Naloxone and opiate overdose

- Death generally occurs within 1-3 hours of overdose (Kin, 2009)
- Bystander Naloxone use is associated with increased odds of recovery (Giglio, 2015)
- Discuss Naloxone with all patients who have an opiate use disorder
- Explain signs and symptoms of overdose (handouts and videos may help)

Naloxone Co-Prescribing

- Should be considered with all chronic opiate prescriptions
  - Death generally occurs within 1-3 hours of overdose (Kim, 2009)
- Bystander naloxone use is associated with increased odds of recovery (Giglio, 2015)
- Explain signs and symptoms of overdose
  - Classic triad: pinpoint pupils/very small pupils, unconsciousness/not responsive/won't wake up, respiratory depression/barely breathing/slow
- Share handouts and review naloxone use
- Share website with videos regarding OD recognition and naloxone use by patients and bystanders

Naloxone for Overdose Prevention

patient name

date of birth

patient address

patient city, state, ZIP code

"IMPORTANT:
Administering
Naloxone to someone
who has NOT used
opiates does NO
harm"

Rx

prescriber name

prescriber address

prescriber city, state, ZIP code

prescriber phone number

Naloxone HCl 1 mg/mL
2 x 2 mL as pre-filleld Luer-Lock needless syringe
(NDC 76329-3369-1)

Refills: _____

2 x Intranasal Mucosal Atomizing Device (MAD 300)

Refills: _____

For suspected opioid overdose, spray 1mL in each nostril.
Repeat after 3 minutes if no or minimal response.

Pharmacist: Call 1-800-788-7999 to order MAD 300.

prescriber signature

date

Detach for patient

How to Avoid Overdose

- Only take medicine prescribed to you
- Don't take more than instructed
- Call a doctor if your pain gets worse
- Never mix pain meds with alcohol
- Avoid sleeping pills when taking pain meds
- Dispose of unused medications
- Store your medicine in a secure place
- Learn how to use naloxone
- Teach your family + friends how to respond to an overdose

Are they breathing? → Call 911 for help

Signs of an overdose:

- Slow or shallow breathing
- Gasping for air when sleeping or weird snoring
- Pale or bluish skin
- Slow heartbeat, low blood pressure
- Won't wake up or respond (rub knuckles on sternum)

All you have to say:
"Someone is unresponsive and not breathing."
Give clear address and location.

Airway → Rescue breathing

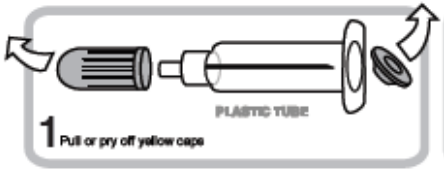
Make sure nothing is inside the person's mouth.

Oxygen saves lives. Breathe for them.
One hand on chin, tilt head back, pinch nose closed.
Make a seal over mouth & breathe in
1 breath every 5 seconds
Chest should rise, not stomach

Prepare Naloxone

Are they any better? Can you get naloxone and prepare it quickly enough that they won't go for too long without your breathing assistance?

PrescribeToPrevent.org



Source: HarmReduction.org

Evaluate + support

- Continue rescue breathing
- Give another 2 sprays of naloxone in 3 minutes if no or minimal breathing or responsiveness
- Naloxone wears off in 30-90 minutes
- Comfort them; withdrawal can be unpleasant
- Get them medical care and help them not use more opiate right away
- Encourage survivors to seek treatment if they feel they have a problem

POISON Help 1-800-222-1222 AAPCC

v02.12.11

Naloxone Product Comparison

	Injectable (and intranasal-IN) generic		Intranasal branded		Injectable generic[1]		Auto-injector branded	
Sig. (for suspected opioid overdose)	Spray 1 ml (1/2 of syringe) into each nostril. Repeat after 2-3 minutes if no or minimal response.		Spray 0.1 mL into one nostril. Repeat with second device into other nostril after 2-3 minutes if no or minimal response.		Inject 1 mL in shoulder or thigh. Repeat after 2-3 minutes if no or minimal response.		Inject into outer thigh as directed by English voice-prompt system. Place black side firmly on outer thigh and depress and hold for 5 seconds. Repeat with second device in 2-3 minutes if no or minimal response.	
Ordering information								
How supplied	Box of 10 Luer-Jet™ prefilled glass syringes		Two-pack of single use intranasal devices		Box of 10 or package of 25 single-dose fliptop vials (1 ml)	Case of 25 multi-dose fliptop vials (10 ml)	Two pack of single use auto-injectors + 1 trainer	
Manufacturer	IMS/ Amphastar	Teleflex (off-label IN adapter)	Adapt Pharma		Pfizer, Mylan and West-Ward Pharmaceuticals	Pfizer	kaléo	
Web address	Amphastar.com	Teleflex. com	Narcannasalspray.com		Pfizerinjectables.com Mylan.com West-ward.com	Pfizerinjectables.com	Evzio.com	
Customer service	800-423-4136	866-246-6990	844-462-7226		877-946-7747 (P) 724-514-1800 (M) 800-631-2174 (W)	877-946-7747 (P)	855-773-8946	
NDC	76329-3369-01	DME- no NDC	69547-353-02	69547-212-04	00409-1215-01 (P) 67457-0292-02 (M) 0641-6132-25 (W)	00409-1219-01	60842-030-01	60842-051-01

[1] Pfizer acquired Hospira in 2015. Pfizer has an additional naloxone product, which is ***not recommended*** for layperson and take-home naloxone use because it is complicated to assemble. (Naloxone Hydrochloride Injection, USP, 0.4 mg/mL Carpuject™ Luer Lock Glass Syringe (no needle) NDC# 0409-1782-69)
[2] This product concentration is not yet currently available. As a result, some of the content is left blank.
[3] EVZIO 2 mg is now available. As of February 2017, EVZIO 0.4 mg will no longer be manufactured, but is still currently available and effective.
[4] There is considerable price variance for each product- local pharmacists are able to provide specific local pricing.
Image development supported by 1R01DA038082-01 Friedmann/Rich

NALOXONE PRICING IN THE COMMUNITY (As of January 2019)					
		naloxone injection (0.4mg/mL)	naloxone prefilled syringe (2 mg/2 mL)	Narcan® nasal spray (4 mg/0.1 mL)	Evzio® auto-injector (2 mg/0.4 mL)
Route of medication		Intramuscular only	Intranasal with atomizer	Intranasal	Intramuscular
Cash Price based on goodrx.com[1]		$12.80 to $21.13*	$20.99 to $36.85	$129.99 to $139.13	>$3,720
CVS Pharmacy[2]		$18.99	$38.99	$95[3]	$2,225.99
Walgreens[4]		NA	$39.99	$135	NA
MassHealth		$3.65†	$3.65†	$3.65†	NA
Fallon Community Health Plan	Commercial 3-Tier or 4-tier Formulary	Tier 1 or Tier 2	Tier 1 or Tier 2	Tier 3 or Tier 4	Tier 3 or Tier 4; PA
	Hybrid Formulary	Tier 1 *$1*	Tier 1 *$1*	Tier 4 *50% coinsurance‡*	Tier 3; PA *$30*
	NaviCare (Medicare Part D)	Generic available through mail-order	Generic available through mail-order	Generic	NA
AllWays Health Partners §	3 Tier, 4 Tier, 5 Tier, 6 Tier Formulary	Tier 1 or Tier 2	$0	Tier 2 or Tier 3	NA
Tufts	Health RITogether	Tier 1	NA	Tier 2; QL: 2 kits/30 days, 1 kit/Rx	Tier 2; QL: 4 units/30 days, 2 units/Rx; PA
	Health Direct	$0	NA	$0	Tier 3; QL: 4 units/30 days, 2 units/Rx; PA
Blue Cross Blue Shield of MA Standard	Standard 3-Tier Pharmacy Program Formulary	Tier 1	Tier 3	Tier 3	Tier 2
Harvard Pilgrim Health Care	3-Tier Prescription Drug Plan	$0; QL: 2 ml/15 days	$0; QL: 2 mL/15 days	$0; QL: 2 bottles/15 days	Not covered

IM=intramuscular, IN=intranasal, IV=intravenous, NA=not available, PA=prior authorization, QL=quantity limit, RX=prescription
*Price per mL
†MassHealth copayment
‡$400 maximum
§ Formerly Neighborhood Health Plan

1. https://www.goodrx.com/
2. CVS Source: 1163 Providence Road, Whitinsville, MA
3. https://cvshealth.com/newsroom/press-releases/cvs-health-expands-efforts-educate-patients-about-naloxone
4. Walgreens Source: 99 Stafford Street, Worcester, MA

Naloxone Standing Order:

- Naloxone is available in Massachusetts without a prescription through a statewide standing order.
- https://www.mass.gov/files/documents/2018/10/18/standing-order-dispensing-naloxone-rescue-kits.pdf

Intranasal administration	Intramuscular injection
Naloxone 4 mg/0.1 mL nasal spray* Directions for use: Administer a single spray of naloxone in one nostril. Repeat after 3 minutes if no or minimal response.	Naloxone 0.4 mg/mL in 1 mL single dose vials* Directions for use: Inject 1 mL IM in shoulder or thigh. Repeat after 3 minutes if no or minimal response.
Naloxone 2 mg/2 mL single-dose Leur jet prefilled syringe*† Directions for use: Spray 1 mL in each nostril. Repeat after 3 minutes if no or minimal response.	Naloxone 2 mg/0.4 mL auto-injector* Directions for use: Follow audio instructions from device. Place on thigh and inject 0.4 mL. Repeat after 3 minutes if no or minimal response.

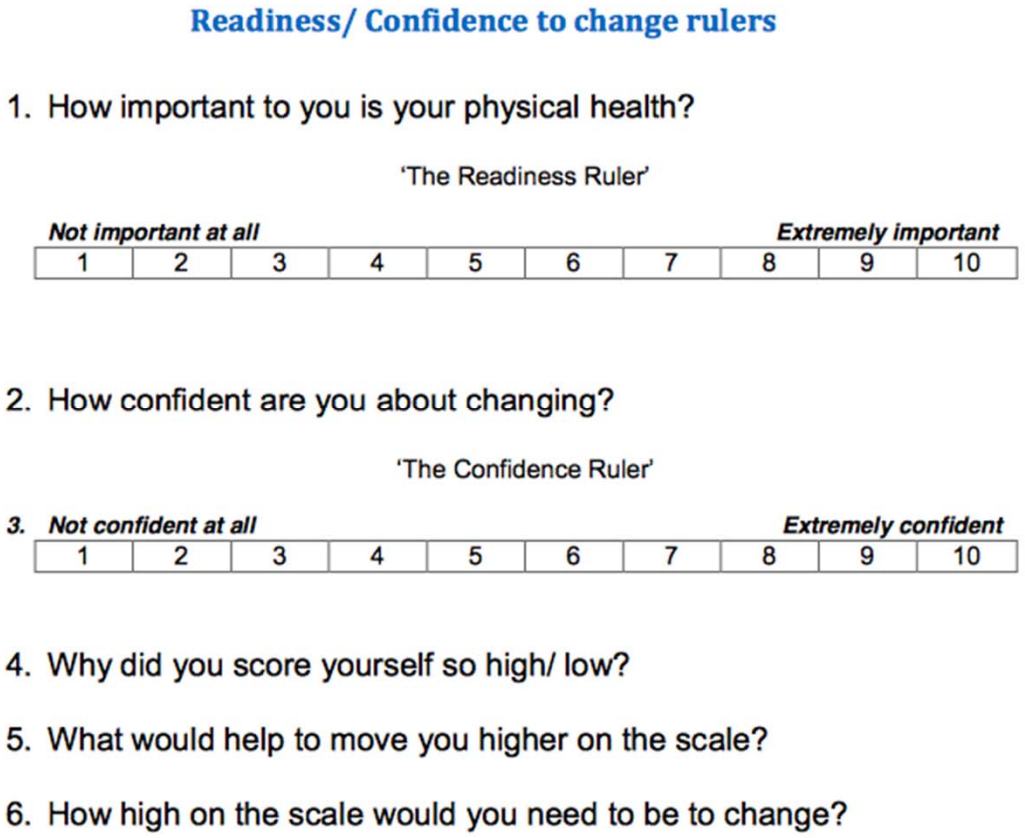
*Dispense two doses
† Atomizer dispensed separately

Other resources related to naloxone procurement:

- Massachusetts Department of Public Health (DPH) Overdose Education and Naloxone Distribution (OEND) https://www.mass.gov/service-details/information-for-community-members-about-how-to-get-naloxone
- AIDS Project Worcester provides free Narcan and Narcan training on a scheduled or walk-in basis through the Joe McKee Care Center. https://www.aidsprojectworcester.org/narcan/
- Evzio Patient Assistance Program: https://evzio.com/patient/in-chronic-pain/kaleo-cares/
    - US citizens without insurance (commercial, state, or federal) and an annual household income <$100,000

Readiness/Confidence to Change

- Provides a framework for allowing the patient to address the motivation to change through importance, readiness, and confidence
- Asks patients to use a 10-point 'ruler' (mostly validated in tobacco and Alcohol behavioral change)
  - – Miller 1991, Rollnick 1997, Boudreaux 2012, Zimmerman 2000
- The patient is asked to score each of these items for the habit being addressed (e.g., heroin use)
- Providers then ask questions about their scoring
  - "Why not lower?" can provide insight into their motivation
  - "Why not higher?" can identify perceived obstacles
- An example ruler follows



Readiness/ Confidence to change rulers

1. How important to you is your physical health?

'The Readiness Ruler'

Not important at all									*Extremely important*
1	2	3	4	5	6	7	8	9	10

2. How confident are you about changing?

'The Confidence Ruler'

3. *Not confident at all* — *Extremely confident*

1	2	3	4	5	6	7	8	9	10

4. Why did you score yourself so high/ low?
5. What would help to move you higher on the scale?
6. How high on the scale would you need to be to change?

Sample Local Substance Use Disorder Treatment Resources in Central MA

Spectrum Health Systems Masshealth and freecare options	Westborough campus Inpatient Detoxification Transitional Support Services (TSS) Residential Program (RP) Women and Children's	508-898-1570
	Outpatient Mental Health Outpatient Substance Abuse Intensive Outpatient Methadone Maintenance Buprenorphine	508-854-3320, ext 1161
Everyday Miracles Peer Recovery Center	25 Pleasant St	508-799-6221
Community Health Link Masshealth and freecare options	Inpatient Detoxification	508-860-1200
	Passages Short Term stabilization (CSS) Transitional stabilization (TSS)	508-860-1142
	Motivating Youth Recovery (MYR) adolescent inpatient detox and stabilization	508-438-5642
	Outpatient mental health Outpatient substance abuse Buprenorphine Homeless Outreach and Advocacy (HOAP)	508-860-1000 508-860-1260
Adcare Inpatient detox private and medicare Outpatient private, Medicare and Masshealth	Inpatient detoxification Intensive outpatient Outpatient Buprenorphine	1-800-ALCOHOL 1-800-252-6465
MA state buprenorphine hotline		617-414-6926
MA state treatment finder	www.helpline-online.com	800-327-5050
UMASS Department of Psychiatry	Mental Health Buprenorphine	508-334-5393
AA	www.AAWorcester.org	508-752-9000
NA	www.centralmassna.org	866-624-3578
Experience Wellness Worcester	Buprenorphine	508-890-0990
Dr. Fajana, Main St. Worcester	Buprenorphine	508-753-4151
Clean Slate, Worcester	Buprenorphine/naltrexone	877-218-2340

Screening, Brief Intervention, Referral to Treatment (SBIRT)

Consists of

- Screening: assess the level of use, reasons for use, and other important factors
- Brief intervention: engage the patient in conversation, consider using ‘ruler’ to assess interest/willingness to change
- Referral to Treatment: based on availability and the patient’s specific needs, interest, insurance.

MOUD Buprenorphine - Emergency Department Initiation (case 105)

Gerardo Gonzalez MD, Jill Terrien PhD ANP-BC, Kavita Babu MD and Melissa Fischer MD MEd

Case Overview

This case engages a patient rescued from heroin overdose with naloxone and brought by ambulance to the ED. The patient is concerned about the heroin relapse and interested in taking medication for opioid use disorder (MOUD, also sometimes called medication for addiction treatment MAT).

Patients with opioid use disorder may benefit from MOUD) with buprenorphine-naloxone (Buprenorphine is the active component). Buprenorphine is a partial opioid agonist with high affinity and slow dissociation from the mu-opioid receptor (MOR). As a partial high-affinity MOR agonist it displaces almost all other opioids. Slow dissociation from the MOR leads to activation reducing opioid withdrawal symptoms, and blocking the MOR from other opioids for ~24 hrs.

Buprenorphine 4-8mg SL occupies about 50% of the MOR and effectively reduces opioid withdrawal symptoms. Higher doses of Buprenorphine of 12-16mg SL daily occupy >70% of the MOR and decrease craving and drug seeking behavior. Occupancy and slow dissociation from the MOR allow safe once daily dosing (increase compliance, reduces relapse [1-3].)

Buprenorphine must be started on patients presenting with mild opioid withdrawal symptoms to avoid worsening withdrawal. Patients should report last use of heroin between 6-12 hrs, opioid analgesics between 12-24 hrs, and methadone between 24-36 hrs. This doesn't apply to the immediate post-overdose period where naloxone was administered as naloxone precipitates opioid withdrawal by rapidly displacing the opioid that caused the overdose.

Buprenorphine (film or tablet) should be placed under the tongue where it dissolves and absorbs. The patient should be instructed to keep their mouth closed and not talk to facilitate absorption and should not eat or drink during and up to 30 minutes after the doses to avoid swallowing, rather than absorbing the medication. Administer the first dose of 2-4 mg SL while in mild opioid withdrawal. A second dose after at least 30 minutes, should be given if there is improvement of the opioid withdrawal. If there is worsening or precipitated withdrawal, then the second dose should be withheld and management of symptoms with clonidine may be used.

Offering MOUD with buprenorphine to patients in the ED who are interested and eligible is expected to increase access to evidence-based treatment for opioid use disorder and reduce the risk of relapse. It is also expected that early engagement in treatment after the naloxone-rescue will facilitate placement in community treatment programs or a Bridging Clinic. The latter offer rapid and open access OUD treatment as a bridge to community programs.

Model for Induction onto Buprenorphine in ED

1. **Patient education about MOUD and assurance of follow-up care (key points and sample language)**
   - Opioid use disorder is a chronic disease with risk of repeated relapses. There are three medications that are approved as Medication for Opioid Use Disorder (MOUD) that include Methadone, Buprenorphine and Naltrexone.
   - Buprenorphine is the medication started in the emergency department because of how it works and its safety profile. We have a program in the ED that in addition to starting the medication we have a team (Bridging service and clinic) that can help you after you leave the ED to get stable in the community program near you.
   - Buprenorphine would reduce your opioid withdrawal symptoms now and decrease craving for opioids and help you achieve complete abstinence from opioid use during the following days.
   - The risk of starting Buprenorphine after this recent overdose and naloxone rescue is worsening opioid withdrawal symptoms or precipitated withdrawal. We will be careful to prevent this from happening.

- We will administer the first 2 doses here in the ED, and you would be involved with the Bridging Service that would help you continue treatment in a community program, or help you get to our Bridging Clinic. In any case, once you start treatment here in the ED our team will be responsible to help you continue with the medication until we help you engage in another community program.
- We will provide you with a prescription for 3 days of buprenorphine so you have enough medication to present to the bridging clinic to continue in the treatment program until you enter a community program. You do not need to return to the ED as our Bridging Service will keep in touch to address your needs.

2. **Buprenorphine Induction - Review of COWS**
   - Your opioid withdrawal symptoms have been measured by the Clinical Opioid Withdrawal Scale already you are in mild opioid withdrawal (COWS >8) and your last dose of naloxone was more than 1 hour ago.
   - I am giving you Buprenorphine-naloxone 2mg now given that you are in opioid withdrawal and you should start feeling better in about 15-30 minutes. If you feel better after this first dose (2mg) with your COWS score improving (COWS <8) or unchanged from the baseline, then we will give you the second dose of 2 or 4 mg. If your opioid withdrawal symptoms worsen we will hold the second dose. This is a very rare complication.
   - If after the 1st dose we precipitate opioid withdrawal symptoms we will treat you with comfort medications and wait longer before we try another dose. We may have to send you home with instructions and our Bridging Service will call you to follow-up on how you are doing and make sure you are comfortable to present to the bridging clinic to be treated.
   - The dose will most likely be increased to Buprenorphine 8mg/1st day, then 12mg/ 2nd day and then 16mg/ 3rd day. You will feel better as the days go by, but on day 5 of treatment your craving and drug seeking behavior is expected to have significantly reduced. Most people do not have side effects with his dose escalation but the Bridging Service at UMass will be available for you along the way. [4,5]

     Instructions during induction
     - Place the film/tablet under your tongue and let is dissolve
     - The medication dissolves and gets absorbed in your mouth. Everything you swallow is lost.
     - Try to keep your mouth closed during this time to keep it moist and facilitate the absorption.
     - It will take about 10-15 minutes to dissolve
     - During this time and up to 30 minutes after the administration do not drink or eat anything as this would remove some of the medication that has not absorbed yet.
     - We need you to wait 30 minutes after this initial dose (2 or 4mg) and you should feel better.
     - If you are feeling better or not worse with the first dose, we will then give you a second dose (2 or 4mg) today before you leave. If you are feeling worse after the first dose, we will not give you the second dose.

3. **Linkage to Outpatient/Bridging Program & prescribing of Naloxone kit**
   - A member of the Bridging Service will meet you to explain the communication and treatment process. If you have questions after you leave, our recovery coach is available and if needed can contact the on-call provider.
   - Please remember to provide an updated phone number to the Bridging Service Team and to make sure you go to the Bridging clinic to continue your treatment plan tomorrow.

SP additional questions

- **I want to go back to NA, will NA approve of this?**

  Most NA groups will not question your treatment with MOUD buprenorphine. Some groups do not consider that you are fully in recovery if you are taking this medication, but the benefits of preventing a relapse and risk of fatal overdose out weights this concern.

- **Isn't this just substituting one drug for another? Won't I get addicted to the buprenorphine?**

  Buprenorphine is a medication that helps stabilize the Mu-receptor in your brain and by doing this, it reduces craving for opioids, reduces drug seeking behavior and facilitates the recovery process. The way buprenorphine acts does not provide a rewarding effect or "high or drug liking', and therefore, it is not associated with cognitive and behavioral changes characteristic of opioid use disorder or Addiction. However, buprenorphine as a partial opioid cannot be stopped abruptly and need to be tapered off slowly to avoid opioid withdrawal symptoms.

- **Will my insurance pay for the medication?**

  Yes, your insurance will cover the use of buprenorphine as medication for opioid use disorders together with other aspects of treatment that are needed to help you achieve abstinence and make lifestyle changes as part of your recovery.

- **How long do I need to remain in MAT with buprenorphine?**

  The current research does not support a specific length of time. Treatment with buprenorphine reduces the risk of relapse while in active treatment, and therefore there are some patients that have remained in treatment for several years. However, if the person wants to discontinue treatment it is usually recommended to wait until everything in their life is stable (i.e. employment, housing, relationship, emotionally) to consider this approach. The risk of relapse unfortunately remains at 50% versus 50% of not relapsing. More research is needed to improve his risk.

References

1. Greenwald M, Johanson CE, Bueller J, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry* 2007;61:101-10.
2. Greenwald MK, Comer SD, Fiellin DA. Buprenorphine maintenance and mu-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. *Drug Alcohol Depend* 2014;144:1-11.
3. Greenwald MK, Johanson CE, Moody DE, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003;28:2000-9.
4. Gonzalez G, Oliveto A, Kosten TR. Combating opiate dependence: a comparison among the available pharmacological options. *Expert Opin Pharmacother* 2004;5:713-25.
5. Romero-Gonzalez M, Shahanaghi A, DiGirolamo GJ, Gonzalez G. Buprenorphine-naloxone treatment responses differ between young adults with heroin and prescription opioid use disorders. *Am J Addict* 2017;26:838-44.

Clinical Opiate Withdrawal Scale

Introduction

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item scale designed to be administered by a clinician. This tool can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time. The summed score for the complete scale can be used to help clinicians determine the stage or severity of opiate withdrawal and assess the level of physical dependence on opioids. Practitioners sometimes express concern about the objectivity of the items in the COWS; however, the symptoms of opioid withdrawal have been likened to a severe influenza infection (e.g., nausea, vomiting, sweating, joint aches, agitation, tremor), and patients should not exceed the lowest score in most categories without exhibiting some observable sign or symptom of withdrawal.

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date and Time ____/____/____:_____

Reason for this assessment:_____

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	**GI Upset**: *over last 1/2 hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face	**Tremor** *observation of outstretched hands* 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 unable to sit still for more than a few seconds	**Yawning** *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute
Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible	**Anxiety or Irritability** 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable or anxious 4 patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort	**Gooseflesh skin** 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing assessment: _____

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

APPENDIX 1
Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: Pat Sheehan Date and Time Initial - Time 0 ___/___/___:_____

Reason for this assessment: Screen for Buprenorphine Induction

Resting Pulse Rate: _____beats/minute
Measured after patient is sitting or lying for one minute
0 pulse rate 80 or below
1 pulse rate 81-100
2 pulse rate 101-120
4 pulse rate greater than 120

GI Upset: *over last 1/2 hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 multiple episodes of diarrhea or vomiting

Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Tremor *observation of outstretched hands*
0 no tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Restlessness *Observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 unable to sit still for more than a few seconds

Yawning *Observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable or anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Gooseflesh skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Runny nose or tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

Total Score 10

The total score is the sum of all 11 items

Initials of person completing assessment: Student

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

This version may be copied and used clinically.

Medication for opioid use disorder (MOUD or MAT)

To date, there is strong evidence to support the use of MAT/MOUD (usually methadone, buprenorphine or naltrexone) in opioid addiction. Yet, there remains a stigma of “replacing one drug with another” and 25% of publicly funded treatment programs offer FDA approved MAT/MOUD.

MAT/MOUD:

- Decreases withdrawal in the early phases of recovery
- Decreases cravings
- Decreases risky activities associated with obtaining medications or drugs
- The POATS study found that approximately 61% of patients taking buprenorphine-naloxone as MAT/MOUD with standard medical management remained abstinent from opioids at 3 ½ years.

Knudsen H, Abraham A, Roman P, “Adoption and Implementation of Medications in Addiction Treatment Programs,” Jrnl Addiction Med 5, no1 (2011):21-7.
Weiss R, Potter J et al, Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. Drug and Alcohol Dependence, March 6, 2015.

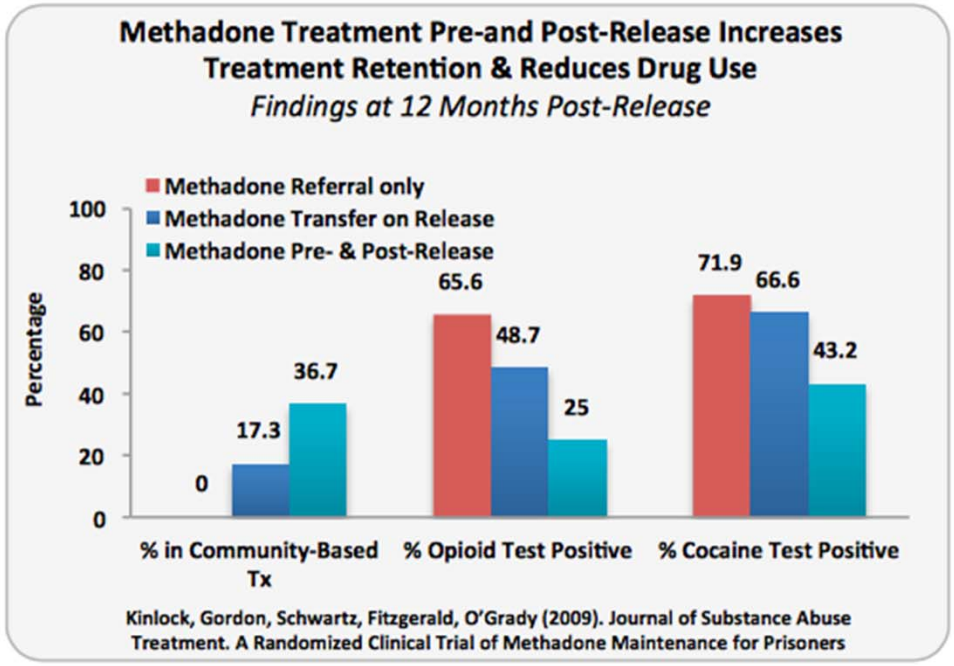
Weiss R, Potter J et al, Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment study. Drug and Alcohol Dependence, March 6, 2015.

MAT

Benefits of Medication-Assisted Treatment – Beyond Reducing Drug Use

Scientific research has established that medication-assisted treatment of opioid addiction increases patient retention and decreases drug use, infectious disease transmission, and criminal activity. For example, studies among criminal offenders, many of whom enter the prison system with drug abuse problems, showed that methadone treatment begun in prison and continued in the community upon release extended the time parolees remained in treatment, reduced further drug use, and produced a three-fold reduction in criminal activity.

Investment in medication-assisted treatment of opioid addiction also makes good economic sense. For methadone, every dollar invested in treatment generates an estimated $4–5 return.



https://www.drugabuse.gov/sites/default/files/tib_mat_opioid.pdf

Drug and Alcohol Dependence 105 (2009) 154–159

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument

D. Andrew Tompkins[a,*], George E. Bigelow[a], Joseph A. Harrison[a], Rolley E. Johnson[a,b], Paul J. Fudala[b], Eric C. Strain[a]

[a] Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA
[b] Reckitt Benckiser Pharmaceuticals Inc., Richmond, VA 23235, USA

ARTICLE INFO

Article history:
Received 10 April 2009
Received in revised form 25 June 2009
Accepted 1 July 2009
Available online 3 August 2009

Keywords:
Opioid withdrawal
Opioid dependence
Clinical Opiate Withdrawal Scale
Clinical Institute Narcotic Assessment
Naloxone
Precipitated withdrawal

ABSTRACT

Introduction: The Clinical Opiate Withdrawal Scale (COWS) is an 11-item clinician-administered scale assessing opioid withdrawal. Though commonly used in clinical practice, it has not been systematically validated. The present study validated the COWS in comparison to the validated Clinical Institute Narcotic Assessment (CINA) scale.
Method: Opioid-dependent volunteers were enrolled in a residential trial and stabilized on morphine 30 mg given subcutaneously four times daily. Subjects then underwent double-blind, randomized challenges of intramuscularly administered placebo and naloxone (0.4 mg) on separate days, during which the COWS, CINA, and visual analog scale (VAS) assessments were concurrently obtained. Subjects completing both challenges were included ($N = 46$). Correlations between mean peak COWS and CINA scores as well as self-report VAS questions were calculated.
Results: Mean peak COWS and CINA scores of 7.6 and 24.4, respectively, occurred on average 30 min post-injection of naloxone. Mean COWS and CINA scores 30 min after placebo injection were 1.3 and 18.9, respectively. The Pearson's correlation coefficient for peak COWS and CINA scores during the naloxone challenge session was 0.85 ($p < 0.001$). Peak COWS scores also correlated well with peak VAS self-report scores of bad drug effect ($r = 0.57$, $p < 0.001$) and feeling sick ($r = 0.57$, $p < 0.001$), providing additional evidence of concurrent validity. Placebo was not associated with any significant elevation of COWS, CINA, or VAS scores, indicating discriminant validity. Cronbach's alpha for the COWS was 0.78, indicating good internal consistency (reliability).
Discussion: COWS, CINA, and certain VAS items are all valid measurement tools for acute opiate withdrawal.

1. Introduction

The opiate withdrawal syndrome, a constellation of characteristic signs and symptoms, has been called "one of the most stereotyped syndromes in clinical medicine" (Isbell, 1950). The first instrument to quantitatively measure withdrawal was developed by Kolb and Himmelsbach in the mid-1930s (Kolb and Himmelsbach, 1938). That scale was based on clinical observations and was weighted heavily towards physical signs of withdrawal, such as systolic blood pressure changes, mydriasis, fever, and respiratory rate changes. In the 1960s, the Opiate Withdrawal Experience Scale, a subset of self-report questions from the Addiction Research Center Inventory (ARCI), was used to quantify the subjective symptoms of withdrawal (Haertzen and Meketon, 1968). However, this scale was time consuming for subjects to complete, even with the derived short form Opiate Withdrawal Questionnaire (Haertzen et al., 1970).

Following development of those initial instruments, multiple other subjective and objective scales have been developed and used (Handelsman et al., 1987; Judson et al., 1980; Wang et al., 1974; Bradley et al., 1987; Gossop, 1990). Methods for using these scales have sought to improve on sensitivity and specificity for detecting withdrawal by controlling the level of physical dependence, the time point within the withdrawal syndrome when the assessment is made, and the possibility of feigned responses. In 1988, Peachey and Lei reported on the reliability and validity of the Clinical Institute Narcotic Assessment (CINA), one of the first scales to include both opiate withdrawal signs and symptoms (Peachey and

* Corresponding author. Tel.: +1 410 550 5953; fax: +1 410 550 0030.
E-mail address: dtompki1@jhmi.edu (D.A. Tompkins).

0376-8716/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2009.07.001

Lei, 1988). This scale was validated using a naloxone challenge in heroin-dependent subjects and the peak score was found to predict the clinically determined maintenance methadone dose used to treat these patients. However, the CINA required nursing support to measure heart rate and blood pressure and contained items which could be easily feigned. As well, there was no fixed upper limit to the scale given the variable contribution of blood pressure and pulse ratings.

Wesson and colleagues, therefore, developed the Clinical Opiate Withdrawal Scale (COWS). This scale was designed to be administered quickly, was intended to improve upon existing measurement tools, and was first published in a training manual for buprenorphine treatment (Wesson et al., 1999). The COWS consisted of an 11-item rating system that could be completed within 2 min by a trained observer and could track opioid withdrawal as differentiated from opioid toxicity through serial measurements. Total scores ranged from 0 to 47, and withdrawal was classified as mild (5–12), moderate (13–24), moderately severe (25–36), or severe (>36). These category scores were not derived using standard statistical techniques but were based upon the authors' clinical expertise (Wesson and Ling, 2003). Because of its clinical utility, its association with buprenorphine maintenance, and ease of application, the COWS has become widely used for assessing opiate withdrawal (Center for Substance Abuse Treatment, 2004). Although the scale was modeled after items on previously validated scales, the COWS itself has never been systematically validated (Wesson and Ling, 2003). The present project assessed the validity of the COWS in comparison to a previously validated instrument, the CINA, using a double-blind, placebo-controlled naloxone challenge in opioid-dependent individuals. As well, comparisons between the COWS, CINA, and single-item subjective ratings (Visual Analogue Scales) were done to examine the validity and possible utility of using one overall item to assess opioid withdrawal.

2. Methods

2.1. Participants

Forty-six out-of-treatment opioid-dependent volunteers participated while residing on a supervised research unit at the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU). Participants were recruited for a clinical trial that will be reported on separately; the trial was registered at www.clinicaltrials.gov, identifier NCT00637000. The analyses in this paper were done as part of the confirmation of opioid physical dependence required for the subsequent opioid clinical pharmacology study. In order to be enrolled, participants had to meet DSM-IV-TR (American Psychiatric Association, 2000) criteria for opioid dependence and be between the ages of 18 and 65, willing to stay on the residential research unit for up to 12 days in order to complete the full clinical trial, and on adequate birth control (if female). Exclusionary factors were clinically significant medical or psychiatric diagnoses (i.e. schizophrenia or active suicidal ideation); engaged in opioid agonist, partial agonist or antagonist treatment immediately prior to admission; pregnant or lactating; physically dependent on alcohol or sedative hypnotics; and poor oral health (i.e. active aphthous stomatitis, active oral herpes, tongue or mouth piercing, or requiring immediate dental attention). This last condition was included because the main clinical trial involved sublingual drug administration.

The Johns Hopkins Institutional Review Board approved this study and all participants provided written, informed consent. Subjects in the present analysis were primarily male (74%), Caucasian (61%) and had a mean age of 41.7 years. The primary opioid abused by subjects was either heroin (mean use 6 years, SD 9.5) or prescription opioids (mean use 4.7 years, SD 4) prior to study entry, and all subjects had been using opioids daily (96%) or near daily (at least 16 days; 4%) in the 30 days before study entry. Forty-nine subjects initially enrolled; the present report includes the 46 who completed both the placebo and naloxone challenges. Two volunteers withdrew for non-study-related personal reasons after one challenge session, and one participant withdrew after experiencing a panic attack during the naloxone challenge session. Additionally, two participants had their naloxone sessions stopped after 30 min for excessive withdrawal symptoms.

2.2. Morphine stabilization phase and description of challenge sessions

Participants were screened on an outpatient basis and then admitted to the research unit where they were stabilized on 30 mg of subcutaneously administered morphine given four times daily (120 mg/day) for 2–8 days prior to the challenge sessions (mean 4.4 days, SD 1.3). After stabilization, participants received intramuscularly administered injections of placebo and 0.4 mg naloxone in a randomized, double-blind fashion in two sessions separated by at least 24 h. Withdrawal assessments and drug effect rating scales, vital signs, and pupil measurements were collected every 15 min, starting 30 min pre- and through 150 min post-injection, except for the time of drug administration (time 0). Trained research assistants, who were present during the entire session, collected the data and administered the scales.

Table 1
Comparison of COWS and CINA item content and scoring.

Sign or symptom	Subjective vs. objective[a]	Possible scores	
		COWS[b]	CINA[b]
Anxiety or irritability	S	0–2, 4	–
Temperature changes	S	–	0–2
GI upset, including abdominal pain[c]	S/O	0–3, 5	0, 2, 4, 6[c]
			0–2[c]
Restlessness	S/O	0, 1, 3, 5	0–3
Bone or joint aches	S/O	0–2, 4	0–2
Sweating	S/O	0–4	0–3
Runny nose or tearing[c]	O	0–2, 4	0–2[c]
			0–2[c]
Tremor	O	0–2, 4	0–3
Gooseflesh	O	0, 3, 5	0–3
Yawning	O	0–2, 4	0–2
Pupil size	O	0–2, 5	–
Pulse rate	O	0–2, 4	Pulse/10
Systolic blood pressure (SBP)	O	–	SBP/10
Maximum possible score		48	30 + pulse/10 and SBP/10

[a] Indicates whether item is a subjective symptom (S) or an objective sign (O). Those listed as (S/O) indicate that an item score includes assessment of both signs and symptoms, with lower scores for subjective symptom report and higher scores for objective signs.

[b] Entries are possible scores on each item for each instrument. If no score is shown, the scale does not include that item.

[c] The CINA contains two separate scores for these items, whereas the COWS has only one.

2.3. Measurements

Withdrawal measurements consisted of the CINA, COWS, and VAS self-report items.

2.3.1. CINA and COWS

The item content and scoring of the CINA and COWS are summarized in Table 1. There is substantial overlap in content, but each scale also includes items absent from the other. The CINA consists of 13 items – 1 purely subjective symptom item, 7 purely objective sign items, and 5 items that included subjective and objective components. The COWS consists of 11 items – 1 purely subjective symptom item, 6 objective sign items, and 4 items that included subjective and objective components. Item scoring options were specified differently for the two scales, but each scale summed the scores of its items to produce a total score. The COWS provided instructions for categorical ratings of pupil size and pulse, including an option for a zero score. On the CINA, the heart rate and blood pressure items ensured a minimum score of approximately 20 even in the absence of any withdrawal.

2.3.2. VAS

Visual analog scales (VASs) were single-item questions that assess subjective drug effects at the time of scale completion (Preston et al., 1988). Ratings were completed on a computer; using a mouse, the subject positioned an arrow along a 100-point line marked at either end with "none" and "extremely." VAS items in the present study were: "Do you feel any DRUG EFFECT?", "Does the drug have any GOOD EFFECTS?", "Does the drug have any BAD EFFECTS?", "How HIGH are you?", "Does this drug make you feel SICK?", and "Do you LIKE the drug?"

2.3.3. Pupil diameter

Pupil diameter was assessed with a digital pupillometer (Neuroptics, Inc.) in constant room lighting. The measurements provided by the pupillometer were also used for the pupil score in the COWS, which required observers to categorize the pupil diameter (Table 1).

2.4. Statistical analysis

Mean scores and standard deviations were calculated for each time point in the naloxone challenge sessions using SAS™ software, Ver. 9.1 (SAS Institute, 2003).

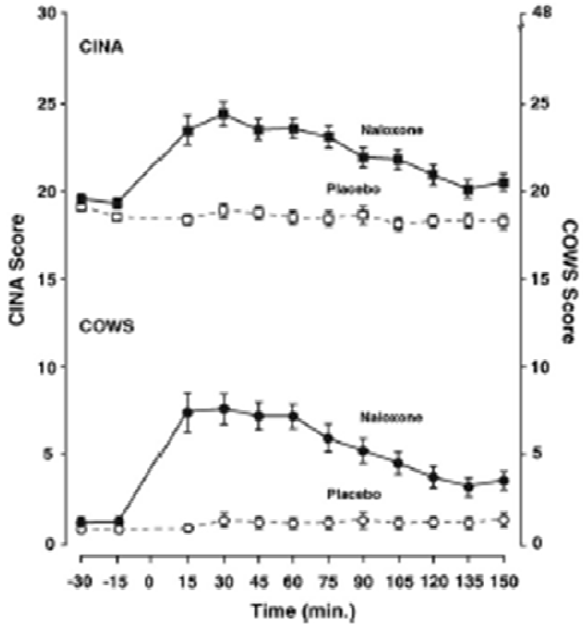


Fig. 1. Mean COWS and CINA scores (±SEM) vs. time. The Clinical Opiate Withdrawal Scale (COWS) and Clinical Institute Narcotic Assessment (CINA) had peak scores in subjects on average 30 min post-naloxone injection (±SEM). The two scales show a similar time course for withdrawal signs and symptoms.

Repeated measures regressions were used to assess significant differences on the separate opioid withdrawal measurements, using drug (naloxone vs. placebo), time, and drug-by-time interaction terms. All the rest of the statistical calculations used SPSS 16.0 (SPSS Inc., Chicago, IL). Concurrent validity was assessed using Pearson's correlation coefficients calculated between peak CINA, COWS, VAS items, and pupil diameter during the naloxone challenge session. Correlations of time to peak on the different measures were similarly calculated. Internal consistency reliability of the 11 COWS items was assessed with Cronbach's alpha statistic. Lastly, inter-item correlation matrices were created to describe the association of individual COWS and CINA items to each other and to the total scale score.

3. Results

3.1. CINA vs. COWS

Overall, the COWS and CINA scales were very similar in terms of both the magnitude and time course of their withdrawal score changes in the naloxone challenge session, demonstrating the concurrent validity of the COWS. Fig. 1 shows the mean scores and standard errors (SEM) of the COWS and CINA graphed vs. time. The mean peak COWS (7.6) and CINA (24.4) scores occurred on average at 30 min post-injection, which is within the expected time range of peak withdrawal following intramuscular naloxone (Daftery, 1974; Wang et al., 1974; Judson et al., 1980). Additionally, time to peak (TTP) analysis revealed positive correlation between COWS TTP and CINA TTP ($r = 0.66$, $p < 0.0001$). Repeated measure regression analysis revealed statistically significant effects on COWS for drug (naloxone vs. placebo) ($F = 79.3$, df = 45, $p < 0.0001$), time ($F = 15.03$, df = 495, $p < 0.0001$), and drug-by-time interaction ($F = 13.82$, df = 476, $p < 0.0001$). There were also significant effects for the above three analyses on the CINA ($F = 77.4$, df = 45, $p < 0.0001$), ($F = 10.35$, df = 495, $p < 0.0001$), and ($F = 10.94$, df = 477, $p < 0.0001$), respectively. Table 2 shows a strong positive correlation between peak COWS and CINA scores ($r = 0.85$, $p < 0.001$) during the naloxone challenge session.

Table 2 also shows the effect of omitting various physiological measurement items from the CINA and COWS. For the COWS, removing the pupil diameter item (COWS noPUP), heart rate item (COWS noHR), and both of these measures (COWS noPHYS) still leave these modified COWS scores highly correlated with the CINA, indicating that these items may not be needed to detect this level of opioid withdrawal with the COWS. The score on the COWS heart rate item is 0 (<80), 1 (81–100), 2 (101–120), or 4 (>120). In this sample, subjects had little change in heart rate during the naloxone session (peak 7.5 bpm change from baseline); therefore, this item rarely affected the total COWS score which may explain high similarity in correlation coefficients between COWS vs. CINA and COWS without the heart rate vs. CINA. Similarly, correlations between the CINA without heart rate item (CINA noHR), systolic blood pressure score (CINA noBP), or both of these measurements (CINA noPHYS) were highly correlated with the CINA total score, as well as the COWS total score and the various modified versions of the COWS.

3.2. CINA and COWS vs. VAS

Two VAS items, bad effects and sick, showed a similar time course but greater variability in mean score than the CINA (Fig. 2). VAS mean peak scores for bad effects and sick occurred on average somewhat later than the CINA peak, with the peak score occurring at 60 min for bad effects (score = 33.2) and 45 min for sick (score = 28.1). The VAS time course of a rapid increase in scores after injection and then a gradual decline over 2.5 h was very similar to the time course seen with the CINA and COWS (Fig. 1). Results from repeated measures regression revealed statistically significant effects for drug condition, time, and drug-by-time interaction on these two VAS items ($p < 0.0001$ in all cases). Correlation analysis showed moderately good association between peak CINA and bad effects ($r = 0.63$, $p < 0.001$) as well as sick ($r = 0.65$, $p < 0.001$)

Table 2
Correlation matrix for select opiate withdrawal assessment tools.

	COWS	COWS noPUP	COWS noHR	COWS noPHYS	CINA	CINA noHR	CINA noBP	CINA noPHYS	Bad effects	Sick
COWS	1	***	***	***	***	***	***	***	***	***
COWS noPUP	0.98	1	***	***	***	***	***	***	***	***
COWS noHR	1	0.98	1	***	***	***	***	***	***	***
COWS noPHYS	0.98	1	0.98	1	***	***	***	***	***	***
CINA	0.85	0.84	0.84	0.82	1	***	***	***	***	***
CINA noHR	0.85	0.85	0.84	0.84	0.98	1	***	***	***	***
CINA noBP	0.88	0.88	0.87	0.86	0.96	0.92	1	***	***	***
CINA noPHYS	0.89	0.90	0.89	0.89	0.93	0.94	0.98	1	***	***
Bad effects	0.57	0.57	0.56	0.56	0.63	0.59	0.64	0.62	1	***
Sick	0.57	0.59	0.56	0.58	0.65	0.64	0.64	0.64	0.88	1

COWS = Clinical Opiate Withdrawal Scale. COWSnoPUP = COWS with pupil diameter categorization score removed. COWSnoHR = COWS with heart rate categorization score removed. COWSnoPHYS = COWS with both pupil diameter and heart rate scores removed. CINA = Clinical Institute Narcotic Assessment. CINAnoHR = CINA with the heart rate score removed. CINAnoBP = CINA with the systolic blood pressure score removed. CINAnoPHYS = CINA with both heart rate and blood pressure scores removed. This matrix shows a strong correlation between COWS and CINA and suggests that certain objective measurements of withdrawal, i.e. heart rate, blood pressure, and pupil size, could be omitted without losing the ability to detect opiate withdrawal. All values are significant at $p < 0.001$.

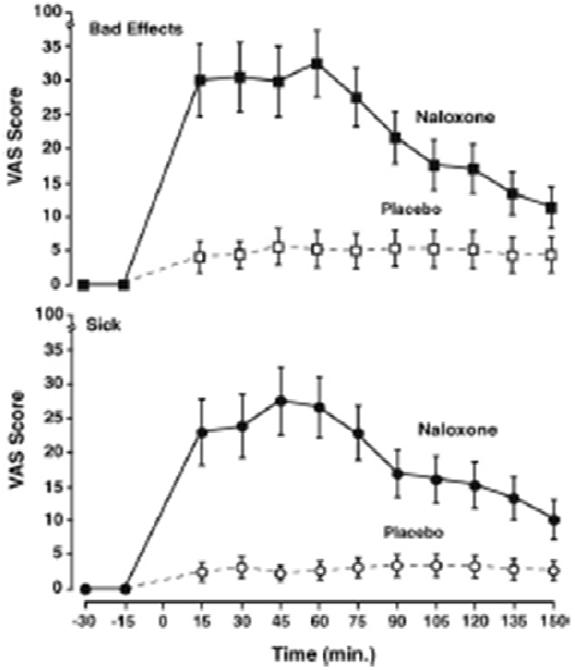


Fig. 2. Mean bad effects and sick effects VAS items (±SEM) vs. time. These graphs show the average (±SEM) time course of subjective response on two Visual Analogue Scale (VAS) questions: (upper panel) "Does the drug have any BAD EFFECTS?" and (lower panel) "Does this drug make you feel SICK?" The over all time courses for both VAS items follow a similar course as the COWS and CINA mean scores seen in Fig. 1.

(Table 2). Correlations between peak VAS and COWS were slightly lower; however, there was a strong correlation between the two VAS items ($r = 0.88$, $p < 0.001$). Lastly, no significant correlations were seen between peak CINA or COWS scores and VAS ratings for good effects, drug liking, or high.

3.3. CINA and COWS vs. quantitative pupil measurements

The time course of pupil diameter change showed a mean peak increase (1.03 mm) that occurred 15 min after naloxone injection, followed by gradual return to baseline. Pupil diameter showed <0.27 mm change from baseline in the placebo session. Repeated measures regression using drug condition, time, and drug-by-time showed significance ($p < 0.001$) in each analysis. Maximum pupil diameter and peak CINA and COWS scores showed a modest correlation ($r = 0.39$, $p = 0.01$ and $r = 0.36$, $p = 0.01$). There was no significant correlation between maximum pupil diameter and bad effects or Sick VAS.

3.4. Internal consistency and inter-item correlations

Analysis of the internal consistency for the eleven COWS items revealed an overall Cronbach's alpha of 0.78, indicating good reliability. As well, there was surprisingly little inter-item correlation between individual COWS items (Table 3). Only combinations of restlessness and anxiety/irritability (0.67) as well as runny nose/tearing and yawning (0.54) were significantly correlated. A similar inter-item correlation matrix for the CINA revealed that the objective physiological measurements did not correlate well with the total CINA score, and similar items showed significant inter-item correlations as with the COWS (Table 4). Finally, the VAS items correlated with the total COWS and CINA scores about as well as did the individual items constituting the scales (Table 2).

3.5. Analysts of atypical subjects

Seven individuals did not differentiate between the effects of placebo vs. naloxone based upon VAS scores of bad effects. Of these individuals, four had opioid withdrawal (COWS scores ≥5) with both placebo and naloxone; two had no withdrawal in either session (COWS <5); and one person had mild withdrawal (COWS score of 6 two hours after injection) with naloxone only. There were no significant differences in demographic or history characteristics that explained those who did or did not differentiate naloxone from placebo. When these individuals were removed, no significant changes occurred in correlation, repeated measures regression, or time to peak analyses.

4. Discussion

The accurate and rapid assessment of opioid withdrawal is important in the clinical management of opioid-dependent patients in both inpatient and outpatient settings. As well, U.S. guidelines for opioid treatment require clinical evidence of dependence in patients, which may include the presence of withdrawal (SAMHSA, 2001). Likewise, office-based outpatient treatment requires a medical professional to assess opioid withdrawal when initiating treatment with buprenorphine or buprenorphine/naloxone (Center for Substance Abuse Treatment, 2004). The present analyses provide validation of a short, easy-to-use scale for withdrawal (COWS) as well as quantification of the relationship of that scale to the CINA and single-item VAS indices of withdrawal. Our results demonstrate that the COWS correlates well with the previously validated

Table 3
Inter-item correlations amongst COWS items.

Item	1	2	3	4	5	6	7	8	9	10	11	12
1. Pulse	1.00	****	***	****	****	***	***	****	***	****	***	****
2. GI upset	0.05*	1.00	***	****	****	***	***	****	***	****	***	****
3. Sweating	0.06*	0.27	1.00	****	****	***	***	****	***	****	***	****
4. Tremor	0.11	0.14	0.10	1.00	****	***	***	****	***	****	***	****
5. Restlessness	−0.03*	0.33	0.35	0.13	1.00	***	***	****	***	****	***	****
6. Yawning	0.09*	0.28	0.34	0.16	0.40	1.00	***	****	***	****	***	****
7. Pupil size	0.27	0.10	0.19	0.10	0.15	0.33	1.00	****	***	****	***	****
8. Anxiety/irritability	0.06*	0.42	0.31	0.14	**0.67**	0.40	0.17	1.00	***	****	***	****
9. Bone/joint aches	0.10	0.22	0.18	0.11	0.18	0.08*	0.09*	0.33	1.00	****	***	****
10. Gooseflesh	0.12	0.29	0.40	0.01*	0.33	0.47	0.24	0.46	0.17	1.00	***	****
11. Runny nose/tearing	0.12	0.28	0.24	0.10	0.41	**0.54**	0.32	0.47	0.23	0.39	1.00	****
12. Total COWS score	0.24	**0.52**	**0.55**	0.26	**0.66**	**0.75**	**0.53**	**0.72**	0.35	**0.69**	**0.69**	1.00

Both the COWS and CINA inter-item correlation matrices were based on 534 observations from the 46 subjects over the entire naloxone challenge session. The overall pattern of correlations did not change appreciably when based on just the $N = 46$ individual observations at peak opioid withdrawal.

* $p \geq 0.05$. All others $p < 0.05$. Bolded items indicate strong correlation ($r \geq 0.5$).

Table 4
Inter-item correlations amongst CINA items.

Item	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Abdominal changes	1.00													
2. Temperature changes	0.27	1.00												
3. Nausea/vomiting	0.35	0.33	1.00											
4. Muscle aches	0.19	0.21	0.22	1.00										
5. Gooseflesh	0.19	0.49	0.24	0.16	1.00									
6. Nasal congestion	0.18	0.36	0.17	0.14	0.36	1.00								
7. Restlessness	0.05*	0.28	0.28	0.14	0.35	0.26	1.00							
8. Tremor	0.10	0.11	0.13	0.11	0.10	−0.03*	0.07*	1.00						
9. Lacrimation	0.14	0.40	0.25	0.21	**0.50**	**0.60**	0.36	0.08*	1.00					
10. Sweating	0.19	0.31	0.24	0.15	0.29	0.21	0.20	0.11	0.22	1.00				
11. Yawning	0.13	0.41	0.23	0.15	0.45	**0.54**	0.31	0.08*	**0.65**	0.23	1.00			
12. HR/10	0.11	0.19	0.01*	0.09	0.20	0.20	−0.04*	0.10	0.15	0.01*	0.19	1.00		
13. SBP/10	0.09	0.07*	−0.02*	−0.11	0.05*	−0.07*	0.04*	0.11	0.10	0.05*	0.03*	−0.13	1.00	
14. CINA Total	0.43	**0.64**	**0.52**	0.35	**0.63**	**0.55**	0.49	0.28	**0.68**	0.43	**0.64**	0.37	0.35	1.00

The items with highest correlation with total CINA score are temperature changes, gooseflesh, lacrimation, and yawning, as compared to restlessness, tremor, lacrimation, and nausea/vomiting in the original CINA validation study (Peachey and Lei, 1988).

* $p \geq 0.05$. All others are $p < 0.05$. Bolded items indicate strong correlation ($r \geq 0.5$).

CINA scale in the context of a standardized naloxone challenge in opioid-dependent persons. The time course of withdrawal as measured by the COWS was congruent with the pharmacologic properties of naloxone. Finally, the overlap in content of the two scales (Table 1) supports the content validity and face validity of the COWS.

Internal consistency of the COWS was high, demonstrating the scale was reliable in measuring the construct of opioid withdrawal. Inter-item correlations indicated little item overlap, providing evidence of content validity (measuring a broad range of symptoms). There was a high degree of consistency across opioid withdrawal measures in terms of identifying and tracking the syndrome over time, demonstrating concurrent validity of these measures. The time course for COWS and CINA were remarkably consistent. The similarity to CINA time course was somewhat less for the two VAS items, but the overall trend of both measures was the same. As well, the variance in the mean scores was relatively minor, except for VAS, which as single items with a larger scale range would be expected to have greater variance. This larger variance of the single-item VAS scores was probably also related to subjects' understanding of the items, personality effects on expressing discomfort, or possibly demographic and history characteristics. Nevertheless, these single-item questions may have utility in following the progress of withdrawal distress and guiding its medical management. Given the strong correlation between CINA and COWS seen in Table 3, both scales are well suited for assessing and tracking opioid withdrawal. Modifying these scales to omit objective physiological indices may not affect each scale's utility in the discrimination of the level of opioid withdrawal or guiding its medical treatment. Therefore, non-medical staff could aid in the assessment of withdrawal, and time of medical staff could be freed up for other needs. However, the physiological measures do provide objective indices to supplement the otherwise subjective responses and could thereby assist the clinician in determining false positive withdrawal responses. The choice of assessment instrument should be determined by site-specific needs, including the probability of feigned responses and the desire for objective indices.

This study has several limitations. First, relatively mild opioid withdrawal was produced, most likely due to the combination of a low naloxone dose (0.4 mg) and a modest level of morphine physical dependence (120 mg/day). However, the recognition of more severe forms of opioid withdrawal is less ambiguous for most clinicians, and the more critical need is to have scales that are sensitive enough to distinguish mild but clinically significant withdrawal. The most useful aspect of an opioid withdrawal scale is in differentiating the presence vs. absence of withdrawal, which the COWS does. The original COWS authors (Wesson and Ling, 2003) had specifically recommended that a validation be done for the low-end of the scale, which this study accomplished. Second, we did not assess external reliability of these measurements; we did not have multiple raters of the same sessions to include inter-rater reliability and did not perform multiple naloxone challenges to calculate test–retest reliability. This could be done in the future. Third, the modest correlation of COWS and CINA with pupil diameter is puzzling, given that mydriasis is a classic sign in opioid withdrawal (Himmelsbach, 1941). However, the measurement tool in this study may have affected this measure. The digital pupillometer decreased the ambient light reaching the eye by surrounding the eye before determining the pupil diameter; the intensity of lighting influences pupillary response to opioids (Weinhold and Bigelow, 1993). Fourth, this study included seven individuals who failed to distinguish placebo from naloxone. This did not change the overall results significantly but it does highlight two important points: prior literature has shown placebo can precipitate mild withdrawal in heroin-dependent individuals (Kanof et al., 1991) and not all opioid-dependent individuals respond to a naloxone challenge with signs or symptoms of withdrawal (Blachly, 1973; Wang et al., 1982). Finally, while these data document the sensitivity of these indices to opioid withdrawal, they do not address their specificity i.e. the extent to which they may be affected by factors other than opioid withdrawal.

Even with these limitations, the validation of the COWS and correlations with the other opioid withdrawal measurement tools provide useful information for future clinical evaluation of this syndrome. The COWS and CINA followed comparable trajectories for the time course of opioid withdrawal. The VAS bad effects and Sick single-item assessments followed a parallel time course for withdrawal, suggesting these easily administered scales might be useful in certain settings for identifying and following opioid withdrawal. Clinicians who are not worried about feigned responses might simply use these questions to screen quickly for withdrawal and treat where appropriate. In other settings, the COWS or CINA could be used for the identification of withdrawal (with or without objective sign measurement) and for monitoring response to treatment interventions. Having easy and reliable quantification has distinct advantages when following withdrawal and setting up treatment protocols based upon these findings.

In summary, this study shows that the COWS is a valid instrument with sufficient sensitivity to detect mild opiate withdrawal. It would therefore be expected to detect moderate to severe withdrawal. The COWS, as well as the VAS items reported here, have potential uses in inpatient and outpatient treatment, in detoxification, and in research protocols. Their brevity and ease of use make them good choices for use in all these settings.

Role of funding source

Reckitt Benckiser Pharmaceuticals Inc. provided support and medications for use in this study. As well, this company's representatives assisted in the preparation of the protocol and review of the manuscript. NIDA also provided funding but had no other role. Grants were R01 DA08045, K24 DA023186, and T32 DA07209.

Contributors

All authors have contributed to and approved the final manuscript. Dr. Tompkins wrote the first draft of the manuscript, contributed to interpreting data analysis and assisted in editing. Dr. Bigelow assisted in protocol development, interpreting data analyses, writing, and editing paper. Mr. Harrison conducted research, assisted in protocol development and manuscript editing. Drs. Johnson and Fudala assisted in protocol design and editing the manuscript. Dr. Strain assisted in protocol design, study execution, supervision, writing, and editing the manuscript.

Conflict of interest

Drs. Tompkins and Bigelow as well as Mr. Harrison have no conflict of interest to report. Drs. Johnson and Fudala are employees of Reckitt Benckiser Pharmaceuticals Inc., which is a maker of buprenorphine and provided the funding and medications for the clinical trial. Dr. Strain also is a paid consultant to Reckitt Benckiser Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Acknowledgements

We appreciate Linda Felch with her help analyzing the data and the many research assistants who ran the study sessions and assisted with data collection. We would especially like to thank Lillian Salinas who helped create the figures and tables.

References

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders, Text Revision, fourth ed. American Psychiatric Association, Washington, DC.

Blachly, P.H., 1973. Naloxone for diagnosis in methadone programs. JAMA 224, 334–335.

Bradley, B.P., Gossop, M., Phillips, G.T., Legarda, J.J., 1987. The development of an opiate withdrawal scale (OWS). Br. J. Addict. 82, 1139–1142.

Center for Substance Abuse Treatment, 2004. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Substance Abuse and Mental Health Services Administration, Rockville, MD.

Daftery, A.V., 1974. Letter: naloxone challenge in propoxyphene dependence. N. Engl. J. Med. 291, 979–980.

Gossop, M., 1990. The development of a short opiate withdrawal scale (SOWS). Addict. Behav. 15, 487–490.

Haertzen, C.A., Meketon, M.J., 1968. Opiate withdrawal as measured by the addiction research center inventory (ARCI). Dis. Nerv. Syst. 29, 450–455.

Haertzen, C.A., Meketon, M.J., Hooks Jr., N.T., 1970. Subjective experiences produced by the withdrawal of opiates. Br. J. Addict. Alcohol Other Drugs 65, 245–255.

Handelsman, L., Cochrane, K.J., Aronson, M.J., Ness, R., Rubinstein, K.J., Kanof, P.D., 1987. Two new rating scales for opiate withdrawal. Am. J. Drug Alcohol Abuse 13, 293–308.

Himmelsbach, C.K., 1941. The morphine abstinence syndrome, its nature and treatment. Ann. Intern. Med. 15, 829–839.

Isbell, H., 1950. Manifestations and treatment of addiction to narcotic drugs and barbiturates. Med. Clin. North Am. 34, 425–438.

Judson, B.A., Himmelberger, D.U., Goldstein, A., 1980. The naloxone test for opiate dependence. Clin. Pharmacol. Ther. 27, 492–501.

Kanof, P.D., Aronson, M.J., Ness, R., Cochrane, K.J., Horvath, T.B., Handelsman, L., 1991. Levels of opioid physical dependence in heroin addicts. Drug Alcohol Depend. 27, 253–262.

Kolb, L., Himmelsbach, C.K., 1938. Clinical studies of drug addiction. III. A critical review of the withdrawal treatments with method of evaluating abstinence syndromes. Am. J. Psychiat. 94, 759–799.

Peachey, J.E., Lei, H., 1988. Assessment of opioid dependence with naloxone. Br. J. Addict. 83, 193–201.

Preston, K.L., Bigelow, G.E., Liebson, I.A., 1988. Butorphanol-precipitated withdrawal in opioid-dependent human volunteers. J. Pharmacol. Exp. Ther. 246, 441–448.

SAS Institute, 2003. SAS Software. SAS Institute, Cary, NC.

Substance Abuse and Mental Health Services Administration, 2001. 42 CFR Part 8: Opioid Drugs in Maintenance and Detoxification Treatment of Opiate Addiction; Final Rule. Federal Register 66, 4076–4102.

Wang, R.I., Kochar, C., Hasegawa, A.T., Roh, B.L., 1982. Initial methadone dose in treating opiate addiction. Int. J. Addict. 17, 357–363.

Wang, R.I., Wiesen, R.L., Lamid, S., Roh, B.L., 1974. Rating the presence and severity of opiate dependence. Clin. Pharmacol. Ther. 16, 653–658.

Weinhold, L.L., Bigelow, G.E., 1993. Opioid miosis: effects of lighting intensity and monocular and binocular exposure. Drug Alcohol Depend. 31, 177–181.

Committee on Treatment of Opioid Dependence, 1999. In: Wesson, D.R., Ling, W., Jara, G. (Eds.), Buprenorphine in Pharmacotherapy of Opioid Addiction: Implementation in Office-Based Medical Practice; Translating the Experience of Clinical Trials into Clinical Practice. California Society of Addiction Medicine, San Francisco, CA.

Wesson, D.R., Ling, W., 2003. The clinical opiate withdrawal scale (COWS). J. Psychoactive Drugs 35, 253–259.

Original Investigation

Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence
A Randomized Clinical Trial

Gail D'Onofrio, MD, MS; Patrick G. O'Connor, MD, MPH; Michael V. Pantalon, PhD; Marek C. Chawarski, PhD; Susan H. Busch, PhD; Patricia H. Owens, MS; Steven L. Bernstein, MD; David A. Fiellin, MD

IMPORTANCE Opioid-dependent patients often use the emergency department (ED) for medical care.

OBJECTIVE To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).

DESIGN, SETTING, AND PARTICIPANTS A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.

INTERVENTIONS After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.

MAIN OUTCOMES AND MEASURES Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.

RESULTS Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95% CI, 70%-85%]) vs 37% in the referral group (38 of 102 [95% CI, 28%-47%]) and 45% in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization ($P < .001$). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) vs a reduction from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group ($P < .001$ for both time and intervention effects; $P = .02$ for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group ($P = .17$). There were no statistically significant differences in HIV risk across groups ($P = .66$). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services ($P < .001$).

CONCLUSIONS AND RELEVANCE Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00913770

JAMA. 2015;313(16):1636-1644. doi:10.1001/jama.2015.3474

JAMA Report Video and Author Video Interview at jama.com

CME Quiz at jamanetworkcme.com and CME Questions page 1670

Author Affiliations: Department of Emergency Medicine, Yale School of Medicine, New Haven, Connecticut (D'Onofrio, Pantalon, Owens, Bernstein); Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (O'Connor, Fiellin); Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut (Chawarski); Yale School of Public Health, New Haven, Connecticut (Busch, Fiellin).

Corresponding Author: Gail D'Onofrio, MD, MS, Department of Emergency Medicine, Yale School of Medicine, 464 Congress Ave, Ste 260, New Haven, CT 06519 (gail.donofrio@yale.edu).

Dependence on prescription opioids and heroin is a major public health problem that is increasing in the United States and internationally.[1,2] Opioid agonist treatment, including methadone and buprenorphine, is the most effective treatment and is associated with individual and societal benefits.[3,4] Patients with opioid dependence are at increased risk of adverse health consequences and often seek medical care in emergency departments (EDs). This may include seeking treatment for their substance use disorder, comorbid medical and psychiatric conditions, or acute illnesses and trauma. Currently, the primary option available to the ED for opioid dependence is referral to addiction treatment services. The introduction of buprenorphine/naloxone (hereinafter referred to as buprenorphine), a partial opioid agonist combined with an antagonist, may provide ED physicians the opportunity to initiate effective medication treatment in conjunction with a brief intervention and referral. Buprenorphine is a treatment for opioid use disorder that decreases withdrawal, craving, and opioid use and that can be prescribed by appropriately trained physicians.[5]

Emergency department and primary care screening, brief intervention, and referral to treatment (SBIRT) can reduce unhealthy alcohol use[6,7] and tobacco use.[8] To date, the evidence supporting the efficacy of SBIRT for drug use in ED and primary care settings is limited.[9,10] Three recent trials failed to demonstrate that patients benefited from the method.[11-13] However, no study has focused exclusively on opioid dependence. Due to the profound neurobiological and behavioral changes that characterize opioid dependence, it is likely that a more potent intervention, such as ED-initiated treatment including buprenorphine, will be needed to produce optimal outcomes. This model is similar to other chronic medical conditions such as hypertension, diabetes, and asthma in which ED clinicians initiate or restart treatment. Thus, our study was designed to test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention and facilitated referral (brief intervention), and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care (buprenorphine).

Methods

Setting and Participants

The study was conducted in a large urban teaching hospital. We attempted to screen all patients 18 years or older during select times when research associates were present, using a health quiz that contained questions on prescription opioid and heroin use embedded in a 20-item health questionnaire. Patients were not screened with the health quiz if they were non-English speaking, critically ill, unable to communicate due to dementia or psychosis, suicidal, or in police custody. Patients who indicated that they had nonmedical use of prescription opioids or any heroin use in the past 30 days were further evaluated and excluded if enrolled in formal addiction treatment, had a medical or psychiatric condition that required hospitalization, or required opioid medication for a pain condition. The Mini-International Neuropsychiatric Interview (MINI) was administered to evaluate for opioid dependence using *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria. Patients with a urine sample that tested positive for opioids (opiates or oxycodone) and a MINI score 3 or higher were considered to have met criteria for opioid dependence and were eligible for inclusion. Research associates reviewed the study procedures and protocol and obtained signed informed consent from those interested in participation. Race and ethnicity were collected by self-report. The study sample was enrolled between April 7, 2009, and June 25, 2013. The study was approved by the Human Investigation Committee of Yale School of Medicine.

Treatment Conditions

After screening, enrolled patients were randomized to the referral group, the brief intervention group or the buprenorphine group (**Figure**). Patients in the referral and brief intervention groups did not receive treatment for withdrawal symptoms as part of their participation in the study. The management of withdrawal symptoms for these patients was at the discretion of the treating ED physician.

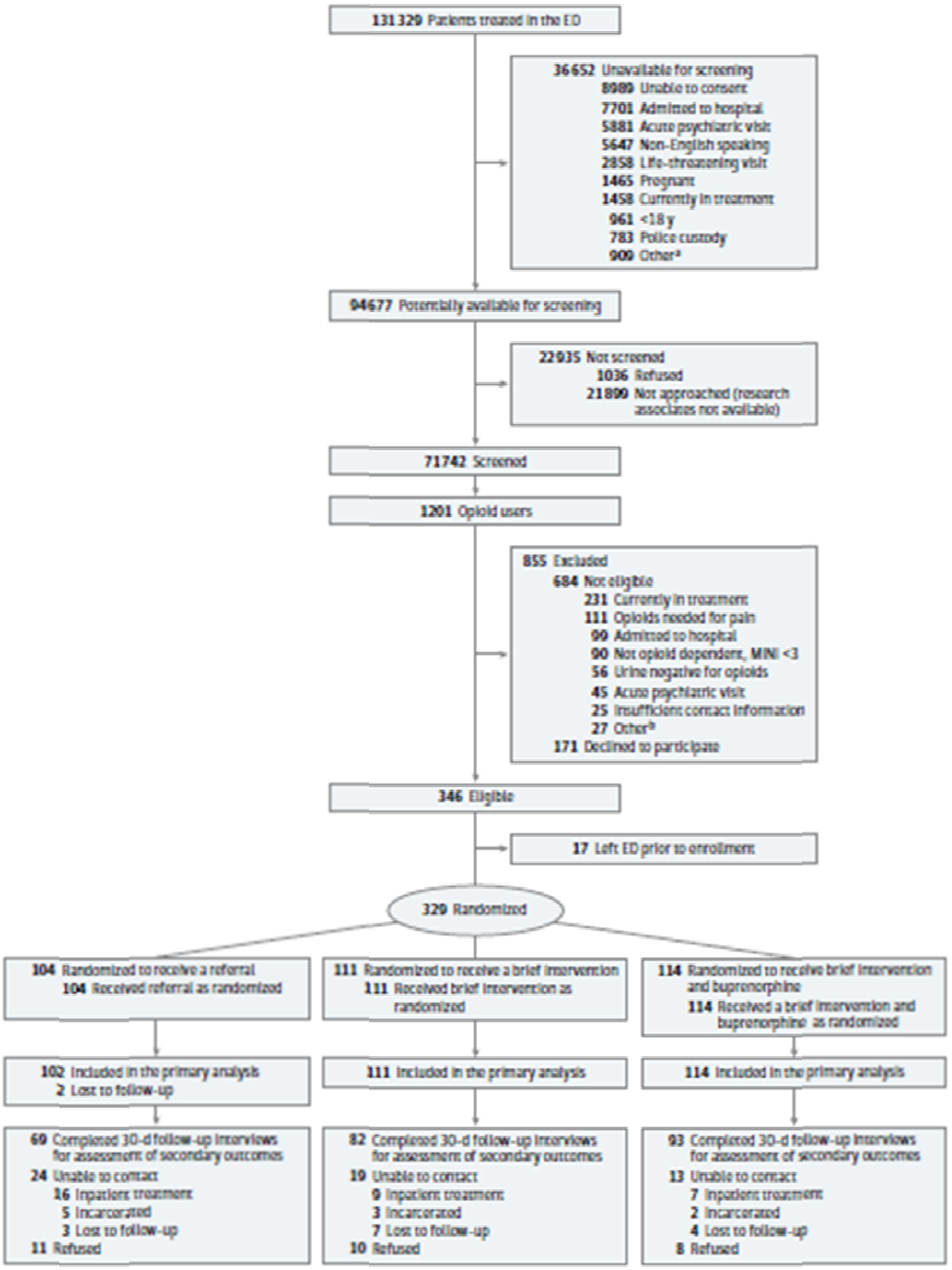
Screening and Referral to Treatment

After undergoing screening, referral patients received a handout from a trained research associate providing names, locations, and telephone numbers of addiction treatment services in the area and telephone access to call a clinician or facility of their choice, which were categorized according to the insurance plans in which they participated. These addiction services included a range of treatments with varying intensity and duration, including opioid treatment programs, inpatient or residential treatment, and outpatient services including intensive outpatient programs and office-based physicians who prescribe buprenorphine or other forms of medication-assisted treatment. The research associate was trained not to use any motivating statements in this simple referral. The conversation was audiotaped to assess for critical actions (fidelity).

Screening, Brief Intervention, and Referral to Treatment

Patients received a 10- to 15-minute manual-driven, audiotaped brief negotiation interview (BNI) from a research associate.[7,14] The Brief Negotiation Interview, previously described,[15] was modified for opioid dependence. It contained 4 components: raise the subject, provide feedback, enhance motivation, and negotiate and advise with a total of 27 critical actions, eg, asking the patient permission to discuss opioid use. The research associate discussed a variety of treatment options in a similar format as what was provided patients in the referral group, based on patient insurance, residence, and preferences. The research associate directly linked the patient with the referral. This included reviewing the patient's eligibility for services, insurance clearance, and arranging transportation.

Figure. Enrollment and Follow-up Flow Diagram for Trial of Interventions for Opioid Dependence



ED indicates emergency department; MINI, Mini-International Neuropsychiatric Interview

[a] Miscellaneous reasons (eg, isolation, sexual assault, deceased).

[b] Miscellaneous reasons (eg, unable to consent, non-English speaking, pregnant, deceased, isolation, age <18 years, police custody).

Screening, Brief Intervention, ED Initiated Treatment With Buprenorphine, and Referral

Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal.[16] Sufficient take-home daily doses were provided to ensure they had adequate medication until a scheduled appointment in the hospital's primary care center, within 72 hours. Buprenorphine doses were 8 mg on day 1 and 16 mg on days 2 and 3. In the 65 patients (57%) not manifesting opioid withdrawal in the ED, buprenorphine was provided for unobserved (eg, home) induction, with a detailed self-medication guide.[17] Office-based buprenorphine treatment was provided for 10 weeks by physicians and nurses using established procedures with visits ranging from weekly to twice monthly based on clinical stability.[18,19] After 10 weeks, patients were transferred for ongoing opioid agonist maintenance treatment to either a community program or a clinician or were offered detoxification over a 2-week period, based on their stability, insurance, and preference.

Assignment of Treatment

After written consent was obtained, patients completed the baseline assessments and were randomly assigned in a 1:1:1 ratio to 1 of the 3 groups. A computerized stratified randomization procedure[20] under the control of an investigator (M.C.C.) who was not involved with enrollment or assessment for eligibility was used to ensure that the groups were balanced with regard to sex, cocaine use in the last 30 days, and primarily prescription opioid or heroin use. A research associate not involved with assessments or randomization then facilitated the assigned treatment and performed the Brief Negotiation Interview if indicated.

Intervention Fidelity

The referral conversation with patients in the referral group and the Brief Negotiation Interview with patients in either the brief intervention group or the buprenorphine group were audiotaped and reviewed by independent trained raters who were blind to the study design and hypothesis to assess for critical actions that were prescribed and proscribed for each condition.

Outcomes

The primary outcome, *engagement in treatment*, is defined as enrollment and receiving formal addiction treatment on the 30th day following randomization, assessed by direct contact with the facility, clinician, or both. Formal addiction treatment included any of a range of clinical settings including an opioid treatment program, inpatient or residential treatment, and outpatient services including intensive outpatient programs and office-based physicians who prescribe buprenorphine or other forms of medication-assisted treatment. Secondary outcomes collected at 30 days included self-reported number of days of illicit opioid use in the past 7 days, urine toxicology for illicit opioid use, HIV risk-taking behavior using an 11-item validated scale for drug use and sexual behavior,[21] and the use of addiction treatment services.[22] Urine samples collected at 30 days were analyzed using a rapid qualitative immunoassay. Addiction services included inpatient, outpatient, and ED-based services used at any point between study enrollment and the 30th day following randomization. Data on all outcomes were collected by research associates not involved in the patients' ED care.

Sample Size Calculation and Statistical Analysis

Power calculations regarding the adequacy of the sample size were based on data from published reports and reviews of studies investigating the efficacy of SBIRT[9,23] as well as on our previous studies of buprenorphine in primary care.[19] In general, these reports suggest a medium effect size of brief interventions (average effect size of $f = 0.5$) for improving rates of treatment engagement and a small- to moderate-range effect size for reducing drug- or sex-related HIV risk behaviors or for reducing medical consequences ($f = 0.2$ to $f = 0.4$). The sample size of 360 provided power of 0.80 or greater to detect significant differences of this magnitude[24] while taking into consideration potential attrition. This corresponds to a statistical power of 0.80 to detect a difference of 35% or greater between the buprenorphine group and the referral group and a difference of 18% or more between the buprenorphine group and brief intervention group for the primary outcome of engagement in treatment at 30 days. Due to time and financial constraints, we enrolled 329 of the planned 360 patients.

We used χ^2 tests or analysis of variance procedures to examine the baseline comparability of the 3 treatment groups. The χ^2 tests were used to evaluate statistical significance of the differences in engagement in treatment on the 30th day following randomization, rates of opioid-negative urine samples, and rates of use of inpatient addiction treatment, and ED visits. We used the mixed-models procedure repeated measures linear models to evaluate the differences between baseline and 30-day follow-up in the number of days per week of illicit opioid use, HIV risk behaviors, and inpatient addiction services across the study groups. This analytical approach uses all available data on each randomized patient; therefore, all study patients, including those with missing data, were included in the analyses; no imputations were required.[25] All analyses involved 2-tailed tests of significance and were performed using SPSS software, version 21. *P* values less than .05 were considered statistically significant. No interim data examination or analyses were performed.

Results

Demographic and Clinical Characteristics

Baseline characteristic of the 3 groups are shown in **Table 1**. Overall, 34% were seeking treatment for opioid dependence at the index visit and 8.8% presented to the ED with an overdose. The remaining patients were identified through screening. Twenty-five percent reported using only prescription opioids and 53% of the total sample reported intravenous drug use. Other substance use during the 30 days prior to the ED visit was prevalent with 88% reporting using cigarettes, 55% cocaine, 53% cannabis, and 47% sedatives. Drinking alcohol to intoxication was reported in a third of the sample. More than 70% reported a lifetime history of prior drug treatment and 14%

Table 1. Baseline Demographic and Clinical Characteristics of Patients

	No. (%) of Patients[a]			
	Overall (n = 329)	Referral (n = 104)	Brief Intervention (n = 111)	Buprenorphine (n = 114)
Demographic Characteristics				
Men	251 (76.3)	81 (77.9)	84 (75.7)	86 (75.4)
Race/ethnicity				
White	248 (75.4)	78 (75.0)	82 (73.9)	88 (77.2)
Black	23 (7.0)	7 (6.7)	8 (7.2)	8 (7.0)
Hispanic	54 (16.4)	16 (15.4)	21 (18.9)	17 (15.0)
Other	4 (1.2)	3 (2.9)	0	1 (0.9)
Age, mean (SD), y	31.4 (10.6)	31.4 (10.6)	31.9 (9.7)	31 (9.8)
Education				
High school graduate or equivalent	136 (41.3)	40 (38.5)	51 (45.9)	45 (39.5)
Some college	113 (34.4)	33 (31.7)	35 (31.5)	45 (39.5)
≥College degree	20 (6.1)	9 (8.7)	8 (7.2)	3 (2.6)
Usual employment, past 3 y				
Full	172 (52.3)	59 (56.7)	57 (51.4)	56 (49.1)
Part time	84 (25.5)	26 (25.0)	28 (25.2)	30 (26.3)
Married	36 (10.9)	12 (11.5)	10 (9.0)	14 (12.3)
No stable living arrangement, past 30 d	30 (9.1)	8 (7.7)	10 (9.0)	12 (10.5)
Health insurance				
Private/commercial	104 (31.6)	33 (31.7)	33 (29.7)	38 (33.3)
Medicare	6 (1.8)	1 (1.0)	3 (2.7)	2 (1.8)
Medicaid	142 (43.2)	48 (46.2)	46 (41.4)	48 (42.0)
None	71 (21.6)	21 (20.2)	26 (23.4)	24 (21.1)
Primary care physician	138 (41.9)	42 (40.4)	46 (41.4)	50 (43.9)
Usual source of care				
Private physician's office	92 (27.9)	30 (28.8)	26 (23.4)	36 (31.6)
Clinic	88 (26.7)	26 (25.0)	35 (31.5)	27 (23.7)
Emergency department or none	149 (45.3)	48 (46.2)	50 (45.0)	51 (44.7)
Clinical Characteristics				
ED identification of participants				
Seeking treatment for opioid dependence	112 (34.0)	32 (30.8)	34 (30.6)	46 (40.4)
Identified via screening	217 (66.0)	72 (69.2)	77 (69.4)	68 (59.6)
Overdose	29 (8.8)	7 (6.7)	10 (9.0)	12 (10.5)
Primary type of opioid drug used and route of administration				
Prescription	82 (24.9)	31 (29.8)	24 (21.6)	27 (23.7)
Heroin	247 (75.1)	73 (70.2)	87 (78.4)	87 (76.3)
Intravenous use	174 (52.9)	46 (44.2)	66 (59.5)	62 (54.4)
Nonopioid substance use, past mo				
Alcohol to intoxication	113 (34.3)	32 (30.8)	47 (42.3)	34 (29.8)
Sedative	156 (47.4)	56 (53.8)	50 (45.0)	50 (43.9)
Cannabis	174 (52.9)	61 (58.7)	54 (48.6)	59 (51.8)
Cocaine	182 (55.3)	57 (54.8)	66 (59.5)	59 (51.8)
Cigarette	290 (88.1)	91 (87.5)	97 (87.4)	102 (89.4)
Mental health history				
Lifetime psychiatric treatment	168 (51.1)	54 (51.9)	59 (53.2)	55 (48.2)
Inpatient	86 (26.1)	28 (26.9)	29 (26.1)	29 (25.4)
Outpatient	138 (41.9)	49 (47.1)	45 (40.5)	44 (38.6)
Any psychiatric symptom, past 30 d[b]	290 (88.1)	93 (89.4)	96 (86.5)	101 (88.6)
Received treatment for depression, past 30 d	40 (12.2)	9 (8.7)	17 (15.3)	14 (12.3)
PHQ9 score, mean (SD)[c]	12.46 (6.5)	12.72 (6.3)	12.26 (6.5)	12.41 (6.6)

(continued)

Table 1. Baseline Demographic and Clinical Characteristics of Patients (continued)

	No. (%) of Patients[a]			
	Overall (n = 329)	Referral (n = 104)	Brief Intervention (n = 111)	Buprenorphine (n = 114)
Acute psychiatry ED evaluation	77 (23.4)	23 (22.1)	30 (27.0)	24 (21.1)
Lifetime treatment for addiction				
Alcohol	46 (14.0)	17 (16.3)	20 (18.0)	9 (7.9)
Drugs	240 (72.9)	73 (70.2)	88 (79.3)	79 (69.3)

Abbreviations: ED, emergency department; PHQ9, Patient Health Questionnaire.

[a] All patients were screened and referred to a treatment program. Patients in the brief intervention group received a 10- to 15-min manual-driven, audiotaped Brief Negotiation Interview and facilitated referral to a treatment program. Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal until a scheduled appointment within 72 h in the hospital's primary care center could be arranged.

[b] From the addiction severity index.

[c] The range of possible scores for the PHQ9[35] is 0 to 27. A score of 5 to 14 suggests the patient may need treatment based on the patient's duration of symptoms and functional impairment. A score of more than 15 warrants treatment for depression, using antidepressant, psychotherapy, or a combination of treatment.

with prior alcohol treatment. Coexisting mental health problems were prevalent with more than half reporting prior psychiatric treatment and 23% of patients requiring a psychiatric evaluation at the index ED visit.

Intervention Participation and Fidelity

A total of 225 patients (100%) in the brief intervention and the buprenorphine groups received a Brief Negotiation Interview at the index ED visit. The mean (SD) Brief Negotiation Interview duration was 10.6 minutes (4.3). The rate of Brief Negotiation Interview critical actions performed was 21.5 of 27 (80%) in the brief intervention group and 20.5 of 27 (76%) in the buprenorphine group. The mean (SD) referral duration was 2.0 minutes (1.3) and the rate of referral critical actions performed was 2.5 of 4 (62%).

Primary Outcome

Engagement in Treatment

Data on enrollment and receiving formal addiction treatment on the 30th day following randomization was obtained by program or by clinician report and was available for 327 of 329 participants (99%). Incarcerated patients were considered not in treatment. Eighty-nine of 114 patients (78%; 95% CI, 70%-85%) in the buprenorphine group were engaged in treatment at significantly higher rates than the 38 of 102 patients (37%; 95% CI, 28%-47%) in the referral group or 50 of 111 patients (45%; 95% CI, 36%-54%) in the brief intervention group ($P < .001$).

Secondary Outcomes

Illicit Opioid Use

Self-report data on illicit opioid use in the past 7 days were collected on 244 of 329 patients (74%), 69 of 104 in the referral group, 82 of 111 in the brief intervention group, and 93 of 114 in the buprenorphine group. This was primarily due to the inability to contact (n = 56); including those who were incarcerated (n = 10), receiving inpatient treatment (n = 22), or lost to follow-up (n = 14). Twenty-nine patients declined the 30-day assessment. The buprenorphine group reported greater reductions in the mean number of days of illicit opioid use per week—from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) than did the referral group, which decreased from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) and the brief intervention group, which decreased from 5.6 days (95% CI, 5.3-5.9) to 2.4 (95% CI, 1.8-3.0). Patients in all groups reduced their illicit opioid use over time ($P < .001$), the between group ($P < .001$), and the group by time interaction ($P = .02$) effects were also statistically significant (Table 2).

The overall rate of urine sample collection was 220 of 329 (66.9%): 65 of 104 (63%) in the referral group, 70 of 111 (63%) in brief intervention group, and 85 of 114 (74.6%) in buprenorphine group. The rates of opioid negative urine toxicology test results did not differ statistically across the treatment groups with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group having tested negative for opioid use ($P = .17$).

HIV Risk Behaviors

Patients in all 3 groups reported significantly reduced HIV risks from baseline to 30 days ($P < .001$). However, the differences in these reductions were not statistically significant across groups. The risk decreased in the referral group from 8.5 (95% CI, 7.0-9.9) to 5.7 (95% CI, 4.2-7.1); in the brief intervention group from 9.2 (95% CI, 7.8-10.7) to 6.2 (95% CI, 4.9-7.6); and in the buprenorphine group from 9.1 (95% CI, 7.7-10.5) to 5.8 (95% CI, 4.5-7.1) ($P = .66$). The interaction between the time and group effects was not statistically significant ($P = .95$).

Addiction Treatment Service Use

There was no difference in the mean number of outpatient visits across the 3 groups (Table 2). Patients in the referral and brief intervention groups used inpatient addiction treatment services at a higher rate than did those in the buprenorphine group: 37% (95% CI, 27%-48%) in the referral group; 35% (95% CI, 25%-37%) in the brief intervention group; and 11% (95% CI, 6%-19%) in the buprenorphine group ($P < .001$). There were no statistically significant differences in ED use for addiction treatment across the 3 groups ($P = .51$).

Post Hoc Analysis

A post hoc analysis of a subgroup of patients who presented to the ED specifically seeking treatment for opioid depen-

Table 2. Baseline and 30-Day Secondary Outcome Measures Among Opioid-Dependent Patients Treated in the Emergency Department[a]

	Referral	Brief Intervention	Buprenorphine	P Value[b]
Days of Self-reported Illicit Opioid Use in the Past 7 Days, Mean (95% CI)				
Baseline	5.4 (5.1-5.7)	5.6 (5.3-5.9)	5.4 (5.1-5.7)	<.001, Treatment effect
30 d	2.3 (1.7-3.0)	2.4 (1.8-3.0)	0.9 (0.5-1.3)	<.001, Time effect .02, Interaction effect
Outpatient Addiction Treatment in the Past 30 Days, Mean (95% CI)[c]				
No. of outpatient visits				
Baseline	0.38 (0.0-1.0)	1.16 (0.6-1.7)	0.20 (0.0-0.8)	.07, Treatment effect
30 d	4.99 (3.1-6.8)	5.67 (4.0-7.4)	3.71 (2.1-5.3)	<.001, Time effect .63, Interaction effect
ED-Based Addiction Treatment in the Past 30 Days, No./Total (%)				
Any addiction-related ED visit				
Baseline	8/104 (7.7)	6/111 (5.4)	5/114 (4.4)	.57
30 d	15/69 (21.7)	12/82 (14.6)	18/93 (19.4)	.51
Inpatient Addiction Treatment in the Past 30 Days, No./Total (%)[d]				
Any inpatient addiction treatment				
Baseline	10/104 (9.6)	7/111 (6.3)	7/114 (6.1)	.55
30 d	31/84 (36.9)	32/91 (35.2)	11/100 (11.0)	<.001

Abbreviation: ED, emergency department.

[a] All patients were screened and referred to a community-based treatment service. Patients in the brief intervention group received a 10- to 15-min manual-driven, audiotaped Brief Negotiation Interview and facilitated referral to treatment services. Patients in the buprenorphine group received a Brief Negotiation Interview and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal until a scheduled appointment within 72 hours in the hospital's primary care center could be arranged.

[b] χ^2 Test with 2 degrees of freedom used to test for differences in inpatient and ED treatment. Mixed-model procedures used to test for differences in days of self-reported illicit opioid use and outpatient addiction treatment; thus, all patients in the sample were included. Treatment × time effect = interaction effect.

[c] Includes both office-based and addiction treatment center visits.

[d] Includes residential and hospital-based treatment.

dence found that rates of treatment engagement at 30 days across the groups were not significantly different from the entire sample: 32 of 46 (70%; 95% CI, 55%-81%) in the buprenorphine; 20 of 34 (59%; 95% CI, 42%-74%) in the brief intervention group; and 13 of 31 (42%; 95% CI, 26%-59%) in the referral group ($P = .054$).

Discussion

In a diverse group of opioid-dependent patients with substantial psychiatric and substance use–related comorbidity, ED-initiated buprenorphine with primary care office-based follow-up for ongoing treatment resulted in a greater percentage of individuals engaged in treatment and fewer days of self-reported illicit opioid use than did referral or SBIRT. The majority of patients who were provided a referral, with or without facilitation, were not engaged in addiction treatment at 30 days.

Our findings demonstrate that ED-initiated buprenorphine with coordinated follow-up for ongoing treatment was more effective than referral with or without brief intervention. To our knowledge, this is the first randomized controlled trial comparing outcomes across these treatment strategies. An earlier observational study helped establish the feasibility of ED-initiated buprenorphine, yet there was no follow-up comparing alternative referral options or evaluating buprenorphine's effect on treatment engagement, drug use, or addiction treatment service use.[27] Few studies have examined the efficacy of SBIRT for drug use.[9,10,28,29] Recent studies in primary care and ED settings[11-13] addressing a broad spectrum of drug type and intensity of drug use found no benefit to SBIRT. The US Preventive Services Task Force[30] has determined that there is insufficient evidence to recommend this practice. However, none of these earlier studies focused exclusively on opioid-dependent ED patients, and none included ED-initiated treatment.

Both of our referral treatments had some success in engaging patients in treatment. Of note, however, the referral group received detailed referral information about community services tailored to their insurance status and the brief intervention group received a psychosocial intervention with a facilitated referral. Both of these interventions go beyond the current standard of ED care and the level of intervention in the referral group may have diminished our ability to detect a difference between the referral and brief intervention groups. The rates of negative urine toxicology test results for illicit opioids were not significantly different across groups. Because opioids can be detected in the urine for approximately 72 hours, collection at a single time point may not accurately reflect the frequency or intensity of opioid use. This decrease in urine sensitivity for drug use may account for the discrepancy between the self-reported number of days of opioid use per week and the urine test results.

Detection and initiation of treatment for chronic and relapsing medical conditions (eg, hypertension, diabetes, and asthma) is standard ED practice. There are promising results on the initiation of smoking cessation treatment.[31,32] The current study extends this work to opioid use disorders, a chronic and relapsing

medical condition that EDs are increasingly encountering.[1] It also extends the literature on "interim" opioid agonist treatment whereby medication treatment is initiated while the patient is awaiting more comprehensive treatment services.[33] The increasing prevalence of opioid use disorders and the increasing toll of overdose deaths due to opioids[2] amplifies the urgency to decrease barriers, such as the delays that can occur with treatment referrals to accessing treatment.

Patients in the buprenorphine group were less likely to use inpatient addiction treatment, suggesting more efficient, less costly resource use. In addition the buprenorphine group was more likely to be engaged in treatment on the 30th day following randomization. While the costs of implementing this intervention need to be considered, including screening costs, these findings are likely to be of interest to individuals or organizations responsible for downstream service costs through episode-based or capitated payment.

Our findings should be considered in light of study design features and limitations. The ED physicians who participated in this study underwent the required training to allow them to prescribe buprenorphine.[5,34] Such training has been incorporated into some residencies,[35] and more than 40 000 physicians have completed it as of 2014. In addition, specific exemptions do exist that currently allow physicians to administer buprenorphine or methadone for the purpose of relieving acute withdrawal symptoms while arranging for referral for ongoing treatment.[36] Prior to implementation, an ED would need to develop a system to correctly diagnose opioid use disorder among those who are misusing opioids. Research staff provided the referrals and performed the Brief Negotiation Interview. In our prior work addressing unhealthy alcohol use, we trained ED practitioners to provide brief interventions[7,14,37] and used health promotion advocates to provide referrals for individuals with substance use disorders.[38] The buprenorphine and the counseling care provided in the study were provided at no expense to the patients. This design feature could potentially bias our results because financial barriers could impact treatment outcomes. We believe this is unlikely because 80% of study patients had health insurance. The study design and its implementation were selected to ensure that costs, insurance coverage, or policies such as prior authorizations would not present barriers to patients accessing the unique services in the buprenorphine group. In light of our findings, future research could be conducted to determine the extent to which reimbursement and coverage barriers impact treatment outcomes.

Although we assessed the use of addiction treatment services, a full-scale cost-effectiveness evaluation is beyond the scope of this article. The buprenorphine group received both ED-initiated buprenorphine and a specific model of follow-up care. It is not possible to disentangle these 2 components in our study and future research should evaluate ED-initiated buprenorphine and referral to a variety of treatment settings. We did not achieve our anticipated sample size but our findings are robust. We were underpowered to perform subgroup analyses. We screened a large number of patients to achieve our sample size; however, in a real-world setting, some excluded patients would be eligible for ED-initiated treatment, such as non-English speakers, patients who were hospitalized, and patients who refused study participation. Finally, 30 days is a short time horizon for a chronic and relapsing condition such as opioid dependence. However, it is unlikely that care provided in the ED will influence results beyond 30 days.

Emergency department–initiated buprenorphine is feasible based on the results of our study, a previous report,[27] and the published research supporting the use of unobserved buprenorphine induction.[17,39] Emergency department clinicians who are interested in providing this treatment should work to identify a network of community-based treatment services for follow-up care. Now that the feasibility and efficacy have been established, future research should focus on assessing the effectiveness and implementation of buprenorphine. In addition, research is needed to improve the efficacy of using a brief intervention for drug use disorders, particularly promoting short-term treatment engagement. The American College of Emergency Physicians should consider broadening the scope of its position statement that indicates that emergency physicians "are positioned and qualified to mitigate the consequences of alcohol abuse through screening programs, brief intervention, and referral to treatment" to include opioid use disorders. Expanded use of ED-initiated buprenorphine with community follow-up should help increase access to treatment options for this chronic and relapsing medical condition that has substantial morbidity and mortality and that affects health care use and costs.

Conclusions

Among opioid-dependent patients presenting for emergency care, ED-initiated buprenorphine, compared with brief intervention and referral, significantly increased engagement in formal addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of positive urine testing for opioids or HIV risk. Although this single-site study supports this ED-initiated treatment strategy, these findings require replication in other centers before widespread adoption.

ARTICLE INFORMATION

Author Contributions: Drs D'Onofrio, Fiellin, and Chawarski had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: D'Onofrio, O'Connor, Pantalon, Chawarski, Busch, Fiellin.
Acquisition, analysis, or interpretation of data: D'Onofrio, O'Connor, Pantalon, Chawarski, Busch, Owens, Bernstein, Fiellin.
Drafting of the manuscript: D'Onofrio, O'Connor, Pantalon, Chawarski, Fiellin.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Chawarski.
Obtained funding: D'Onofrio, O'Connor, Pantalon, Chawarski, Owens, Fiellin.
Administrative, technical, or material support: D'Onofrio, O'Connor, Pantalon, Owens, Bernstein, Fiellin.
Study supervision: D'Onofrio, O'Connor, Pantalon, Bernstein, Fiellin.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest. Dr Fiellin reported that he has received honoraria from Pinney Associates for serving on an external advisory board monitoring the diversion and abuse of buprenorphine. No other disclosures were reported.

Funding/Support: The study was supported by grant 5R01DA025991 from the National Institute on Drug Abuse (NIDA), and Reckitt-Benckiser Pharmaceuticals provided buprenorphine through NIDA.

Role of the Funder/Sponsor: The funding organization had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Emergency department visits involving nonmedical use of selected prescription drugs—United States, 2004-2008. *MMWR Morb Mortal Wkly Rep*. 2010;59(23):705-709.

2. Centers for Disease Control and Prevention (CDC). CDC grand rounds: prescription drug overdoses—a US epidemic. *MMWR Morb Mortal Wkly Rep*. 2012;61(1):10-13.

3. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev*. 2011;8(8):CD004145.

4. *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. Geneva, Switzerland: World Health Organization; 2009.

5. Sullivan LE, Fiellin DA. Narrative review: buprenorphine for opioid-dependent patients in office practice. *Ann Intern Med*. 2008;148(9):662-670.

6. Jonas DE, Garbutt JC, Amick HR, et al. Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the US Preventive Services Task Force. *Ann Intern Med*. 2012;157(9):645-654.

7. D'Onofrio G, Fiellin DA, Pantalon MV, et al. A brief intervention reduces hazardous and harmful drinking in emergency department patients. *Ann Emerg Med*. 2012;60(2):181-192.

8. Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz N, Curry SJ; 2008 PHS Guideline Update Panel, Liaisons, and Staff. Treating tobacco use and dependence: 2008 update US Public Health Service Clinical Practice Guideline executive summary. *Respir Care*. 2008;53(9):1217-1222.

9. Bernstein J, Bernstein E, Tassiopoulos K, Heeren T, Levenson S, Hingson R. Brief motivational intervention at a clinic visit reduces cocaine and heroin use. *Drug Alcohol Depend*. 2005;77(1):49-59.

10. Bernstein E, Edwards E, Dorfman D, Heeren T, Bliss C, Bernstein J. Screening and brief intervention to reduce marijuana use among youth and young adults in a pediatric emergency department. *Acad Emerg Med*. 2009;16(11):1174-1185.

11. Saitz R, Palfai TP, Cheng DM, et al. Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. *JAMA*. 2014;312(5):502-513.

12. Roy-Byrne P, Bumgardner K, Krupski A, et al. Brief intervention for problem drug use in safety-net primary care settings: a randomized clinical trial. *JAMA*. 2014;312(5):492-501.

13. Bogenschutz MP, Donovan DM, Mandler RN, et al. Brief intervention for patients with problematic drug use presenting in emergency departments: a randomized clinical trial. *JAMA Intern Med*. 2014;174(11):1736-1745.

14. D'Onofrio G, Pantalon MV, Degutis LC, et al. Brief intervention for hazardous and harmful drinkers in the emergency department. *Ann Emerg Med*. 2008;51(6):742-750.e2.

15. D'Onofrio G, Pantalon MV, Degutis LC, Fiellin DA, O'Connor PG. Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. *Acad Emerg Med*. 2005;12(3):249-256.

16. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs*. 2003;35(2):253-259.

17. Lee JD, Grossman E, DiRocco D, Gourevitch MN. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med*. 2009;24(2):226-232.

18. Fiellin DA, Barry DT, Sullivan LE, et al. A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. *Am J Med*. 2013;126(1):74.e11-74.e17.

19. Fiellin DA, Pantalon MV, Chawarski MC, et al. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *N Engl J Med*. 2006;355(4):365-374.

20. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet*. 2002;359(9305):515-519.

21. Darke S, Hall W, Heather N, Ward J, Wodak A. The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS*. 1991;5(2):181-185.

22. McLellan AT, Alterman AI, Cacciola J, Metzger D, O'Brien CP. A new measure of substance abuse treatment: initial studies of the treatment services review. *J Nerv Ment Dis*. 1992;180(2):101-110.

23. Stein MD, Charuvastra A, Maksad J, Anderson BJ. A randomized trial of a brief alcohol intervention for needle exchangers (BRAINE). *Addiction*. 2002;97(6):691-700.

24. Barber J, Crits-Christoph P. Development of a therapist adherence/competence rating scale for supportive-expressive dynamic psychotherapy. *Psychother Res*. 1996;6(2):81-94.

25. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the *Archives of General Psychiatry*. *Arch Gen Psychiatry*. 2004;61(3):310-317.

26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613.

27. Berg ML, Idrees U, Ding R, Nesbit SA, Liang HK, McCarthy ML. Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department. *Drug Alcohol Depend*. 2007;86(2-3):239-244.

28. Humeniuk R, Ali R, Babor T, et al. A randomized controlled trial of a brief intervention for illicit drugs linked to the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in clients recruited from primary health-care settings in four countries. *Addiction*. 2012;107(5):957-966.

29. Madras BK, Compton WM, Avula D, Stegbauer T, Stein JB, Clark HW. Screening, brief interventions, referral to treatment (SBIRT) for illicit drug and alcohol use at multiple healthcare sites. *Drug Alcohol Depend*. 2009;99(1-3):280-295.

30. Drug use, illicit screening, US Preventive Services Task Force web page. http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/drug-use-illicit-screening. Released January 2008. Accessed November 12, 2014.

31. Bernstein SL, Bijur P, Cooperman N, et al. Efficacy of an emergency department-based multicomponent intervention for smokers with substance use disorders. *J Subst Abuse Treat*. 2013;44(1):139-142.

32. Rabe GL, Wallmann J, Bagos P, et al. Efficacy of emergency department-initiated tobacco control. *Nicotine Tob Res*. 2013;15(3):643-655.

33. Schwartz RP, Highfield DA, Jaffe JH, et al. A randomized controlled trial of interim methadone maintenance. *Arch Gen Psychiatry*. 2006;63(1):102-109.

34. Fiellin DA, O'Connor PG. New federal initiatives to enhance the medical treatment of opioid dependence. *Ann Intern Med*. 2002;137(8):688-692.

35. Kunins HV, Sohler NL, Giovanniello A, Thompson D, Cunningham CO. A buprenorphine education and training program for primary care residents. *Subst Abus*. 2013;34(3):242-247.

36. Prescriptions. Food and Drugs, Drug Enforcement Administration, Department of Justice. 21 *CFR* 1306.07(b), 71-72.

37. Pantalon MV, Martino S, Dziura J, et al. Development of a scale to measure practitioner adherence to a brief intervention in the emergency department. *J Subst Abuse Treat*. 2012;43(4):382-388.

38. D'Onofrio G, Degutis LC. Integrating Project ASSERT: a screening, intervention, and referral to treatment program for unhealthy alcohol and drug use into an urban emergency department. *Acad Emerg Med*. 2010;17(8):903-911.

39. Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction. *Addict Behav*. 2010;35(5):537-540.

Emergency Department-Initiated Buprenorphine for Opioid Dependence with Continuation in Primary Care: Outcomes During and After Intervention

Gail D'Onofrio, MD, MS[1], Marek C. Chawarski, PhD[1,2], Patrick G. O'Connor, MD, MPH[3], Michael V. Pantalon, PhD[1], Susan H. Busch, PhD[4], Patricia H. Owens, MS[1], Kathryn Hawk, MD, MHS[1], Steven L. Bernstein, MD[1], and David A. Fiellin, MD[3,4]

[1]Department of Emergency Medicine, Yale School of Medicine, New Haven, CT, USA; [2]Department of Psychiatry, Yale School of Medicine, New Haven, CT, USA; [3]Department of General Medicine, Yale School of Medicine, New Haven, CT, USA; [4]Yale School of Public Health, New Haven, CT, USA.

BACKGROUND: Emergency department (ED)-initiated buprenorphine/naloxone with continuation in primary care was found to increase engagement in addiction treatment and reduce illicit opioid use at 30 days compared to referral only or a brief intervention with referral.

OBJECTIVE: To evaluate the long-term outcomes at 2, 6 and 12 months following ED interventions.

DESIGN: Evaluation of treatment engagement, drug use, and HIV risk among a cohort of patients from a randomized trial who completed at least one long-term follow-up assessment.

PARTICIPANTS: A total of 290/329 patients (88% of the randomized sample) were included. The followed cohort did not differ significantly from the randomized sample.

INTERVENTIONS: ED-initiated buprenorphine with 10-week continuation in primary care, referral, or brief intervention were provided in the ED at study entry.

MAIN MEASURES: Self-reported engagement in formal addiction treatment, days of illicit opioid use, and HIV risk (2, 6, 12 months); urine toxicology (2, 6 months).

KEY RESULTS: A greater number of patients in the buprenorphine group were engaged in addiction treatment at 2 months [68/92 (74%), 95% CI 65–83] compared with referral [42/79 (53%), 95% CI 42–64] and brief intervention [39/83 (47%), 95% CI 37–58; $p<0.001$]. The differences were not significant at 6 months [51/92 (55%), 95% CI 45–65; 46/70 (66%) 95% CI 54–76; 43/76 (57%) 95% CI 45–67; $p=0.37$] or 12 months [42/86 (49%) 95% CI 39–59; 37/73 (51%) 95% CI 39–62; 49/78 (63%) 95% CI 52–73; $p=0.16$]. At 2 months, the buprenorphine group reported fewer days of illicit opioid use [1.1 (95% CI 0.6–1.6)] versus referral [1.8 (95% CI 1.2–2.3)] and brief intervention [2.0 (95% CI 1.5–2.6), $p=0.04$]. No significant differences in illicit opioid use were observed at 6 or 12 months. There were no significant differences in HIV risk or rates of opioid-negative urine results at any time.

CONCLUSIONS: ED-initiated buprenorphine was associated with increased engagement in addiction treatment and reduced illicit opioid use during the 2-month interval when buprenorphine was continued in primary care. Outcomes at 6 and 12 months were comparable across all groups.

ClinicalTrials.gov Identifier NCT00913377

Received July 29, 2016
Revised November 30, 2016
Accepted January 11, 2017
Published online February 13, 2017

KEY WORDS: opioid use disorder; substance use disorder; emergency medicine; primary care.
J Gen Intern Med 32(6):660–6
DOI: 10.1007/s11606-017-3993-2

INTRODUCTION

The prevalence of the non-medical use of prescription opioids, the use of heroin, and opioid overdose mortality have escalated to epidemic proportions, prompting urgent calls for expanded access to treatment for opioid use disorder (previously referred to as opioid dependence).[1–3] Opioid agonist treatment, including methadone and buprenorphine/naloxone (hereafter referred to as buprenorphine), is the most effective treatment and is associated with improved health and social outcomes and disease prevention.[4,5] Patients with opioid use disorder are at increased risk for adverse health consequences, and often use the emergency department (ED) to treat these problems. Thus, the ED offers an opportunity to screen for opioid use disorder, provide interventions and facilitate referral to ongoing treatment.

We previously published 30-day outcomes from a clinical trial of patients who met criteria for opioid dependence (currently classified as moderate/severe opioid use disorder, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [DSM-5]) that were randomized to one of three interventions: referral, brief intervention or ED-initiated buprenorphine followed by 10 weeks of continued buprenorphine treatment in a primary care setting.[6] Patients receiving ED-initiated buprenorphine with continuation in primary care were more likely to be engaged in formal addiction treatment at 30 days than were those in the brief intervention or referral groups (78% vs. 45% vs. 37%, respectively, $p<0.001$). This finding provides a new paradigm for ED-initiated treatment of patients with moderate/severe opioid use disorder.

ED-based interventions typically focus on the acute stabilization and treatment of medical conditions, with the goal of ED care to engage patients in ongoing treatment. Similar to ED presentations of exacerbations of other chronic diseases such as diabetes and asthma, our results demonstrate that ED providers can initiate buprenorphine treatment for moderate/severe opioid use disorders and facilitate linkage to community-based providers including primary care and other office-based physicians who prescribe buprenorphine. However, it is unknown how long the benefits of ED-initiated buprenorphine with continuation in primary care will last. We now present the results of a cohort from our original sample and outcomes observed at 2 months (during primary care-based buprenorphine treatment provided as a part of the randomized clinical trial) and at 6 and 12 months.

METHODS

Setting and Participants

We report on a cohort of patients that completed at least one follow-up assessment at 2, 6 or 12 months, who were recruited into a randomized trial conducted at a large urban teaching hospital and its affiliated primary care center from April 7, 2009, to June 25, 2013. The methods have been reported in detail previously.[6]

ED patients 18 years of age and older were screened using a 20-item health questionnaire containing embedded questions related to prescription opioid and heroin use. Patients were excluded if they were non-English-speaking, critically ill, unable to communicate due to dementia or psychosis, suicidal, or in police custody. Patients reporting non-medical use of prescription opioids or any heroin use in the past 30 days were excluded if they were enrolled in formal addiction treatment, required hospitalization or were receiving opioid medication for pain. Patients with an opioid-positive urine test (opiates or oxycodone) and a Mini International Neuropsychiatric Interview score ≥ 3 for opioid dependence using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria[7] were eligible for inclusion. Informed consent was obtained by research associates (RAs). The study was approved by the Human Investigation Committee of Yale School of Medicine.

Treatment Conditions

Patients were randomly assigned in a 1:1:1 ratio to one of three study groups. The use of a computerized stratified randomization procedure[8] by an investigator (MCC) ensured that the groups were balanced with regard to sex, cocaine use in the last 30 days, and primarily prescription opioid or heroin use.

Referral. Referral patients received a handout providing names, locations and phone numbers of addiction treatment services consistent with their insurance plan in the area and telephone access. These addiction services included a range of treatments of varying intensity and duration, including opioid treatment programs, inpatient or residential treatment, and outpatient services including intensive outpatient programs and office-based providers of buprenorphine or other forms of treatment. The RA avoided motivating statements. Patients in the referral and brief intervention groups described below received management of withdrawal symptoms at the discretion of the ED physician.

Brief Intervention. A 10–15-minute manual-driven audiotaped Brief Negotiation Interview (BNI) was performed by an RA.[9] The BNI, described previously,[10] was modified for opioid dependence and contained four components: Raise the Subject, Provide Feedback, Enhance Motivation, and Negotiate and Advise. The RA discussed a variety of treatment options based on patient insurance, residence and preferences, and directly linked the patient with the referral. This included reviewing the patient's eligibility for services, obtaining insurance clearance and arranging transportation.

Buprenorphine. Patients in the buprenorphine group received a BNI and ED-initiated treatment with buprenorphine if they exhibited moderate to severe opioid withdrawal.[11] Sufficient take-home daily doses were provided to ensure they had adequate medication until a scheduled appointment in the hospital's primary care center, within 72 hours. Buprenorphine doses were 8 mg on day 1 and 16 mg on days 2 and 3. In the 65 (57%) patients not manifesting opioid withdrawal in the ED, buprenorphine was provided for unobserved (e.g., home) induction, with a detailed self-medication guide.[12]

Primary care-based buprenorphine treatment was continued for 10 weeks by physicians and nurses using established procedures, with visits ranging from weekly to twice monthly based on clinical stability.[13,14] Clinicians and study investigators providing buprenorphine treatment were blinded to research assessments. Receipt of buprenorphine treatment was not contingent upon abstinence from illicit drug use. After completing 10 weeks of primary care-based buprenorphine treatment within this study, all patients were offered referral for transitioning to an opioid agonist treatment program tailored to their stability, insurance and preference in a non-study community-based treatment setting. As an alternative, patients who requested it were provided detoxification over a 2-week period and a referral for ongoing care (e.g., naltrexone and counseling).

Long-Term Follow-Up Assessments

The long-term follow-up assessments at 2, 6 and 12 months included the Treatment Services Review,[15,16] timeline follow-back assessment of illicit opioid use in the preceding 7 days,[17] and an 11-item validated scale for and HIV risk-taking related to drug use and sexual behavior.[18] Assessments at 2 and 6 months were completed primarily face-to-face (88% and 82% face-to-face and 12% and 18% telephone, respectively) by

trained, supervised and scripted RAs in a clinical setting separate from primary care or other treatment sites. The 12-month assessment was completed primarily by phone (84% telephone, 16% face-to-face) by the same research personnel. The RAs were blinded to group assignment and not involved in any aspect of the patient's care. Patients who completed face-to-face interviews at 2 and 6 months also provided a urine sample for drug toxicology testing. Urine samples were tested for opioid metabolites (morphine, oxycodone) using a rapid qualitative immunoassay. Patients did not receive feedback regarding the results of their urine tests and were informed that all research assessment data were confidential and not available to the treatment providers. To minimize bias, surveillance for and determination of all outcome data were carried out in a uniform manner across all three treatment conditions. The follow-up assessment sessions lasted between 20 and 30 min on average, and patients received $50.00 gift cards for participation in each of the follow-up assessments.

Outcomes

The primary outcome for the current study, engagement in formal addiction treatment at the time of the 2-, 6- and 12-month assessments, was by self-report using the Treatment Services Review.[15,16] Formal addiction treatment was defined as a range of providers including opioid treatment programs, inpatient or residential treatment, and outpatient services including intensive outpatient programs, office-based providers of buprenorphine or other forms of treatment. Secondary outcomes, collected by self-report at 2, 6 and 12 months, included the number of days of illicit opioid use in the past 7 days and the summary score of the HIV risk assessment instrument.[18] Rates of opioid-negative urine test results were also compared among the study groups at 2 and 6 months.

Data Analytical Strategy

The study sample ($N = 290$) represented 88% of the patients enrolled and randomized in the original trial who provided data during at least one of the 2-, 6- and 12-month follow-up assessments. The numbers of patients in the referral, brief intervention and buprenorphine groups who provided data were 79, 83 and 92 for the 2-month, 70, 75 and 92 for the 6-month, and 73, 78 and 86 for the 12-month assessments, respectively. This followed sample was comparable to the randomized sample on all evaluated characteristics, and there were no statistical differences in follow-up rates across the three groups ($p = 0.654$; Fig. 1).

We used chi-square tests or analysis of variance (ANOVA) to examine the comparability of the three study groups. Chi-square tests were used to evaluate the statistical significance of between-group differences for all categorical outcomes (e.g., engagement in formal addiction treatment, rates of opioid-negative urine tests) and we used ANOVA to evaluate the statistical significance of between-group differences for all continuous outcomes (e.g., days of illicit opioid use, HIV risk behaviors) at all follow-up assessments. All analyses involved two-tailed tests of significance and were performed using SPSS version 21 software.[19]

RESULTS

Demographic and Clinical Characteristics

Baseline demographic and clinical characteristics are shown in Table 1. There were no statistical differences among groups. Thirty-three percent were seeking treatment for opioid dependence at the index visit, 9% presented with an overdose, and the remaining 58% were identified through screening. Patients reported substantial use of other substances. Mental health problems were prevalent, with 23% requiring an acute psychiatric evaluation in the ED.

Outcomes

Engagement in Formal Addiction Treatment at the Time of the 2-, 6- and 12-Month Assessment (Fig. 2).

Patients in the buprenorphine group were receiving formal addiction treatment at a significantly higher rate at the 2-month assessment [68/92 (74%) 95% CI 65–83] than those in the referral [42/79 (53%), 95% CI 42–64] or brief intervention groups [39/83 (47%) 95% CI 36–58; $p < 0.001$]. This difference between the buprenorphine, referral and brief intervention groups did not persist at 6 months [49/92 (53%) 95% CI 43–64; 42/70 (60%) 95% CI 48–72; 39/76 (51%) 95% CI 40–63] or 12 months [42/86 (49%) 95% CI 38–60; 36/73 (49%) 95% CI 38–61; 49/78 (63%) 95% CI 52–74; $p = 0.546$ and $p = 0.136$, respectively].

Illicit Opioid Use and HIV Risk Behaviors (Table 2).

At 2 months, the buprenorphine group reported significantly less illicit opioid use, with 1.1 (95% CI 0.7–1.5) days of illicit opioid use in the past 7 days, compared with 1.8 (95% CI 1.2–2.4) in the referral group and 2.0 (95% CI 1.4–2.6) in the brief intervention group ($p = 0.040$). There was a significant temporal trend toward reduction in illicit opioid use in all groups from baseline to 12 months, but there were no longer between-group differences.

There were no statistically significant differences among the three groups regarding HIV risk behaviors at any of the assessment points.

Urine Toxicology. The overall rate of urine sample collection was 224/290 (77%) at 2 months and 194/290 (67%) at 6 months. The rates of illicit opioid-negative urine toxicology tests were not significantly different at 2 months [52/83 (62.7%) in the buprenorphine group, 42/71 (59.2%) in the referral group, and 41/70 (58.6%) in the brief intervention

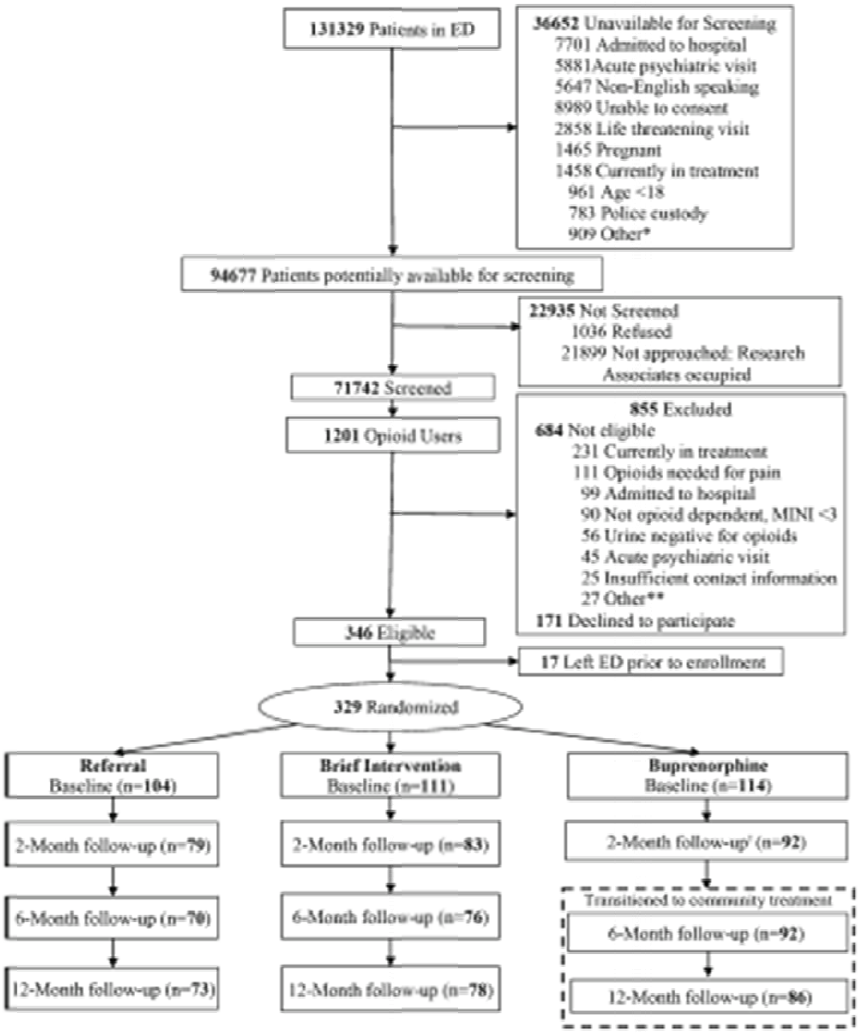


Figure 1 Enrollment and follow-up flow diagram for trial of interventions for opioid dependence. *Miscellaneous reasons (e.g., isolation, sexual assault, deceased). **Miscellaneous reasons (e.g., unable to consent, non-English-speaking, pregnant, deceased, isolation, age <18, police custody). †The 2-month follow-up occurred during the 10-week treatment period. — box represents patients transitioned to non-study community treatment per study protocol. *MINI* Mini International Neuropsychiatric Interview, *Referral* referral only, *Brief Intervention* brief intervention and referral, *Buprenorphine* ED-initiated buprenorphine and referral.

group] or at 6 months [47/74 (63.5%) in the buprenorphine group, 33/59 (55.9%) in the referral group, and 32/61 (52.5%) in the brief intervention group].

DISCUSSION

Opioid-dependent patients who received ED-initiated buprenorphine with continuation in primary care were more likely to be engaged in treatment and reported less use of illicit opioids at the time of follow-up assessments at 2 months. The 2-month assessment occurred while patients were still receiving buprenorphine through primary care, as the study treatment was provided for a total of 10 weeks. These differences in outcomes did not persist at the 6- and 12-month follow-up. After 10 weeks, patients were transitioned to other outpatient treatment providers offering treatments for opioid dependence or were tapered off buprenorphine, depending on patient preference and insurance coverage. It is unlikely that engagement in treatment at 6 and 12 months was related to the ED-initiated buprenorphine or 10-week buprenorphine treatment provided as part of this study. There were no significant differences in HIV risk behaviors or rates of opioid-negative urine test results at any assessment point.

This study demonstrates that the relative benefit of ED-initiated buprenorphine with referral for ongoing treatment in primary care persists at 2 months. Our findings at 2 months in the buprenorphine treatment group are consistent with those of other studies of primary care office-based buprenorphine treatment for opioid dependence. For example, in a

Table 1 Patient Baseline Demographic and Clinical Characteristics

	Overall ($n=290$) no. (%)	Referral ($n=90$) no. (%)	Brief intervention ($n=97$) no. (%)	Buprenorphine ($n=103$) no. (%)
Demographic characteristics				
Male sex, no. (%)	220 (75.9)	69 (76.7)	73 (75.3)	78 (75.7)
Race/ethnicity, no. (%)				
White	219 (75.5)	66 (73.3)	71 (73.2)	82 (79.6)
Black	19 (6.6)	6 (6.7)	6 (6.2)	7 (6.8)
Hispanic	49 (16.9)	16 (17.8)	20 (20.6)	13 (12.6)
Other	3 (1.0)	2 (2.2)	0	1 (1.0)
Age, mean (SD), years	31.5 (10.0)	31.9 (10.6)	31.7 (9.7)	31.1 (10.0)
Education, no. (%)				
High school graduate or equivalent	117 (40.3)	33 (36.7)	44 (45.4)	40 (38.8)
Some college	101 (34.9)	29 (32.3)	32 (33.0)	40 (38.8)
College degree or more	19 (6.6)	8 (8.9)	8 (8.2)	3 (2.9)
Usual employment, past 3 years, no. (%)				
Full-time	148 (51.0)	48 (53.3)	49 (50.5)	51 (49.5)
Part-time	77 (26.6)	24 (26.7)	26 (26.8)	27 (26.2)
Married, no. (%)	32 (11.0)	10 (11.1)	8 (8.2)	14 (13.6)
No stable living arrangement, past 30 days, no. (%)	24 (8.3)	7 (7.8)	6 (6.2)	11 (10.7)
Health insurance, no. (%)				
Private/commercial	85 (29.3)	24 (26.7)	28 (28.9)	33 (32.0)
Medicare	6 (2.1)	1 (1.1)	3 (3.1)	2 (1.9)
Medicaid	131 (45.2)	45 (50.0)	41 (42.3)	45 (43.7)
None	66 (22.8)	20 (22.2)	24 (24.7)	22 (21.4)
Primary care physician, no. (%)	120 (41.4)	33 (36.7)	41 (42.3)	46 (44.7)
Usual source of care, no. (%)				
Private physician's office	80 (27.6)	24 (26.7)	24 (24.7)	32 (31.1)
Clinic	76 (26.2)	23 (25.5)	28 (28.9)	25 (24.3)
Emergency department or none	134 (46.2)	43 (47.8)	45 (46.4)	46 (44.6)
Clinical characteristics				
ED identification of patients:				
Seeking treatment for opioid dependence	96 (33.1)	28 (31.1)	27 (27.8)	41 (39.8)
Identified via screening	194 (66.9)	62 (68.9)	70 (72.2)	62 (60.2)
Overdose	27 (9.3)	7 (7.8)	9 (9.3)	11 (10.7)
Primary type of opioid drug used and route of administration, no. (%)				
Prescription	70 (24.1)	23 (25.6)	22 (22.7)	25 (24.3)
Heroin	220 (75.9)	67 (74.4)	75 (77.3)	78 (75.7)
Intravenous use	154 (53.1)	41 (45.6)	57 (58.8)	56 (54.4)
Non-opioid substance use, past month, no. (%)				
Alcohol to intoxication	102 (35.2)	31 (34.4)	41 (42.3)	30 (29.1)
Sedative use	141 (48.6)	49 (54.4)	45 (46.4)	47 (45.6)
Cannabis use	153 (52.8)	51 (56.7)	50 (51.5)	52 (50.5)
Cocaine use	158 (54.5)	50 (55.6)	54 (55.7)	54 (52.4)
Cigarette use	256 (88.3)	78 (86.6)	85 (87.6)	93 (90.3)
Mental health history				
Lifetime psychiatric treatment, no. (%)	148 (51.0)	49 (54.4)	53 (54.6)	46 (44.7)
Inpatient	79 (27.2)	28 (31.1)	27 (27.8)	24 (23.3)
Outpatient	123 (42.4)	44 (48.9)	41 (42.3)	38 (36.9)
Currently receiving treatment for depression, no. (%)	37 (12.8)	8 (8.9)	15 (15.5)	14 (13.6)
PHQ-9* score, mean (SD)	12.45 (6.5)	13.04 (6.4)	12.17 (6.7)	12.20 (6.5)
Acute psychiatric ED evaluation, no. (%)	68 (23.4)	20 (22.2)	27 (27.8)	21 (20.4)
Lifetime treatment for addiction, no. (%)				
Alcohol	42 (14.5)	17 (18.9)	16 (16.5)	9 (8.7)
Drugs	213 (73.4)	65 (72.2)	76 (78.4)	72 (69.9)

ED emergency department, PHQ-9 Patient Health Questionnaire
**The range of possible scores for the PHQ-9 is 0–27. A score of 5–14 suggests the patient may need treatment based on the duration of symptoms and functional impairment. A score of more than 15 warrants treatment for depression, using antidepressant, psychotherapy and/or a combination of treatment*

14-week clinical trial in prescription opioid-dependent individuals, which compared the efficacy of buprenorphine taper versus ongoing maintenance in primary care, 66% of patients in the maintenance group remained in treatment at 14 weeks, compared to 76% at 2 months in our current study.[20] Similarly, another study in primary care reported that 78% remained in treatment at 12 weeks.[21] Thus, our findings at 2 months are consistent with previous research on the use on buprenorphine in primary care. In the current study, patients in the buprenorphine group were transitioned to other treatment providers or tapered off buprenorphine after 10 weeks. While we do not have information on the specific treatments these patients selected, we do know from previous research that buprenorphine tapering is much less efficacious than ongoing buprenorphine therapy in terms of both treatment retention and illicit opioid use.[20] Longer-term outcome studies on buprenorphine in primary care have demonstrated retention rates including 59% at 24 weeks,[22] 55% at 6 months,[23] 44% and 57% at 12 months,[24,25] and 38% at 2 years.[26]

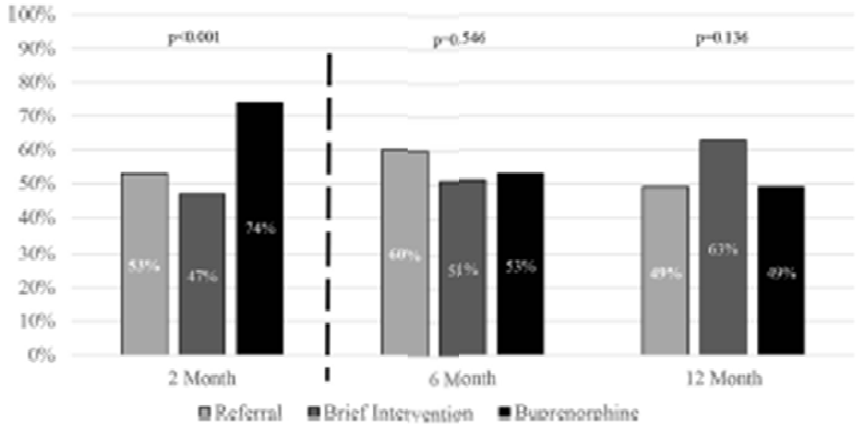


Figure 2 Engagement in formal addiction treatment.

This study has several limitations. First, this paper reports on a cohort of patients with long-term follow-up, representing 88% of our original randomized trial sample. The 39 patients lost to follow-up (11 buprenorphine, 14 brief intervention, 14 referral) did not differ from the followed cohort with regard to age, gender, type of drugs used, injection drug use, medical insurance status, treatment-seeking status or presentation with an overdose. We also utilized one ED and one site for primary care-based buprenorphine treatment—both of which are located at the same urban academic medical center. Future studies will need to demonstrate that this approach is generalizable to other settings suitable for the provision of buprenorphine treatment in this manner. While the fact that these two sites were part of the same institution may seem to be a limitation of the study, it may also serve as a model for how these services can be effectively integrated within a medical center or health care system that provides comprehensive health care services. Such models are becoming increasingly prevalent as consolidation occurs within the U.S. health care system. In addition, the data regarding engagement in formal addiction treatment at 2, 6 and 12 months are based on self-report and were not confirmed with treatment providers. We attempted to limit bias and social desirability by completing 2- and 6-month assessments in a clinical setting separate from primary care or other treatment sites conducted by RAs not involved in any aspect of their care. Patients were informed that their answers and urine test results were confidential and were stored in de-identified (anonymous) form in the data sets, and that reimbursement for their time was not dependent on their responses.

We focused on engagement in treatment at specific time points, which does not take into consideration that patients may have been engaged in treatment at other times. While this may underestimate the true proportion of patients engaged in treatment, we believe this is appropriate given the relapsing nature of opioid use disorder. The outcomes observed in the referral and brief intervention groups may appear better than expected. This could be due to the extent to which these conditions provided resources that are beyond usual care, the availability of treatment resources in the surrounding area, or other unmeasured confounders. To our knowledge, no other study has followed an ED population of patients with opioid use disorder up to 12 months. Either way, these factors would bias against a positive finding with the ED-initiated buprenorphine treatment condition. Finally, we were able to obtain urine samples for opioids on only a subset of patients at 2 and 6 months, leading to the potential for bias. For this reason, and since urine tests assess opioid use only within the prior 72 hours, we caution against placing undue emphasis on these

Table 2 Past-7-Day Illicit Opioid Use and HIV Risk Behaviors: Baseline and 2, 6 and 12 Months

	Referral	Brief intervention	Buprenorphine	*p* value
Days of self-reported illicit opioid use in the past 7 days,* mean (95% CI)				
Baseline	5.3 (4.9–5.7)	5.6 (5.3–5.9)	5.3 (5.0–5.7)	0.40
2 Months	1.8 (1.2–2.4)	2.0 (1.4–2.6)	1.1 (0.7–1.5)	0.04
6 Months	1.5 (0.9–2.1)	2.0 (1.4–2.6)	1.6 (1.1–2.2)	0.54
12 Months	1.5 (0.9–2.1)	0.9 (0.5–1.4)	0.7 (0.3–1.2)	0.09
HIV risk behaviors,† mean (95% CI)				
Baseline	8.7 (7.1–10.2)	9.4 (7.9–10.9)	9.4 (7.7–11.0)	0.78
2 Months	6.1 (4.6–7.6)	4.9 (3.8–6.1)	4.8 (3.7–5.9)	0.30
6 Months	5.4 (3.9–7.0)	5.3 (3.8–6.7)	4.4 (3.4–5.4)	0.45
12 Months	3.8 (2.7–4.9)	5.3 (3.9–6.8)	4.1 (3.1–5.2)	0.18

**Timeline follow-back method*
†HIV Risk Behavior Scale

findings or the discrepancy between urine testing and self-report of drug use, which was assessed over a longer 7-day time frame.

Despite these limitations, our study provides evidence that ED-initiated buprenorphine treatment with linkage to ongoing treatment in primary care increases engagement in formal addiction treatment and reduces self-reported illicit opioid use while such treatment is continued. For 27% of the enrolled ED patients, the index ED visit represented their first treatment contact. Thus, the ED visit is an opportunity to engage patients with opioid use disorder in effective medication-assisted treatment. Future research should focus on evaluating the implementation of this model in a diverse array of emergency departments and other health care settings.

Contributors: *GD, MC, PGO, SHB, PHO, SLB and DF were involved in the study conception, and obtained funding; GD, PGO, MP, PHO, SLB and DF supervised the conduct of the trial and data collection; MC and PHO managed the data, including quality control; MC and SHB provided statistical advice on study design and analyzed the data; all authors were involved in interpreting the data; GD, MC, PGO, PHO, KH and DF drafted the manuscript, and all authors contributed substantially to its revision; GD and DF take responsibility for the paper as a whole. There are no others to report, aside from research staff who collected data.*

Corresponding Author: *Gail D'Onofrio, MD, MS; Department of Emergency Medicine Yale School of Medicine, New Haven, CT, USA (e-mail: gail.donofrio@yale.edu).*

Compliance with Ethical Standards:

Conflict of Interest: *Dr. Fiellin has received honoraria from Pfizer Associates for serving on an external advisory board monitoring the diversion and abuse of buprenorphine. The remaining authors have no conflicts.*

Funders: *The study was supported by grants 5R01DA025991 and K12DA033312 from the National Institute on Drug Abuse (NIDA), and Reckitt Benckiser Pharmaceuticals provided buprenorphine through NIDA. The funding organization had no role in the design or conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.*

Prior Presentation: *The College on Problems of Drug Dependence, June 2015, Phoenix, Arizona.*

REFERENCES

1. **Centers for Disease Control, Prevention.** Emergency department visits involving nonmedical use of selected prescription drugs - United States, 2004-2008. MMWR Morb Mortal Wkly Rep. 2010;59(23):705-9.
2. **Centers for Disease Control, Prevention.** CDC grand rounds: prescription drug overdoses - a U.S. epidemic. MMWR Morb Mortal Wkly Rep. 2012;61(1):10-3.
3. Surgeon General Report: U.S. Department of Health and Human Services (HHS), Office of the Surgeon General, Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health, Executive Summary. Washington, DC: HHS, November 2016.
4. **Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R.** Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2011;8:CD004145.
5. **Anonymous.** Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009.
6. **D'Onofrio G, O'Connor PG, Pantalon MV, et al.** Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015;313(16):1636-44.
7. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR: Text Revision: American Psychiatric Press Incorporated (DC); 2000.
8. **Schulz KF, Grimes DA.** Generation of allocation sequences in randomised trials: chance, not choice. Lancet. 2002;359(9305):515-9.
9. **D'Onofrio G, Pantalon MV, Degutis LC, et al.** Brief intervention for hazardous and harmful drinkers in the emergency department. Ann Emerg Med. 2008;51(6):742-50.
10. **D'Onofrio G, Pantalon MV, Degutis LC, et al.** Development and implementation of an emergency practitioner-performed brief intervention for hazardous and harmful drinkers in the emergency department. Acad Emerg Med. 2005;12(3):249-56.
11. **Wesson DR, Ling W.** The clinical opiate withdrawal scale (COWS). J Psychoactive Drugs. 2003;35(2):253-9.
12. **Lee JD, Grossman E, DiRocco D, Gourevitch MN.** Home buprenorphine/naloxone induction in primary care. J Gen Intern Med. 2009;24(2):226-32.
13. **Fiellin DA, Barry DT, Sullivan LE, et al.** A randomized trial of cognitive behavioral therapy in primary care-based buprenorphine. Am J Med. 2013;126(1):74-e11.
14. **Fiellin DA, Pantalon MV, Chawarski MC, et al.** Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. N Engl J Med. 2006;355(4):365-74.
15. **McLellan TA, Zanis D, Incmikoski R.** Treatment Service Review (TSR). Philadelphia: The Center for Studies in Addiction, Department of Psychiatry: Philadelphia VA Medical Center & The University of Pennsylvania; 1989.
16. **McLellan AT, Alterman AI, Cacciola J, Metzger D.** A new measure of substance abuse treatment. Initial studies of the treatment services review. J Nerv Ment Dis. 1992;180(2):101-10.
17. **Sobell L, Sobell M.** Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R, Allen J, eds. Measuring Alcohol Consumption: Psychosocial and Biological Methods. Totowa, NJ: Humana Press; 1992:41-72.
18. **Darke S, Hall W, Heather N, Ward J, Wodak A.** The reliability and validity of a scale to measure HIV risk taking behaviour among intravenous drug users. Aids. 1991;5(2):181-186.
19. **IBM Corp.** Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.
20. **Fiellin DA, Schottenfeld RS, Cutter CJ, Moore BA, Barry DT, O'Connor PG.** Primary care-based buprenorphine taper vs maintenance therapy for prescription opioid dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(12):1947-54.
21. **O'Connor P, Oliveto A, Shi J, et al.** A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. Am J Med. 1998;105(2):100-5.
22. **Stein MD, Cioe P, Friedmann PD.** Buprenorphine retention in primary care. J Gen Intern Med. 2005;20(11):1038-41.
23. **Sunkl J, Matthews ML, Brick D, et al.** Implementation of a collaborative care management program with buprenorphine in primary care: a comparison between opioid-dependent patients and chronic pain patients using opioids non-medically. J Opioid Manag. 2014;10(3):159.
24. **Soeffing JM, Martin LD, Fingerhood MI, Jasinski DR, Rastegar DA.** Buprenorphine maintenance treatment in a primary care setting: outcomes at 1 year. J Subst Abus Treat. 2009;37(4):426-30.
25. **Alford DP, LaBelle CT, Kretsch N, et al.** Collaborative care of opioid-addicted patients in primary care using buprenorphine: five-year experience. Arch Intern Med. 2011;171(5):425-31.
26. **Fiellin DA, Moore BA, Sullivan LE, et al.** Long-term treatment with buprenorphine/naloxone in primary care: results at 2-5 years. Am J Addict. 2008;17(2):116-20.

Key Concepts for OSTI

- Opioid use disorder is and should be treated as a chronic illness.
- The opiate epidemic has impacted communities of color for years. The current national focus suggests bias in the healthcare system, policy-makers and media.
- Safe-prescribing does not mean NO prescribing, even for patients in recovery.
- The prescription monitoring program (PMP or MassPAT) provides accurate, up-to-date prescribing information and must be accessed before prescribing
- Co-prescribing naloxone should be considered for any patient on chronic opiates.
- Best practices include risk assessment (including for diversion), informed consent, monitoring, safe storage and disposal counseling.
- Medication assisted treatment/Medications for opioid use disorder with agents such as methadone, buprenorphine or naltrexone can act as a bridge or long-term therapy to assist patients in overcoming opioid use disorders.