THE OPPOSITE OF MACRO?

LOW-DOSE BUPRENORPHINE INDUCTION

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, Walter M, Dürsteler KM, Vogel M. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil. 2016 Jul 20;7:99-105

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journal homepage: www.elsevier.com/locate/drugalcdep

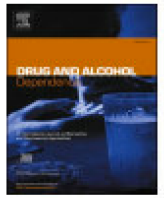


Table 1
Dosing strategies utilized.

Rapid Dosing Strategy	
Hour of therapy	**Buprenorphine Titration**
0–6	Buprenorphine 0.3 mg IV every 6 h x 2 doses
12–18	Buprenorphine 0.6 mg IV every 6 h x 2 doses
24	Buprenorphine 4 mg SL x 1 dose[a]
Moderate Dosing Strategy	
Hour of therapy	**Buprenorphine Titration**
0–6	Buprenorphine 0.15 mg IV every 6 h x 2 doses
12–18	Buprenorphine 0.3 mg IV every 6 h x 2 doses
24–30	Buprenorphine 0.6 mg IV every 6 h x 2 doses
36	Buprenorphine 4 mg SL x 1 dose[a]
Slow Dosing Strategy	
Hour of therapy	**Buprenorphine Titration**
0–18	Buprenorphine 0.15 mg IV every 6 h x 4 doses
24–30	Buprenorphine 0.3 mg IV every 6 h x 2 doses
36–42	Buprenorphine 0.6 mg IV every 6 h x 2 doses
48	Buprenorphine 4 mg SL x 1 dose[a]

[a]Following the 4 mg SL dose, buprenorphine is titrated to a therapeutic dose based on patient response
IV = intravenous; SL = sublingual

Jablonski LA, Bodnar AR, Stewart RW. Development of an intravenous low-dose buprenorphine initiation protocol. Drug Alcohol Depend. 2022 Aug 1;237:109541. doi: 10.1016/j.drugalcdep.2022.109541. Epub 2022 Jun 20. PMID: 35753281.

Table 3
Low-dose initiation (LDI) outcomes across sub-groups.

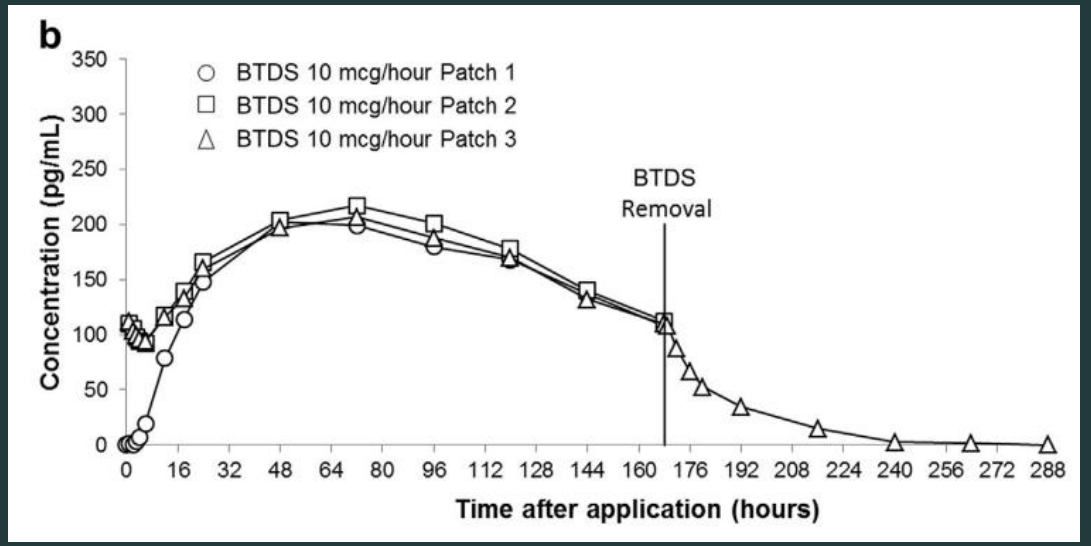
	All (n = 59)	**Pain** (n = 47)	**Fentanyl** (n = 42)	**Methadone** (n = 17)
Additional Reasons for LDI, n (%)	47 (80)	–	34 (81)	9 (53)
Acute pain	42 (71)	34 (72)	–	8 (47)
Fentanyl	17 (29)	9 (19)	8 (19)	–
Methadone				
Completed LDI, n (%)	54 (92)	43 (91)	39 (93)	15 (88)
Tolerated LDI, n (%)	43 (73)	35 (74)	29 (69)	11 (65)
Maximum COWS, median (IQR)	5 (3–8)	5 (2–8)	5 (3–9)	6 (4–8)
Adherent, n (%)	44 (75)	34 (72)	31 (74)	15 (88)
Dosing strategy, n (%)				
Rapid	12 (20)	10 (21)	8 (19)	0 (0)
Moderate	16 (27)	14 (30)	15 (36)	2 (12)
Slow	16 (27)	10 (21)	8 (19)	13 (76)
Nonadherent	15 (25)	13 (28)	11 (26)	2 (12)
Adjunctive medication administration, n (%)	14 (24)	11 (23)	12 (29)	4 (24)
Clonidine	19 (32)	12 (26)	14 (33)	9 (53)
Dicyclomine	39 (66)	33 (70)	29 (69)	10 (59)
Hydroxyzine	6 (10)	5 (11)	4 (10)	3 (18)
Loperamide	15 (25)	14 (30)	12 (29)	5 (29)
Ondansetron				
Duration (hr), median (IQR)	41 (32–48)	38 (30–48)	40 (34–48)	48 (46–51)
Time to cumulative 16 mg buprenorphine dose (hr), median (IQR)	65 (56–72)	63 (53–72)	64 (56–72)	73 (70–79)
Final total daily buprenorphine dose, n (%)	2 (3)	1 (2)	2 (5)	1 (7)
	22 (37)	14 (30)	16 (38)	8 (53)
8 mg	21 (36)	20 (43)	15 (36)	4 (27)
16 mg	9 (15)	8 (17)	6 (14)	2 (13)
24 mg	5 (8)	4 (9)	3 (7)	2 (13)
32 mg				
N/A[a]				

IQR = interquartile range
COWS = Clinical Opiate Withdrawal Scale
[a] LDI not completed

WHAT IF WE DON'T HAVE IV BUPRENORPHINE?

TRANSDERMAL BUPRENORPHINE INDUCTION

- 35mcg transdermal patch ~equivalent to 0.8mg/day
- Peak concentrations reached at 48-72 hours
- Multiple case reports and case series with varying strategies
- Goal to transition with minimal to no withdrawal



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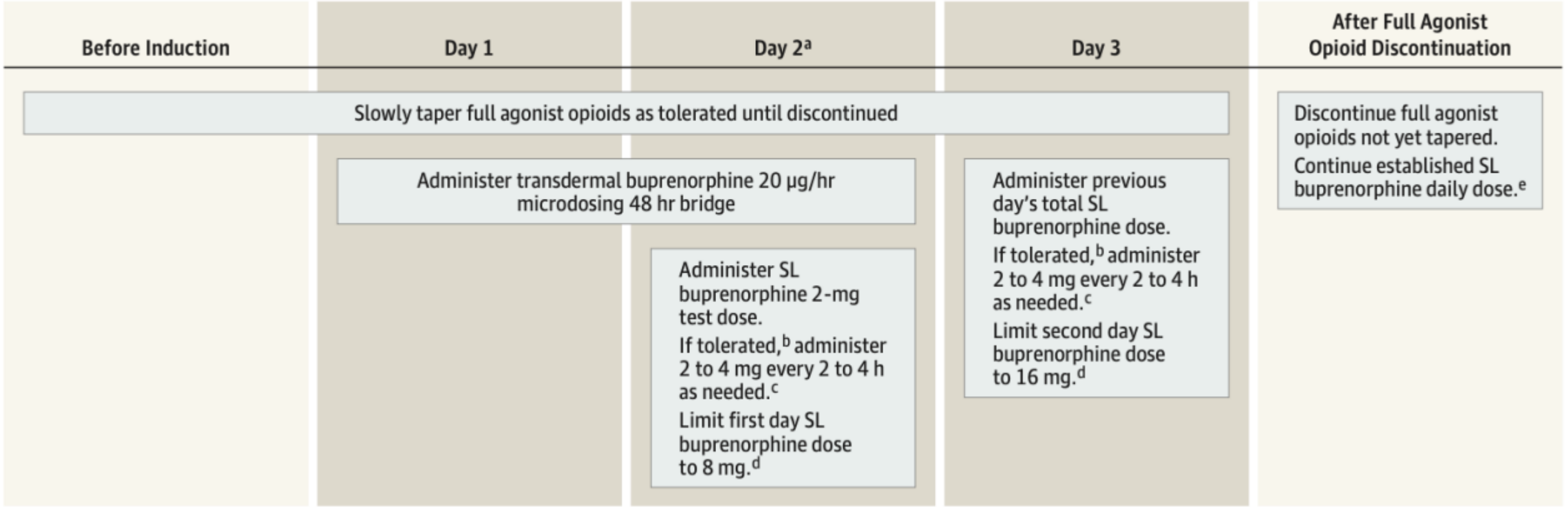
LITERATURE STRATEGY

Figure. Buprenorphine Induction With Transdermal Buprenorphine Microdosing



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UNIVERSITY OF PITTSBURGH EXPERIENCE

- ~500 hospitalized patients
- Differing patient populations
  Methadone transition
  Continued full agonist therapy for pain
  Discontinuation of full agonist
- Day 1: Transdermal buprenorphine 20-40mcg
- 24-48 hours: Buprenorphine 2-0.5mg SL q2 x 4 doses
  Ideally 4-6 hour pause of full opioid agonist prior to induction
- Maintenance Buprenorphine 8-2mg SL BID
- Rare cases of precipitated withdrawal

UNIVERSITY OF PITTSBURGH EXPERIENCE

Inclusion: received a TBP for SL buprenorphine prescribed FOAs within 24 hours of SL induction

Results: Of 66 patients, only 6 (9%) experienced precipitated withdrawal

TBP dose and patch time was 40 mcg and 39.9 hours respectively

147. Pumping the Brakes on Precipitated Withdrawal with a Transdermal Buprenorphine Patch

Alek Q Adkins[1], David A Goldfarb[1], David Barton[1], Melissa Kukowski[2], Anthony F Pizon[1]

FINISHING ON THE POSITIVE: IT MAKES A DIFFERENCE!

Buprenorphine Treatment for Hospitalized, Opioid-Dependent Patients
A Randomized Clinical Trial

Jane M. Liebschutz, MD, MPH; Denise Crooks, MPH; Debra Herman, PhD; Bradley Anderson, PhD; Judith Tsui, MD, MPH; Lidia Z. Meshesha, BA; Shernaz Dossabhoy, BA; Michael Stein, MD

- During follow-up, linkage participants were more likely to enter buprenorphine OAT than those in the detoxification group (52 [72.2%] vs 8 [11.9%], P < .001).
- At 6 months, 12 linkage participants (16.7%) and 2 detoxification participants (3.0%) were receiving buprenorphine OAT (P = .007).
- Compared with those in the detoxification group, participants randomized to the linkage group reported less illicit opioid use in the 30 days before the 6-month interview (incidence rate ratio, 0.60; 95% CI, 0.46-0.73; P < .01) in an intent-to-treat analysis.

Questions?

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