City of Lynchburg Opioid Abatement Authority Funding Proposal

Attachments

Attachment 1: Proof of evidence-based services for proposed project

Supporting documents:

Patient and Program Factors that Bridge the Detoxification-Treatment Gap: A Structured Evidence Review. This paper is a meta-analysis of substance use detoxification highlighting factors associated with successful completion rates, including motivational-based approaches similar to those used by Horizon Behavioral Health.

Pharmacologic treatments for opioid dependence: detoxification and maintenance options. This paper highlights the gold standard for MOUD, buprenorphine, which is prescribed in Horizon's Office-Based Addiction Treatment (OBAT) clinic.

A randomized pilot clinical trial to evaluate the efficacy of Community Reinforcement and Family Training for Treatment Retention (CRAFT-T) for improving outcomes for patients completing opioid detoxification. This paper highlights Community Reinforcement Approach (CRA), an evidence-based psychosocial treatment used at Horizon for the past 17 years. Its efficacy is well-established with clients with an opioid use disorder. Horizon has CRA trained clinicians and a CRA trained supervisor and consultant on staff.

Attachment 2: Letters of support

Lynchburg Police Department (Chief Ryan Zuidema)

Miriam's House (Executive Director Sarah Quarantotto)

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Patient and Program Factors that Bridge the Detoxification-Treatment Gap: A Structured Evidence Review

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ABSTRACT

Although completion of detoxification (detox) and a successful transition from detox to substance use disorder (SUD) treatment and/or mutual-help groups are associated with better SUD outcomes, many patients do not complete detox or do not receive SUD care following detox. The purpose of this structured evidence review, summarizing data extraction on a yield of 26 articles, is to identify patient, program, and system factors associated with the outcomes of completion of alcohol detox and successful transitions from alcohol detox to SUD treatment and mutual-help group participation. The review found wide variability among studies in the rates at which patients complete a detox episode (45 to 95%) and enter SUD treatment or mutual-help groups after detox (14 to 92%). Within program factors, behavioral practices that contribute to both detox completion and transitioning to SUD care after detox entail involving the patient's family and utilizing motivational-based approaches. Such practices should be targeted at younger patients, who are less likely to complete detox. Although more studies using a randomized controlled trial design are needed, the evidence suggests that barriers to detox completion and transition to SUD care can be overcome to improve patient outcomes.

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1. Introduction

An estimated 19.3 million Americans need treatment for an alcohol problem in a given year (Substance Abuse & Mental Health Services Administration [SAMHSA], 2009a). Of annual admissions to substance use disorder (SUD) services, approximately 400,000, or 22%, are for detoxification (detox) in inpatient, freestanding residential, or outpatient programs (SAMHSA, 2009b). Inpatient detox accounts for 24% of annual admissions to publicly-funded SUD health care facilities and is a frequent request of patients in emergency departments (SAMHSA, 2009c). Of annual detox admissions, about 220,000, or 53%, are for alcohol as the primary substance (SAMHSA, 2009b).

Detoxification is not considered SUD treatment. Rather, it is the medical management of substance withdrawal to prevent complications, such as seizures or delirium tremens, which may be fatal. Completion of detox and a successful transition from detox to SUD treatment and/or mutual-help groups are associated with better SUD outcomes (Lee et al., 2014). Although detox services are unlikely to be effective if they are not completed and not followed by SUD care, many patients do not complete detox or do not receive SUD care following detox (Lee et al., 2014).

1.1. Detox completion and post-detox SUD care

Of 326,365 detoxification discharges in 2009 captured by SAMHSA's Treatment Episode Data Set (TEDS), 66% of detox episodes, with a median duration of 4 days, were completed (SAMHSA, 2012). Of these same detox discharges, only 11% were followed by transfer to SUD treatment (SAMHSA, 2012). However, rates of SUD treatment post-detox vary widely depending on the sample (Garnick, Lee, Horgan, & Acevedo, 2009). In Fiscal Year 2006, 18.5% of Delaware's public patients who completed detox were admitted to SUD treatment within 30 days (Haley, Dugosh, & Lynch, 2011). Among individuals with private health insurance, 48.7% of detox episodes were subsequently followed by substance abuse or mental health treatment within 30 days of detox, compared to only 32.3% among people with Medicaid coverage and/or treated by public agencies (Mark, Dilonardo, Chalk, & Coffey, 2002). Mark et al. (2002) noted that their results overestimate the true linkage between detox and SUD treatment because they used a broad definition of receiving treatment. Although detox is a clear opportunity to link patients

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to SUD treatment, as well as peer-based 12-step mutual-help groups (e.g., Alcoholics Anonymous), to improve long-term outcomes such as lower rates of substance use, the majority of patients discharged from detox do not enter SUD treatment.

1.2. Associations of detox completion and post-detox SUD treatment with outcomes

It has been firmly established that a longer duration of treatment and treatment completion at each phase of SUD care (detox, intensive SUD treatment, continuing SUD treatment) is one of the best predictors of better SUD outcomes (Castaneda, Lifshutz, Galanter, Medalia, & Franco, 1992; Ford & Zarate, 2010; McKay & Weiss, 2001; Moos, 2003; Simpson, Joe, & Rowan-Szal, 1997). In addition, following detox with SUD treatment and mutual-help group participation is associated with lower rates of relapse to substance use. Patients who sustain abstinence after detoxification are distinguished by greater time spent in addiction treatment and mutual-help groups post-detox (Carroll, Triplett, & Mondimore, 2009; Ford & Zarate, 2010; Hubbard, Craddock, Flynn, Anderson, & Etheridge, 1997). For example, abstinence rates were higher at 1-year post-detox among patients who had obtained residential treatment (49% abstinent) than those who had not obtained any treatment (28% abstinent) (McCusker, Bigelow, Luippold, Zorn, & Lewis, 1995). Alcohol detoxification patients had better drinking outcomes up to 1 year post-detox when they obtained ongoing social support through Alcoholics Anonymous (AA; Klijnsma, Cameron, Burns, & McGuigan, 1995; Noone, Dua, & Markham, 1999). Patients who received treatment within 1 month of detox discharge were also significantly less likely to be readmitted for detox and had a significantly longer time until a detox readmission (Mark, Vandivort-Warren, & Montejano, 2006). Detox represents an opportunity to help patients transition to treatment and achieve improvements in longer term drinking outcomes.

1.3. Present study

The purpose of the present study is to identify patient, program, and system factors associated with the outcomes of completion of alcohol detox and successful transitions from alcohol detox to SUD treatment and mutual-help group participation. We focused on alcohol detox to the exclusion of drug (opioids, benzodiazepines) detox because medical management is recommended for alcohol withdrawal syndrome (Carlson et al., 2012), whereas for opiates, agonist maintenance therapy is the recommended treatment due to its superior outcomes relative to detox (Stotts, Dodrill, & Kosten, 2009). In addition, detox is necessary from alcohol dependence because withdrawal from alcohol that is not medically managed can lead to autonomic instability, seizures, delirium, or death. In contrast, opioid withdrawal syndrome itself poses virtually no risk of mortality, although it can be protracted with intense symptoms (Department of Veterans Affairs & Department of Defense,, 2009; Maldonado, 2010). Finally, detox practice guidelines differ for alcohol, opioids, and benzodiazepines in terms of risk factors for the development of withdrawal, signs and symptoms of withdrawal, validated clinical tools to assess patients with withdrawal syndromes, appropriate pharmacology options, and integration of detox into clinical practice (Alvanzo, Chaudhry, Phillips, Poland, & Rastegar, 2013).

Research related to completion of detox and transition to SUD treatment has generally focused on patient characteristics, to the relative neglect of program factors such as behavioral strategies and practices associated with increasing rates of these clinical processes (Haley et al., 2011). We conducted a structured evidence review focused on identifying program and system factors in addition to patient characteristics, given that the former are modifiable and can be targeted for change to achieve better outcomes related to detox completion and transition to SUD care. Patient factors included demographic and clinical characteristics (e.g., mental health problems, treatment history). Program factors covered both structural aspects of programs (e.g., inpatient or outpatient setting, size), and behavioral treatment approaches (e.g., motivational- or family-based) utilized by the program. System factors were those determined by the health care facility in which the program was located (e.g., provision of housing during detox, or transportation to SUD treatment). This review is intended to fill a critical gap in the literature in that identification of factors that promote higher rates of detox completion and subsequent addiction treatment, particularly factors that also efficiently utilize resources (Dennis, Scott, & Laudet, 2014; Laudet & Humphreys, 2013), will be useful to clinical providers and managers of detoxification and SUD services seeking to achieve better outcomes among their patients.

2. Materials and methods

We searched PubMed using the term "alcohol detoxification." A separate search was not conducted regarding drug detox to ensure that our methods regarding search terms were consistent with those of other studies reporting meta-analyses and reviews on alcohol (Del Re, Maisel, Blodgett, Wilbourne, & Finney, 2013). The search (conducted on April 18, 2014) was limited to studies of humans reported in English language journal articles. Excluded were case studies, abstracts, reviews, and commentaries. A total of 1718 unique citations were screened for inclusion. Each citation was reviewed twice by study authors, taking a conservative approach of a full article review if at all indicated. Studies eliminated at this stage mainly focused on (a) efficacy and safety of a specific medication for detox; and (b) biochemical, pharmacokinetic, metabolic, or neuropsychological mechanisms and effects of alcohol use in specific groups (e.g., patients with acute liver injury; elderly cardiac patients). With this approach, 101 articles were retained for full text review because they possibly addressed patient, program, or system characteristics for facilitating completion of alcohol detox and/or access to SUD treatment or mutual-help group participation post-detoxification (Fig. 1). Three authors conducted data extraction on the final 26 articles. Data collected from each study examining patient characteristics included study design, total number of participants (and by gender), setting (inpatient or outpatient detox, country), detox completion rate (or transition rate), and patients' demographic and clinical factors associated with detox completion (Table 1) or transitions to SUD treatment (Table 3). Data collected from each study examining program and system factors were study design, numbers of participants, setting, detox completion rate, and program or system factors associated with detox completion (Table 2) or successful transitions to SUD treatment (Table 4).

Regarding study design, the US Preventive Services Task Force's quality rating criteria for individual studies (Harris et al., 2001) rates randomized controlled trials higher than cohort or case-control studies, which are rated higher than quasi-experimental studies. More fine-grained criteria rate prospective cohort higher than retrospective cohort studies, and rate cohort studies higher than case-control studies (Petticrew & Roberts, 2003). Based on these guidelines, we use the following hierarchy when discussing findings of the review in terms of study quality: RCT > prospective cohort > retrospective cohort > case-control > quasi-experimental.

3. Results

3.1. Completion of detox

3.1.1. Patient predictors

A total of 12 studies examined patient characteristics associated with a higher likelihood of completing a detoxification episode or a longer length of stay in detox (Table 1). Of these, five studies used a prospective cohort design and four used a retrospective cohort design. Studies took place mainly in inpatient ($n = 10$) rather than outpatient ($n = 2$) detox settings, in Canada ($n = 3$), Germany ($n = 3$), the USA ($n = 3$), Australia ($n = 2$), and the UK ($n = 1$). Detox completion

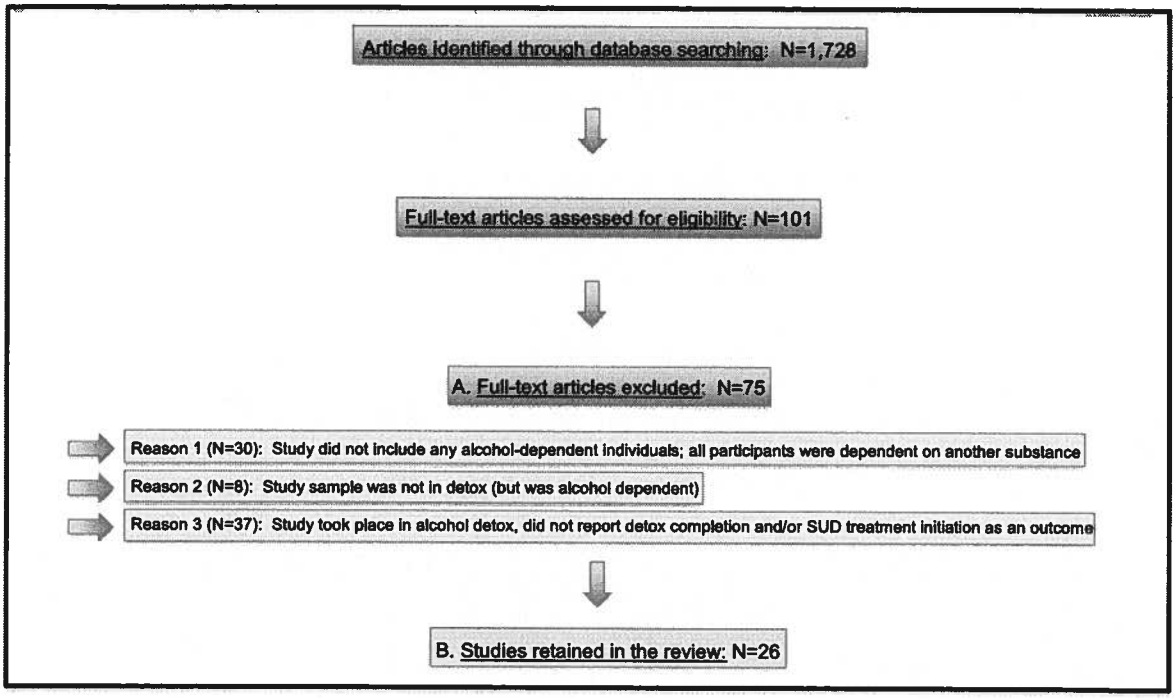

Fig. 1. Article selection process for behavioral practices to bridge the detoxification-treatment gap. (Adapted from "Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement").

rates ranged from 45% (Odenwald & Semrau, 2013) to 94% (Soyka & Horak, 2004). Of patients' demographic characteristics associated with a higher likelihood of detox completion, the only consistent factor across studies was being of older age ($n = 5$). Regarding clinical predictors, patients with the primary substance of alcohol rather than opiates were consistently more likely to complete detox ($n = 6$). In addition, patients having no history of injection drug use ($n = 2$), testing negative for Hepatitis C ($n = 2$), and having less trauma ($n = 2$) and more motivation ($n = 2$) were more likely to complete detox.

3.1.2. Program and system predictors

We identified 7 studies that examined program or system factors associated with alcohol detoxification completion or longer length of stay, using retrospective cohort ($n = 3$), RCT ($n = 1$), prospective cohort ($n = 1$), case-control ($n = 1$), and quasi-experimental ($n = 1$) designs (Table 2). These studies took place in outpatient ($n = 2$), inpatient ($n = 3$), or both outpatient and inpatient ($n = 2$) detox settings. They were located in the USA ($n = 5$) or Germany ($n = 2$). Detox completion rates ranged from 45% (treatment as usual in Odenwald & Semrau, 2012) to 95% among inpatients (Hayashida et al., 1989).

Specifically, Hayashida et al. (1989), in a randomized controlled trial, found that patients assigned to inpatient detox were more likely to complete the program than those assigned to outpatient care. A study of predictors of length of stay in 20 publicly-funded inpatient detox programs found larger programs (35 or more beds) to have longer patient stays ($M = 7.7$ days, *SD* not provided) than smaller programs ($M = 5.4$ days) (Jonkman, McCarty, Harwood, Normand, & Caspi, 2005). Another study compared patients who dropped out of detox against medical advice to those who completed the program (Blondell, Amadasu, Servoss, & Smith, 2006). Having been treated mainly by a single provider was a predictor of completion.

Soyka and Horak (2004), in a single-group study of a 3-hour motivational-oriented therapy, achieved a high outpatient detox completion rate (94%). Similarly, Odenwald and Semrau (2012) found that detox inpatients receiving PAST, a psychoeducational intervention on alcohol consumption related to stress and trauma, were more likely to complete detox than patients receiving treatment-as-usual. Feldman, Pattison, Sobell, Graham, and Sobell (1975) attributed the high rate of outpatient detox completion (82%) to the program's provision of peers in recovery and its involvement of family members. Wiseman, Henderson, and Briggs (1997) attributed the high rate of outpatient detox completion (88%) to the program's provision of housing, standardized assessments, and psychosocial treatment activities.

3.2. Detox to SUD treatment transition

3.2.1. Patient predictors

Nine studies examined patient characteristics associated with a higher likelihood of transitioning to inpatient or outpatient SUD treatment or mutual-help from a detoxification episode within different time periods (i.e., 7, 30, 90, or 180 days; Table 3). Of these, four were RCTs, three studies used a prospective cohort design, and two used a retrospective cohort design. Studies took place mainly in inpatient ($n = 8$) detox settings (and one in a mix of inpatient and outpatient settings), in the USA ($n = 7$; with one in Germany, and one in the UK). Transition rates ranged from a low of 13.7% (John, Veltrup, Driessen, Wetterling, & Dilling, 2003; the outcome was mutual-help participation after individual treatment during detox) to 79% (Stein, Orlando, & Sturm, 2000; outpatient treatment within 30 days of inpatient detox). Regarding demographics, white patients ($n = 2$) with more education ($n = 2$) were more likely to successfully transition from detox to SUD treatment or mutual-help. In addition, patients with a history of previous detox ($n = 2$) or addiction treatment ($n = 2$) episodes were more likely to successfully transition.

3.2.2. Program and system predictors

Eight studies examined program and system factors as determinants of transitions to SUD treatment or mutual-help groups following detoxification (Table 4). All but one used a RCT design, all but two were located in the USA, and all took place in inpatient settings. Chutuape, Katz, and Stitzer (2001) randomized detox inpatients to one of three methods for referring patients to SUD treatment: standard referral, standard

Table 1
Summary of published studies on patient factors associated with alcohol detoxification length of stay or completion.

Author, year	Study design	*n* (F, M)	Detox setting	Completion rate (%)	Demographic predictors	Clinical predictors
McGovern & Caputo, 1983	Prospective cohort	100 (0, 100)	Inpatient USA	LOS range 1–7 days		Internal locus of control
Martinez-Ragam, Marshall, Keaney, Ball, & Strang, 2002	Retrospective cohort	467 (121, 346)	Inpatient UK	67.2	Older age	Fewer alcohol-related problems Started drinking at older age Depressed No use of drugs besides alcohol Negative for hepatitis C No personality disorder
Callaghan & Cunningham, 2002	Retrospective cohort	1454 (474, 980)	Inpatient Canada	76.2 F 84.1 M	Male	Primary substance is alcohol (vs. opiates)
Callaghan, 2003	Retrospective cohort	877 (334, 543)	Inpatient Canada	71	Male Older age Employed Residentially stable	Primary substance is alcohol No injection drug use Not self-referred to detox No prior detox
Soyka & Horak, 2004; [a]	Prospective cohort	331 (109, 222)	Outpatient Germany	94	Has health insurance	More motivation
Jonkman et al., 2005; [a]	Retrospective cohort	21,311 (6180, 15,131)	20 inpatient USA	Mean LOS range = 4–9 days	Female 51 years old or older Not white Homeless ≥High school education Unemployed No insurance	Primary substance is alcohol (vs. opiates) Mental health problem Prior detox
Sannibale, Fucito, O'Connor, & Curry, 2005	Prospective cohort	76 (29, 47)	Outpatient Australia	71		No use of injection drugs
Blondell et al., 2006; [a]	Case-control	517 (135, 382)	Inpatient USA	83.8	Older age White Have health insurance	Primary substance is alcohol
Li, Sun, Puri, Marsh, & Anis, 2007	Prospective cohort	1673 (631, 1042)	Inpatient Canada	76.6 F 81.8 M	Male White Older age	Primary substance is alcohol Negative for hepatitis C
Silins, Sannibale, Larney, Wodak, & Mattick, 2008	Mixed methods	80 (11, 69)	Inpatient Australia	90		Primary substance is alcohol (vs. opiates)
Odenwald & Semrau, 2012	Quasi-experimental	66 (21, 45)	Inpatient Germany	45.5 TAU 81.8 INT		Low trauma load
Odenwald & Semrau, 2013	Prospective cohort	55 (15, 40)	Inpatient Germany	44.6		Fewer traumatic events More motivation to change, especially among patients with more trauma

Notes: F = female, M = male, LOS = length of stay, USA = United States of America, UK = United Kingdom, TAU = treatment as usual, INT = intervention.
[a] Study appears on Tables 1 and 2.

referral with an incentive (standard + incentive, with the incentive consisting of up to $13 worth of bus tokens or gas certificates), or staff escort from detox to treatment with the incentive (escort + incentive). Patients in the escort + incentive condition were more likely to complete treatment intake procedures than patients in the other two conditions. In another RCT, detox inpatients randomized to brief family

Table 2
Summary of published studies on program and system factors associated with alcohol detoxification completion.

Author, year	Study design	*n* (F, M)	Detox setting	Completion rate (%)	Completion predictors
Feldman et al., 1975	Retrospective cohort	267 (34, 233)	Inpatient and outpatient, USA	73	Provision of peers in recovery, involvement of family
Hayashida et al., 1989	RCT	164 (0, 164)	Inpatient vs. outpatient, USA	Inpatient: 95 Outpatient: 72	Inpatient rather than outpatient detox
Wiseman et al., 1997	Retrospective cohort	517 (12, 505)	Outpatient USA	88	Provision of housing during detox Psychosocial activities Standardized assessment to determine detox setting
Soyka & Horak, 2004; [a]	Prospective cohort	331 (109, 222)	Outpatient Germany	94	Motivational-oriented psychotherapy
Jonkman et al., 2005; [a]	Retrospective cohort	21,311 (6180, 15,131)	20 inpatient USA	Mean LOS range = 4–9 days	Larger program size
Blondell et al., 2006; [a]	Case-Control	517 (135, 382)	Inpatient USA	83.8	Treated by one physician
Odenwald & Semrau, 2012	Quasi-experimental	66 (21, 45)	Inpatient Germany	45.5 TAU 81.8 INT	INT: PAST (vs. TAU) Psychoeducation on Alcohol related to Stress and Trauma

Notes: RCT = randomized controlled trial, F = female, M = male, USA = United States of America, LOS = length of stay, TAU = treatment as usual, INT = intervention.
[a] Study appears on Tables 1 and 2.

Table 3
Summary of published studies on patient factors associated with transition to treatment or mutual-help groups from alcohol detoxification.

Author, year	Study design	*n* (F, M)	Detox setting	Outcome	Transition rate (%)	Demographic predictors	Clinical predictor
Castaneda et al., 1992	Prospective cohort	109 (0, 109)	Inpatient USA	Treatment (time frame not specified)	47	More education Employed	
Hien & Scheier, 1996	Prospective cohort	101 (101, 0)	Inpatient USA	Treatment within 7 days	59.4		Previous detox Previous treatment Heavier alcohol use
Stein et al., 2000	Retrospective cohort	1062 (352, 701)	Inpatient USA	Outpatient treatment within 30 days	79	Lower copayments	
Chutuape et al., 2001; [a]	RCT	166 (41, 125)	Inpatient USA	Outpatient treatment within 7 days	E + I 76 S + I 44 Std 24		4 or more previous treatment episodes
John et al., 2003; [a]	RCT	322 (90, 232)	Inpatient Germany	Mutual-help within 180 days	Group 25.5 Individual 13.7		Previous detox
Frydrych et al., 2009; [a]	Prospective cohort	136 (43, 93)	Inpatient USA	Treatment or mutual-help within 7 days	77	≥High school education	
Stein, Kogan, & Sorbero, 2009	Retrospective cohort	1156 episodes	Inpatient or outpatient USA	Outpatient treatment within 30 days	32.8	Female White	Serious mental illness Primary substance is alcohol (vs. opiates)
Blondell et al., 2011; [a]	RCT	150 (52, 98)	Inpatient USA	Inpatient treatment within 90 days	MET 61 P-TSF 31 TAU 45	White	No injection drug use
Manning et al., 2012; [a]	RCT	151 (49, 102)	Inpatient UK		49.2		Previous AA affiliation

Notes: RCT = randomized controlled trial, F = female, M = male, USA = United States of America, UK = United Kingdom, E + I = escort plus incentive, S + I = standard plus incentive, Std = standard, MET = motivational enhancement therapy, P-TSF = peer twelve step facilitation, TAU = treatment as usual, AA = Alcoholics Anonymous.
[a] Study appears on Tables 3 and 4.

treatment (BFT) to promote continuing addiction treatment post-discharge were more likely to enter treatment than patients assigned to treatment-as-usual (O'Farrell, Murphy, Alter, & Fals-Stewart, 2008). (We have not included an earlier report with similar findings from the same project by O'Farrell, Murphy, Alter, and Fals-Stewart [2007].) The BFT intervention consisted of an in-person or phone meeting with the patient and a family member (spouse or parent) with whom the patient lived to review and recommend potential continuing care plans for the patient. Frydrych, Greene, Blondell, and Purdy (2009) found that detox inpatients reporting more mutual-help components (e.g., mutual-help group

Table 4
Summary of published studies on program and system factors associated with transitions to treatment or mutual-help groups after detoxification.

Author, year	Study design	*n* (F, M)	Detox setting	Outcome	Transition rate (%)	Transition predictors
Chutuape et al., 2001; [a]	RCT	166 (41, 125)	Inpatient USA	Outpatient treatment within 7 days	E + I 76 S + I 44 Std 24	E + I > S + I, Std
John et al., 2003; [a]	RCT	322 (90, 232)	Inpatient Germany	Mutual-help within 180 days	Group 25.5 Ind 13.7	Group (vs. individual) treatment component
Kahler et al., 2004	RCT	48 (11, 37)	Inpatient USA	% days of 12-step attendance, Mo. 6	BA M = 30.5 SD = 31.7 ME-12 M = 28.4, 38.2	ME-12 (vs. BA) among patients with less mutual-help group experience; BA (vs. ME-12) among patients with more experience
O'Farrell et al., 2008	RCT	45 (2, 43)	Inpatient USA	Treatment within 90 days	92 BFT 62 TAU	BFT (vs. TAU)
Frydrych et al., 2009; [a]	Prospective cohort	136 (43, 93)	Inpatient USA	Treatment or mutual-help within 7 days	77	Self-help treatment components
Blondell et al., 2011; [a]	RCT	150 (52, 98)	Inpatient USA	Inpatient treatment within 90 days	MET 61 P-TSF 31 TAU 45	MET (vs. P-TSF, TAU)
Manning et al., 2012; [a]	RCT	151 (49, 102)	Inpatient UK	12-step meeting within 90 days	PI 64.4 DI 47.6 NI 33.3	PI (vs. NI)
Vederhus et al., 2014	RCT	140 (46, 94)	Inpatient Norway	AAAS scores, Mo. 6	MI M = 2.5 BA M = 1.6	MI (vs. BA)

Notes: RCT = randomized controlled trial, F = female, M = male, USA = United States of America, UK = United Kingdom, AAAS = AA Affiliation Scale, E + I = escort plus incentive, S + I = standard plus incentive, Std = standard, Ind = individual, BA = brief advice, ME-12 = motivational enhancement for 12-step, BFT = brief family treatment, TAU = treatment as usual, MET = motivational enhancement therapy, P-TSF = peer-delivered twelve step facilitation, PI = peer intervention, DI = doctor intervention, NI = no intervention; MI = motivational intervention.
[a] Study appears on Tables 3 and 4.

literature, patients having phone numbers of mutual-help group members) were more likely to enter treatment or mutual-help groups within 7 days of detox discharge.

Another RCT assigned detox inpatients to individual counseling during detox or group counseling both during detox and post-discharge; extended counseling was associated with more mutual-help group participation at a 6-month, but not a 12-month, follow-up (John et al., 2003). An additional RCT that focused on mutual-help group attendance post-detox randomized inpatients to the referral method of Brief Advice (a 5-minute individual session stressing that the patient had a significant alcohol problem, the importance of abstinence, and the benefits of 12-step groups, with the provision of meeting schedules), or motivational enhancement (a 60-minute individual session, with a follow-up letter, providing normative feedback on alcohol use and its consequences, and focusing on increased commitment to abstinence and the benefits of 12-step groups, while also stressing the patient's responsibility for decisions; Kahler et al., 2004). There was no main effect for condition, but patients with less mutual-help group experience attended more meetings when they received motivational enhancement, whereas patients with more experience attended more meetings when they received brief advice. Consistently, a study of patients with little mutual-help group experience found the referral method of a motivational intervention to be associated with more AA affiliation than brief advice (Vederhus, Timko, Kristensen, Hjemdahl, & Clausen, 2014).

Also in an RCT, patients assigned to motivational enhancement therapy delivered by a treatment provider to promote behavior change were more likely to enter inpatient addiction treatment than patients assigned to peer-delivered twelve-step facilitation or usual care (Blondell et al., 2011); this study took place in the USA. In contrast, among detox inpatients in the UK, those assigned to a peer intervention were more likely to attend 12-step meetings post-discharge than those receiving usual care; and, patients receiving a physician intervention were no more likely to attend meetings than those receiving no intervention (Manning et al., 2012).

4. Discussion

This structured evidence review, summarizing 26 articles published between 1975 and 2014, found wide variability in the rates at which patients complete a detox episode (45% to 95%) and enter SUD treatment or mutual-help groups after detox (14% to 92%). Successfully completing a detox episode and transitioning to treatment or 12-step group participation represent the accomplishment of system and program goals that are important for patients' attaining and sustaining substance-free and productive lives (Knight, Logan, & Simpson, 2001; Simpson, Joe, Dansereau, & Chatham, 1997). This review identified program, system, and patient factors associated with detox completion and transition to SUD treatment to help clinical providers and managers of detox and SUD services implement procedures linked to patients' achieving better outcomes.

4.1. Detox completion

The seven studies examining program and system factors associated with alcohol detox completion were limited in terms of methodological quality (only one was an RCT, and only one used a prospective cohort design), and showed little consistency in specific factors examined (Table 2). Factors varied from practices that may be relatively feasible to implement across detox programs having different levels of resources (i.e., practices of having mainly one provider treat the patient, having inpatient programs of larger size) to those that may be out of reach for many programs (e.g., provision of inpatient rather than outpatient detox; provision of housing during outpatient detox). Several factors to which detox completion was attributed, requiring a moderate level of resources, involved the provision of standardized assessments and adjunct psychosocial counseling, such as motivational interviewing or stress and coping approaches, as well as the inclusion of recovery peers and family members.

Possibly, larger programs have more resources to offer clients, such as specialized staff and services, which may facilitate retention and completion (Campbell, Alexander, & Lemak, 2009). These resources may include the capability of having a single provider involved throughout the detox episode. Such continuity in care might enable more provider empathy, which, for addiction settings in particular, predicts increased retention and less alcohol consumption (Miller & Moyers, 2014; Moyers & Miller, 2014).

Larger detox programs may also be able to offer motivational interviewing, a client-centered, semi-directive therapeutic style to enhance intrinsic readiness for change by helping patients explore and resolve ambivalence toward change (Miller & Rollnick, 2002). Consistent with this review's finding that a motivational intervention was associated with detox completion (Soyka & Horak, 2004), research shows that even brief motivational conversations between a health care professional and an individual using substances are often effective and time-efficient for reducing alcohol intake and adverse consequences of alcohol use (Babor et al., 2007; Madras et al., 2009). It may be important to provide, during detox, counseling that encompasses education, support, and encouragement to stay, and addresses any barriers to staying, such as previous trauma. Furthermore, 12-step facilitation interventions, whereby patients with SUDs are linked to peers in recovery, are effective in improving substance-related outcomes (Kaskutas, Subbaraman, Witbrodt, & Zemore, 2009; Timko & DeBenedetti, 2007), although they have yet to be examined in relation to increasing detox completion rates.

Hayashida et al.'s (1989) finding from the only RCT in this subset of studies (Table 2), that inpatients were more likely than outpatients to complete detox, should be placed in the context that inpatient detox is one of the most expensive forms of addiction care in terms of cost per day (Haley et al., 2011). Thus clinically-supported shifts to outpatient detox should yield considerable cost savings (Stephens et al., 2014). Because inpatient programs allow patients to remain in residence, they may be more likely to provide the approaches associated with detox completion such as motivational, psychoeducational, and peer recovery components. The relative ease of scheduling inpatients for activities is likely one reason that the majority of studies in this review took place in inpatient settings. Studies are needed to determine how best to engage detox outpatients in the therapeutic activities that may be associated with completion of this phase of treatment if outpatient detox is to achieve both long-term cost savings and better substance use outcomes.

4.2. Program and system predictors of post-detox treatment or mutual-help

The 8 studies examining program or system factors associated with successful transitions from detox to SUD treatment or mutual-help group participation (Table 3) were of higher methodological quality than those examining detox completion (Table 2), in that all but one were RCTs. In addition, studies of successful transitions tended to be more recent (2001–2014) than studies of detox completion (1975–2011). Similarly, in a review of SUD continuing care interventions, McKay (2009) observed possible trends from older to newer studies in having better designed studies, better continuing care interventions, or both. The 8 studies on transitions also varied in terms of approach and resources needed to implement the approach. As seen in the studies of detox completion, motivational enhancement approaches, requiring moderate resources in terms of provider training and time, can be used to support patients as they transition into care post-detox (Blondell et al., 2011; Kahler et al., 2004; Vederhus et al., 2014). A more resource-intensive but efficacious approach to facilitating detox-treatment transitions was Chutuape et al.'s (2001) escort plus incentive condition. This intervention may not be feasible to implement routinely in many health care systems because of the requirement for staff resources, and

because the treatment program to be entered may be uncertain at the time of discharge, distant from the detox setting, or have a significant delay until the patient's first appointment (Carroll et al., 2009). However, small monetary rewards are associated with early treatment engagement, which in turn is associated with treatment retention and better outcomes (Villano, Rosenblum, Magura, & Fong, 2002), and thus should be considered as a method for improving post-detox transitions to SUD care.

John et al.'s (2003) RCT indicated the potential usefulness of monitoring patients' treatment and 12-step group utilization post-detox. It will be useful for researchers to identify low-resource methods to conduct such monitoring, such as via telephone contacts, and whether this task can be centralized (i.e., a dedicated staff member is assigned to monitoring treatment and 12-step group entry after patients' detox) or whether monitoring is effective only when the detox provider also monitors the desired transition. John et al.'s (2003) result, showing only a short-term benefit of initial monitoring, suggests the possible usefulness of extending low-intensity monitoring over time to promote utilization of 12-step groups and professional SUD treatment. In this regard, McKay et al. (2009) noted that evidence supports the effectiveness of extended monitoring of substance use and recovery-oriented behaviors, with durations of at least 1 year and preferably longer, and some form of objective data such as collateral reports, strongly recommended.

Future research should also pursue interventions to promote successful transitions to treatment or mutual-help groups that show promise but have not yet been firmly established as evidence-based practices, such as brief family therapy (O'Farrell et al., 2008) and physician or peer-delivered 12-step facilitation (Blondell et al., 2011; Manning et al., 2012). None of these interventions requires prohibitive program resources. Although the question remains of which patient subgroups, such as those with more or less mutual-help group experience, benefit more from physician- or peer-delivered approaches, neither approach requires intensive resource expenditures.

4.3. Patient predictors of detox completion and transition to care

Patient characteristics are indicative of personal needs and resources. Consistent with this review finding older age to be associated with detox completion (although only in studies using cohort or case-control designs), in SUD treatment programs, clients who were older were more likely to complete treatment (Brecht, Greenwell, & Anglin, 2005; Stack, Cortina, Samples, Zapata, & Arcand, 2000) and to be abstinent post-treatment (Heinrich & Fournier, 2004). Regarding clinical predictors, cohort and case-control studies in this review showed that patients with the primary substance of alcohol rather than opiates were more likely to complete their detox episode. As noted, withdrawal from alcohol that is not medically managed can lead to severe medical complications, whereas the opioid withdrawal syndrome, although potentially extremely uncomfortable, does not (Department of Veterans Affairs, 2009). These considerations may help to explain why higher proportions of patients complete alcohol detox.

4.4. Limitations

The major limitation of this study is that we relied on one database, PubMed, for the search of the literature. However, PubMed, a service of the US National Library of Medicine, provides access to MEDLINE, the NLM database of indexed citations and abstracts to medical, nursing, dental, health care, and preclinical sciences journal articles, and includes additional life sciences journals not in MEDLINE. We also selected only English-language articles, although there may be publications relevant to this review that are not in English. Future systematic reviews are needed to address the additional limitation that this study focused on alcohol detox to the exclusion of detox from other substances.

4.5. Conclusion

This structured evidence review suggests that a program factor, behavioral practices during alcohol detox, contributes to both detox completion and transitioning to SUD care after detox. These behavioral practices entail motivational- and psychoeducation-based approaches to counseling, and involving family and peers in the care process. Possibly, younger detox patients should be specially targeted for these practices to increase the chances of detox completion. We caution that the methodological quality of the body of research on transitioning to SUD care, and particularly on completing detox, needs improvement through the contribution of additional investigations using RCT designs. Nevertheless, this review's conclusions echo those within the larger health care transition literature, which suggests that it is critical to address potential barriers to accessing the next phase of care, such as lack of family or other social support and low motivation, during the present treatment episode, to help increase the likelihood of successful care transitions (Cucciare, Coleman, Saitz, & Timko, in press; Cucciare, Coleman, & Timko, 2014). Together, studies in this structured evidence review suggest that barriers can be overcome to improve detox and care transition processes and ultimately improve patient outcomes.

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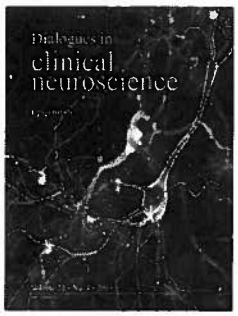

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Pharmacologic treatments for opioid dependence: detoxification and maintenance options

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Pharmacologic treatments for opioid dependence: detoxification and maintenance options

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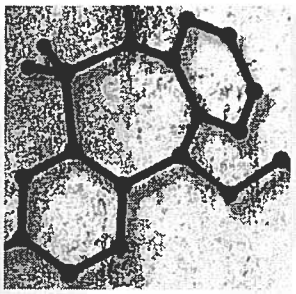

Detoxification

Although agonist maintenance therapies yield better outcomes for most opioid addicts,[1-3] they continue to seek opioid withdrawal primarily to lower the cost of their habit or as pretreatment before the residential therapeutic community or opioid antagonist maintenance. High relapse rates are probably less a function of withdrawal method and due more to reasons for seeking detoxifica-

While opioid dependence has more treatment agents available than other abused drugs, none are curative. They can, however, markedly diminish withdrawal symptoms and craving, and block opioid effects due to lapses.

The most effective withdrawal method is substituting and tapering methadone or buprenorphine. α-2 Adrenergic agents can ameliorate untreated symptoms or substitute for agonists if not available. Shortening withdrawal by precipitating it with narcotic antagonists has been studied, but the methods are plagued by safety issues or persisting symptoms. Neither the withdrawal agents nor the methods are associated with better long-term outcome, which appears mostly related to post-detoxification treatment.

Excluding those with short-term habits, the best outcome occurs with long-term maintenance on methadone or buprenorphine accompanied by appropriate psychosocial interventions. Those with strong external motivation may do well on the antagonist naltrexone. Currently, optimum duration of maintenance on either is unclear. Better agents are needed to impact the brain changes related to addiction.

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tion, postwithdrawal treatment, or brain changes developed during dependence. Those who complete detoxification tend to have longer times to relapse than dropouts.[4,5]

Clinical issues

Symptom severity is related to the specific narcotic used (short-acting yields more severe withdrawal); amount used; duration of use (at least 2 to 3 weeks, daily); and set and setting factors. Withdrawal phenomena are generally the opposite of acute agonist effects. Withdrawal from heroin begins with anxiety and craving 8 to 12 hours after the last dose, reaches its peak between 36 and 72 hours, and subsides substantially within 5 days. Methadone withdrawal begins at 24 to 36 hours, peaks at 96 to 144 hours, and may last for weeks. Individuals differ markedly, both as to which symptoms are present and their severity.[6] Acute opioid withdrawal symptoms are followed by a protracted abstinence syndrome, including dysphoria, fatigue, insomnia and irritability, for 6 to 8 months.[7]

Withdrawal agents

Methadone

Methadone is orally effective, long-acting—thus producing smoother withdrawal—and safe, if care is taken with initial dosing.

Because 40 mg of methadone has been a fatal dose in some nontolerant individuals, the initial dose should be less, eg, 10 to 20 mg. If withdrawal symptoms are not suppressed within 1 hour, more can be given, but in general the initial dose should not exceed 30 mg, and the total 24-hour dose should not exceed 40 mg the first few days. In a *nontolerant* individual, an initial tolerated dose can become risky if continued beyond 2 days because of rising methadone blood levels.[8] The clinician should be alert for signs of drowsiness or motor impairment.

Physical dependence can be ascertained by: (i) waiting until the patient develops withdrawal signs and symptoms; or (ii) precipitating withdrawal via naloxone (if pregnancy has been ruled out).

After the patient is stabilized, the dosage is gradually reduced, either by decreasing the methadone 5 mg/day until zero dosage is reached, or decreasing 10 mg/day until 10 mg is reached and then by 2 mg/day.[9]

Inpatient methadone substitution and taper is usually accomplished in 5 to 7 days, and has a retention rate of 80%; with outpatient detoxification it takes longer to minimize withdrawal symptoms and to decrease dropout and relapse, but only about 20% complete it.[10] Lingering protracted withdrawal symptoms can be helped by clonidine.

Buprenorphine

The Food and Drug administration (FDA) approved sublingual buprenorphine in 2002 for office-based treatment for detoxification or maintenance of opioid dependence. Buprenorphine is long-acting, safe, and effective by the sublingual route, but may precipitate withdrawal symptoms if given too soon after an opioid agonist. If the patient has withdrawal symptoms and has waited at least 12 hours after short-acting opioids and 36 hours after methadone, buprenorphine usually serves to relieve these symptoms and is less likely to precipitate withdrawal. It may also be useful in emergency department settings.[11]

Heroin detoxification is managed by administering buprenorphine 2 to 4 mg sublingually after the emergence of mild-to-moderate withdrawal. A second dose of buprenorphine 2 to 4 mg may be administered approximately 1 to 2 hours later, depending on the patient's comfort level. Usually a total of 8 to 12 mg of buprenorphine is sufficient the first day. For most patients, a slow taper over a week or so is a safe and well tolerated strategy. Any buprenorphine dose that worsens withdrawal symptoms suggests the buprenorphine dose is too high compared with the level of withdrawal. The symptoms should be treated with clonidine, and further buprenorphine doses withheld for at least 6 to 8 hours. Buprenorphine, even at doses of 16 mg, may not suppress all signs and symptoms of withdrawal if the patient had a very severe habit,[12] but most symptoms respond to adding clonidine 0.1 mg every 4 to 6 hours.

The duration of withdrawal from abrupt buprenorphine cessation is variable even from patient to patient. In one study, about one fifth of the patients maintained on daily buprenorphine 16 mg sublingually for 10 days experienced significant withdrawal symptoms after abrupt stopping.[13] Buprenorphine can be used to transfer patients from methadone maintenance to buprenorphine maintenance or to a drug-free state. The patient needs to be at least in mild withdrawal, and the methadone dose 40 mg or less for at least a week prior to beginning buprenorphine.[14]

Another way of using buprenorphine is for rapid withdrawal. A randomized study in heroin addicts[15] compared

anesthesia-assisted with buprenorphine-assisted detoxification, followed by antagonist induction. The buprenorphine group received a single dose of 8 mg on day 0, none on day 1, and naltrexone on day 2 at 12.5 mg, titrated up to 50 mg/day over 2 days. Symptom severity and retention at 1 month were similar in both groups. Another study also found that prior buprenorphine preparation markedly decreased post procedure morbidity.[16]

A recent systematic review compared buprenorphine to other detoxification strategies.[17] Compared with clonidine, buprenorphine was found to be more effective in ameliorating withdrawal symptoms; patients stayed in treatment longer, especially in outpatient settings, and were more likely to complete withdrawal. When compared with methadone-aided withdrawal, buprenorphine produced no significant difference in treatment completion, or severity of withdrawal, but withdrawal symptoms resolved more quickly.

Other detoxification agents and methods

Clonidine

The antihypertensive, α_2-adrenergic agonist drug clonidine has been used to facilitate opioid withdrawal in both inpatient and outpatient settings for over 25 years.[18-21] It works by binding to α_2 autoreceptors in the locus coeruleus and suppressing its hyperactivity during withdrawal. Doses of 0.4 to 1.2 mg/day or higher reduce many of the autonomic components of the opioid withdrawal syndrome, but symptoms such as insomnia, lethargy, muscle aches, and restlessness may not be adequately handled.[22]

Compared with methadone-aided withdrawal, clonidine has more side effects, especially hypotension, but is less likely to lead to post-withdrawal rebound. Dropouts are more likely to occur early with clonidine and later with methadone. In a study of heroin detoxification, buprenorphine did better on retention, heroin use, and withdrawal severity than the clonidine group.[12] Since clonidine has mild analgesic effects, added analgesia may not be needed during the withdrawal period for medical opioid addicts.

Lofexidine

Hypotensive effects may limit the optimal dosing of clonidine for opioid withdrawal. Lofexidine, an analogue of clonidine, has been approved in the UK and may be as effective as clonidine for opioid withdrawal with less hypotension and sedation.[23,24] Combining lofexidine with low-dose naloxone appears to improve retention symptoms and time to relapse.[4,25-28]

Supportive measures

Insomnia is both common and debilitating. Clonazepam, trazodone, and zolpidem have all been used for withdrawal-related insomnia, but the decision to use a benzodiazepine needs to be made carefully, especially for outpatient detoxification.

Treatments for ancillary withdrawal symptoms include nonsteroidal anti-inflammatory drugs (eg, ibuprofen or ketorolac tromethamine) for muscle cramps or pain; bismuth subsalicylate for diarrhea; prochlorperazine or ondansetron for nausea and vomiting; and α_2-adrenergic agents (eg, clonidine) for flu-like symptoms. Vitamin and mineral supplements are often given.

Rapid detoxification methods

Clonidine-naltrexone detoxification

This method[29-31] combines a rapid, precipitated withdrawal by naltrexone producing severe withdrawal symptoms, with high doses of clonidine and benzodiazepines before and after the naltrexone to ameliorate the symptoms. While shortening withdrawal to 2 to 3 days, evidence is lacking of longer abstinence or naltrexone retention.[32]

Rapid opioid withdrawal under general anesthesia

To decrease further the time needed for withdrawal, a rapid detoxification procedure using general anesthesia was developed[33] and gradually improved.[34-37] A variety of medications have been used, including naltrexone or nalmefene, propofol anesthesia or heavy midazolam sedation, the antiemetic ondansetron, the antidiarrheal octreotide, and clonidine and benzodiazepines for other withdrawal symptoms, and has been carried out on either an inpatient or outpatient basis. Post-procedure therapy varies widely. Claims of high rates of abstinence months after detoxification have been made, but no objective verification exists, and the samples are not representative.[38] Significant withdrawal symptoms may persist for days or even weeks after the procedure in humans[15,39,40] or in rats,[41] and there appears to be no longer-term improved outcome at 1 to 3 months

later.[15,42,43] Internationally, over one dozen deaths have been reported, usually within 72 hours of the procedure, with pulmonary edema a common complication.[44-47]

Pregnancy

Illicit opioid use during pregnancy can have numerous harmful effects on the woman, fetus, and neonate. Residential abstinent treatment is usually not available. Methadone maintenance is thus the standard approach.[48] While the infant will be physically dependent on methadone and about half need to be withdrawn, no birth defects are associated with such exposure, if prenatal care is adequate. Withdrawal from methadone maintenance is usually not preferable, but if carried out it should occur during the second trimester at no greater than 5 mg/week. Methadone metabolism is increased during pregnancy, and plasma half-life decreased. The clinician must balance the risk of illicit opioid use if the dose is too low, and the risks of the neonatal abstinence syndrome (NAS) if the dose is too high. This can be somewhat ameliorated by split dosing. Studies of pregnant methadone-maintained women found decreased narcotic use and improved health and prenatal care. Fetal growth and perinatal outcomes also improved. These benefits diminish with continued use/abuse of licit (alcohol and tobacco) or illicit (cocaine and marijuana) substances.[49]
Maintenance on buprenorphine is a more recent development with published reports of over 300 pregnancies, with good fetal outcomes. Buprenorphine appears comparable to methadone on outcome measures as assessed by NAS and maternal and neonatal safety.[50-54] One study[52] reported shorter hospital stays for babies born to buprenorphine-maintained mothers in comparison to methadone. Long-term effects beyond the neonatal period, however, are not sufficiently studied.

Agonist maintenance: methadone

Pioneering work by Dole and Nyswander in the 1960s[55-57] provided the initial scientific basis for using the long-acting opioid agonist methadone for maintenance. Numerous studies since then[58-62] have demonstrated that methadone maintenance of opioid addicts substantially reduces mortality and morbidity, the risk of new human immunodeficiency virus (HIV) infection, criminal activity, and illicit opioid use, especially when used with enhanced ancillary services.[63] Unfortunately, many programs do not provide these services, both because of decreased government funding and increased private ownership. In the US, there are over 240 000 individuals maintained on methadone, while in some other countries, eg, Russia, government opposition to agonist maintenance prevents its use, even when high HIV rates exist.

Federal regulations

With a few exceptions, methadone may only be dispensed for opioid detoxification or maintenance treatment by opioid treatment programs certified by the Substance Abuse and Mental Health Administration (SAMHSA) and approved by the appropriate state agency. Depending on criteria such as continued illicit drug use and employment, an increasing number of take-home doses is permitted, up to a maximum of a 1-month supply after 2 years or longer.

Pharmacology

While heroin is short-acting and relatively ineffective orally, methadone is a long-acting, and orally effective, opioid. It is excreted primarily in the urine and is an agonist at μ and δ opiate receptors.
Methadone is primarily metabolized through cytochrome P450 (CYP) enzymes, predominantly involving the CYP3A4 pathway. Drugs that increase the P450 enzymes, such as the retroviral agents for treating HIV, may increase methadone metabolism and lead to withdrawal symptoms, even in stable maintained patients. In contrast, drugs that inhibit these enzymes, such as some selective serotonin reuptake inhibitor (SSRI) antidepressants, may increase methadone levels and sedation.[64-68] Effects are more likely early in treatment before plasma levels have stabilized.[69] Physicians using methadone are advised to consult tables of drug interactions for complete listings.

Dosing

Methadone's plasma half-life, once stabilized, averages 24 to 36 hours[70] with a range of 13 to 50 hours, making it a useful once-daily maintenance medication compared with morphine or heroin. However, up to 10 days may be needed for such a steady state and before that, new patients, either in maintenance or given methadone for analgesia, are at risk of fatal overdose.[8,71] Doses should not exceed 40 mg/day the first day of dosing or be

increased over the next 2 weeks by more than 5 to 10 mg every 2 to 3 days. Individual differences in rate of metabolism may produce complaints of withdrawal symptoms, even in those on a stable dose.

Doses of 30 to 40 mg of methadone prevent most withdrawal symptoms and craving, but are not high enough to block the reinforcing effects of high doses of potent heroin. Doses of greater than 80 mg/day are associated with fewer positive urine tests than 40 mg, and programs with average doses of 80 to 120 mg have consistently better results than those with lower average doses.[72-75] As heroin potency increased, the average daily dose of methadone doubled in the 1990s.[76] Some programs today dose as high as 350 mg/day using the rationale of individual metabolic differences. Such doses have at times been associated with increased street sales.

Safety

Studies of methadone maintenance have not found long-term damage to the heart, kidneys, liver, or lungs.[77-79] Further, long-acting maintenance medications normalize the neuroendocrine alterations induced by short-acting opioids and with minimal psychoactive impairment,[80] unless accompanied by high concomitant use of benzodiazepines and alcohol found in many methadone programs. The most common side effects of methadone maintenance are constipation, sweating, urinary retention, and dose-related orgasm dysfunction in men.

Methadone overdose has been a problem with accidental ingestion by children (10 mg has been a fatal dose), use by nondependent opioid users experimenting with methadone, or during initiation of maintenance. While rapid treatment of overdose with narcotic antagonists can lead to full recovery, it is important to keep such individuals under observation for at least 24 hours and follow the initial naloxone treatment with a long-acting antagonist such as nalmefene. Death may occur even 24 hours or more after the methadone intake. Other factors associated with increased risk of overdose include medications that inhibit CYP3A4, use of alcohol or benzodiazepines, or liver disease. The possibility of cardiac conduction defects with methadone, especially at doses higher than 120 mg/day,[81] led to a black-box warning for methadone in December 2006.

Driving by patients on long-term methadone maintenance has not been found to be impaired,[82] but patients should be warned about driving after using alcohol, illicit drugs, or sedating medications. As with patients withdrawing from alcohol, patients beginning methadone maintenance may have some short-term cognitive impairment early in treatment.[83]

Nonpharmacologic components

Methadone is a medication, not a treatment. To achieve its potential, methadone maintenance should be combined with counseling aimed at lifestyle change. A classic study[63] demonstrated this by randomly assigning patients to minimal counseling, standard drug counseling, or enhanced services while maintaining them on identical standard daily methadone doses. Patients in the minimal counseling group had substantially higher illicit cocaine and opioid use than the other 2 groups. By 12 weeks, 69% of the patients in the minimal counseling group had 8 consecutive weeks of illicit opiate or cocaine use or three emergency situations compared with 41% of those receiving standard counseling and 19% of those receiving enhanced services. Recently a number of behavioral approaches, eg, contingency contracting and voucher incentives, have also shown efficacy, especially if staff is appropriately trained.[84]

While appropriate therapy is better than no therapy, some randomized studies have suggested that methadone alone is better than being on a waiting list.[85,86] Such methadone maintenance is permitted for up to 120 days in areas with long waiting lists.

Co-occurring disorders

There is high prevalence of comorbid psychiatric and substance abuse disorders among opioid addicts, as well as diseases common because of drug lifestyle, eg, acquired immune deficiency syndrome (AIDS), hepatitis B or C, and tuberculosis.[87] Since treatments for HIV and hepatitis C can stabilize these disorders, methadone programs need to screen and refer patients for medical treatment, as well as providing or referring for psychiatric disorders if patients are to adequately recover.

Pain

Over one third of methadone maintenance patients are estimated to have moderate-to-severe chronic pain. They have become tolerant to methadone's analgesic properties and may even have increased pain sensitivity.[88]

Pharmacological aspects

Treating methadone-maintained patients for acute pain with opioid analgesics has not been found to lead to relapse or higher methadone doses post-treatment.[89] The regular, daily methadone dose should be continued, and analgesic medications including nonopioid analgesics or short-acting opioids added as clinically indicated.[90,91] Since methadone occupies less than one third of the μ opioid receptors, unoccupied receptors are available for analgesic response.[92] However, methadone-maintained patients might require higher doses or more frequent administration of opioid analgesics than nonmaintained patients.

Office-based methadone maintenance treatment

Office-based methadone maintenance has been permitted on a limited basis for patients who have been stable for at least a few years. In general, patients on this "medical maintenance" have been successful[93,94] but a number increased their use of illicit drugs.[95-98] While the number of patients on methadone maintenance has increased to 240 000, there remain many parts of the country with inadequate availability and long waiting lists.

Discontinuation of methadone maintenance

How long patients should remain on methadone maintenance is controversial. Those on methadone do better than those who stop, with relapse common in this latter group. Methadone maintenance's contributions to improved health and functioning may increase slowly over time, but markedly decreases when methadone is discontinued. The risk of relapse following withdrawal from methadone maintenance is high, even for patients who have been on it for long periods and have made substantial changes in lifestyle. In this era of AIDS, the risk of serious adverse consequences following relapse suggest that for many patients lifetime maintenance may be necessary.[99-101]
There is substantial political opposition to methadone maintenance, which manifests itself in problems locating clinic sites, lack of economic support, and family opposition. The clinic–based nature of the programs, which mix stable patients and newly maintained patients, along with inadequate staffing, and minimal incentives for patient change, can lead to a culture of continued illicit drug use and chronic unemployment.[94] In spite of many decades of improving and saving lives, methadone maintenance is often viewed as perpetuating addiction or being immoral. The traditional method of withdrawal is decreasing the methadone dose rapidly until 30 mg is reached, and then slowly tapering from that, eg 5 mg/week or switching to clonidine.[102,103] A more recent approach involves transferring the patient to buprenorphine/naloxone and then tapering as described in the section on discontinuing buprenorphine.[103]

Partial agonist maintenance

Buprenorphine

Buprenorphine, a Schedule III controlled substance, is a high affinity partial μ-opioid agonist, κ antagonist, and ORL-1 receptor agonist.[104] Studies from 1980 on found it useful for treating opioid withdrawal and dependence.[105-109] Office-based buprenorphine maintenance has already increased treatment availability for opioid-dependent individuals and brought into treatment populations that had been unable or unwilling to attend methadone maintenance clinics, eg, prescription opioid addicts. Prescription opioid addicts seeking office-based buprenorphine are likely to present different issues than heroin addicts applying for methadone maintenance.[110] Primary-care physicians who have not treated opioid dependence will also present new challenges to the field. Anecdotal reports describe patients on buprenorphine as feeling more clear-headed, more energetic, and more aware of emotions than on methadone maintenance.[111] To diminish possible diversion to parenteral use, the recommended form of buprenorphine is a 4:1 combination with naloxone (Suboxone). The mono form (Subutex) is used for pregnant women and, at times, for induction.

Federal regulations

In 2002, the FDA approved buprenorphine for the treatment of opioid dependence in office-based practice. It was already being used for such treatment in other countries. Physicians need to receive 8 hours of specialized training in person or online, and then apply for a waiver from the Department of Health and Human Services. They are limited to 30 patients on buprenorphine for the first year, and can then apply to increase the number to 100.

Pharmacology

Buprenorphine binds to the μ receptor and activates it, but as the dose increases, there is a ceiling on some opi-

oid agonist effects, such as respiratory depression, making it safer than a full agonist as far as overdose. This has been demonstrated by the differential effects on overdose deaths in France of methadone and buprenorphine.[112] The ceiling effect is approximately 32 mg of sublingual buprenorphine, but it may be possible to increase analgesic effects above that.

Because buprenorphine is best absorbed parenterally and poorest orally,[113-115] with sublingual bioavailability in between, and naloxone is poorly absorbed orally but about 20 times more parenterally, the sublingual combination tablet yields primarily a buprenorphine effect. If crushed and injected, both drugs are bioavailable.[114,115] Naloxone will then precipitate opioid withdrawal if the individual is opioid-dependent, unless only on buprenorphine. Buprenorphine alone will also precipitate withdrawal by displacing other opiates from the receptor. Individuals who use *only* buprenorphine can get high even if they inject the combination product, but it is not as reinforcing.[116]

There have been a number of reports of buprenorphine abuse in some countries, including France,[117] Finland,[118] Great Britain,[119] and Australia.[120] Only Finland has, since 2004, the combination product. A recent study from Finland found a very high rate of buprenorphine intravenous (IV) use but 75% of such users said they were using it to self-medicate addiction or withdrawal. Over two thirds had tried the combination IV but 80% said they had a "bad experience." As a result, the street price of the combination was less than half of the mono product.[121]

Buprenorphine undergoes metabolism by the liver, primarily by the cytochrome P450 3A4 enzyme system[122,123] but studies have not found clinically significant interactions with HIV medications that interact with this system,[124] with the possible exception of atazanavir/retonavir.[125] Buprenorphine's terminal half-life of 37 hours and slow-onset and offset enables every-other-day dosing, although that tends not to be the preferred spacing by patients. Buprenorphine's high affinity at the μ receptor means it will block most opioid agonist effects,[126,127] but because of its ceiling effect, one can override the blockade by using higher agonist doses.[128,129]

Induction

For practical reasons, buprenorphine induction is usually done on an outpatient basis, with induction divided into two visits: initial evaluation for suitability, answering questions and giving instructions for the second visit; and actual induction. Induction may take 2 hours or longer, and patients should not drive that first day. When distance or other factors prevent two visits, careful telephone preparation is important.

Buprenorphine can displace a full opioid agonist from the μ receptor, but since it is only a partial agonist there could be precipitated opioid withdrawal. At induction, therefore, the addicted patient should be in withdrawal: off short-acting opioids for at least 12 to 16 hours and long-acting ones for at least 36 hours. When the patient is transferring from methadone maintenance, the program needs to verify the methadone dose as 40 mg or less and history of compliance with rules, especially drug use.

While 4 mg of buprenorphine is often used as the initial dose,[103] if there is doubt about the patient's withdrawal symptoms, the buprenorphine dose should be lowered to 2 mg. If the initial dose of 2 or 4 mg is tolerated, a similar second dose can be given an hour later and then 4 mg 6 to 8 hours later. The total dose on day 1 usually should not exceed 8 to 12 mg. If any dose *worsens* withdrawal symptoms, the buprenorphine should be temporarily halted and the symptoms treated with oral clonidine 0.1-0.2 mg. Once symptoms have improved, the buprenorphine can be restarted. *It is better to err on the side of incomplete suppression of withdrawal on day 1 than to have precipitated withdrawal, which may drive the patient away.*

By day 2 or 3, a dose of 12 to 16 mg is usually reached and resolves most withdrawal symptoms. Clonidine can be used to treat residual mild symptoms for a few days to a week as long as the patient does not become hypotensive. The most difficult and distressing symptom is usually insomnia. Depending whether there is a history of benzodiazepine abuse, agents chosen to treat this include trazodone, zolpidem, or clonazepam.

The usual maintenance dose is 16 to 24 mg/day although some patients are comfortable at 8 to 12 mg and others need 24 to 32 mg. Many patients prefer taking the buprenorphine in divided doses, two or three times a day, as opposed to only once.

Patient selection issues

The patient first needs to meet the criteria for opioid dependence. Abuse of, or dependence on, other sub-

stances such as alcohol, benzodiazepines, and cocaine, along with need for sedative detoxification, history of previous treatments, and psychiatric problems should all be explored.

Detoxification or maintenance

Many patients initially request buprenorphine detoxification and then change their minds a few weeks later and request maintenance. Given the high relapse rate post-withdrawal, this request may be reasonable. However, buprenorphine is relatively easy to detoxify *with* but harder to detoxify *from*. Thus, withdrawal should not be stretched out longer than 2 to 3 weeks if maintenance is not the ultimate goal.

Maintenance on buprenorphine vs methadone

If the patient's lifestyle is unstable, eg, homelessness, or needs the structure of regular attendance in a dispensing situation, or needs the wider range of services available in a comprehensive methadone maintenance program, or lacks the insurance or financial wherewithal to pay for buprenorphine medication and therapy, the patient may be better served by a methadone maintenance program. Since buprenorphine is a partial μ agonist with maximal efficacy approximately equal to 70 mg of methadone, it may not be adequate for some patients. Optimal methadone doses average around 100 mg/day and some patients require much higher doses.[129] A meta-analysis[130] found that both methadone and buprenorphine maintenance could be equally effective, but there was a wide variation in the studies covered. A way around this dilemma is to use a stepped approach whereby patients would be started on buprenorphine and increased as necessary up to 32 mg/day. If clinical results are inadequate, the patient would be moved to methadone maintenance and dosed as needed.[131] For patients who clearly need the structure of a methadone program, but prefer buprenorphine, it could be dispensed by a methadone program using the same rules as methadone.

Use of buprenorphine vs the buprenorphine/naloxone combination

It is preferable to maintain patients on the combination product unless they are pregnant or trying to become so. Many clinicians prefer the mono form for the initial induction, either because of concern for possible pregnancy or so that they do not need to worry about whether unrelieved withdrawal symptoms are due to increased amounts of naloxone being absorbed. The patient should be switched to the combination form once stable.

Age

While buprenorphine withdrawal or maintenance is legal above the age of 16, short-term dependence may be better handled by withdrawal and intensive counseling.

Other laboratory tests

In addition to testing for drugs of abuse, patients should be evaluated at baseline by the usual medical screening tests, as well as pregnancy, when appropriate, and tests for hepatitis B, C, HIV, and tuberculosis. Baseline tests can be carried out by the patient's own physician or ordered by the prescribing doctor.

Use of other drugs

The safety of buprenorphine on respiratory depression can be thwarted by concomitant use of benzodiazepines or other sedatives, especially when both the buprenorphine and the benzodiazepines are injected. A number of deaths have been reported from France due to this.[112,132] Low-dose oral benzodiazepines used judiciously do not appear to present the same problem.

The effect of buprenorphine maintenance on cocaine use in opiate addicts remains unclear. Some clinical studies have demonstrated efficacy in reducing cocaine use[133,134] while others have been inconclusive[135] or negative.[136]

Maintenance

Counseling

Buprenorphine and methadone are medications, not treatments, and should be combined with appropriate counseling services. The prescriber does not have to provide the counseling but convenient access will enhance compliance. Counseling can be individual, group or family therapy, or combinations. However, therapists have reported that many patients feel so well on buprenorphine compared with either methadone or their previous illicit drug use that they resist counseling.[111]

Urine testing

Drug testing, via "dipsticks" or commercial laboratories, can detect use of illicit opioids, cocaine, or benzodiazepines. The testing strips are easily used in the office but the standard opiate strips usually do not test for buprenorphine, methadone, hydrocodone, or oxycodone, so specific tests for these drugs are necessary to avoid false-negative results.[103] The test frequency and whether it is scheduled or random is a function of the physician's judgment in each case.

Maintenance

Once symptoms of opiate withdrawal and use of other opioids has been significantly decreased or eliminated, the maintenance phase begins. Dose increases may occur either because the patient is continuing illicit opioid use while apparently complying with the buprenorphine (monitored dosing may be necessary), or because the patient complains that the dose is not sufficient. Changing the frequency or scheduling of the buprenorphine doses may improve the latter. Although buprenorphine has a long half-life, some patients report better results by dosing 3 times/day, eg, 8 mg AM, PM, and late evening. The final dose is usually 8 to 24 mg/day[103] but some patients appear to need 32 mg. If illicit opioid use continues in spite of high buprenorphine doses and therapy, referral for methadone maintenance or depot naltrexone may be necessary. Before that final step, it may be worthwhile to try contingency contracting using frequency of visits or weeks prescribed as the reward.[137] Psychiatric problems can be common (over 50% in one unsolicited sample).[138] Appropriate medications or other approaches might markedly reduce the illicit drug use and make transferring unnecessary.
Office visits once a week are usually recommended initially[103] and can be reduced if the dose is stable, illicit drug use has stopped, and more intense psychological intervention is not needed. However, there may be practical obstacles to this, such as distance from the physician or problems paying for the medication and doctor's visit if not adequately covered by insurance. Frequency can be reduced gradually with stable patients to once monthly.

Side effects

Buprenorphine does not appear to cause liver abnormalities but, as with other narcotics, side effects such as constipation, nausea, and decreased sexual interest have been reported.[139] Unlike methadone, buprenorphine maintenance does not appear to be associated with electrocardiographic abnormalities.[140] Buprenorphine's desirable mood effects compared with methadone[111] may relate to methadone's producing a significant opioid effect lasting from 2 to 5 hours after dosing in maintained patients.[141,142] This may interfere with everyday activities.

Other issues

Acute pain

Acute pain is more difficult to manage with buprenorphine compared with a full agonist, but there are a number of options. These include dividing the daily buprenorphine dose into 3 or 4 doses and adding nonopioid analgesics; adding a full μ opioid analgesic on top of the buprenorphine dose; switching the patient temporarily over to a short-acting full μ agonist and increasing the dose until adequate pain relief occurs; or using nonopioid ways of dealing with pain such as regional or general anesthesia in a hospital setting.[90,91,143]

Chronic pain

Many patients with chronic pain can be treated with buprenorphine doses of 24 to 32 mg divided into 3 or 4 daily doses and supplemented if necessary by nonopioid analgesics. If pain relief is not sufficient, or the patient is resorting to illicit opioid use to control it, transfer to methadone maintenance may be needed.

Discontinuation of buprenorphine maintenance

While there is no legal limit to the length of buprenorphine maintenance, many patients ask to be withdrawn a few months after being maintained. The usual reasons are desire to be off all narcotics or the cost. Patients often have an unrealistic expectation of how easy it will be to remain abstinent[144,145] and many (perhaps most) will relapse within a short period.
Patients should be encouraged to remain on maintenance and, when possible, alternative solutions sought for issues like cost, eg, reducing frequency of visits, or exploring insurance options. There is no adequate data on the optimal length of time; each patient must be judged indi-

vidually using issues such as previous relapses, addiction history, and lifestyle stability. It is not uncommon to need a number of episodes of opioid maintenance or even long-term maintenance.

There is no consensus on the best way to withdraw from buprenorphine maintenance other than to do it gradually, eg, 2 mg/week until 4 mg is reached and then 1 mg decreased every other week or monthly. Clonidine may be useful in the final weeks to deal with the withdrawal symptoms. Relapse back to illicit opioid use should be taken seriously and the dose raised until the use stops. Continued use should probably be handled by resuming full-scale maintenance. As yet, there are no adequate controlled studies comparing the ease or severity of withdrawal from maintained buprenorphine vs methadone patients, although earlier studies suggested that buprenorphine withdrawal might be better tolerated.[146,147]

Once the patient has completed detoxification, use of naltrexone for at least 3 months may help prevent relapse. The 1-month depot naltrexone is preferable, but may be too expensive unless covered by insurance.

Naltrexone

Naltrexone was approved by the FDA as an opioid antagonist in 1984. It is effective orally and is long-acting, depending upon dose. While methadone blocks heroin effects by cross-tolerance, naltrexone blocks the effects by competitive antagonism at the μ receptor. The degree of blockade is a function of the concentrations of agonist to antagonist, and their receptor affinity.

Because of the blocking action of naltrexone, self-administration of opioids at usual doses produces no euphoria so that either individuals cease heroin use or cease taking the naltrexone.[148] Its long duration of action means that naltrexone can be given two or three times per week, but daily administration is usually preferred, both because of developing a regular habit of use and of creating a higher blockade. Less frequent administration is usually employed when an individual is taking monitored doses. Tolerance does not develop to the opioid antagonism, even after almost 2 years of regular use.[149] The FDA approved a 1-month acting depot preparation of naltrexone in 2006 for the treatment of alcoholism,[150] but it can be used off-label for treatment of opioid dependence.[151]

Dropout rates with naltrexone are high, but are significantly better where there is substantial external motivation, such as in physicians whose performance is being impaired, those involved with the criminal justice system, and those facing loss of an important job.[152-156] Retention is also better (43% at 6 months) in Russia, where addicts are often young adults living with parents who monitor intake and no agonist maintenance is permitted.[157]

Clinical aspects

If naltrexone is given to an opioid-dependent individual, it displaces the drugs from the receptor, producing rapid, unpleasant withdrawal. To avoid this, 5 to 7 days after the last use of a short-acting opioid or 7 to 10 days after the last dose of methadone is necessary before naltrexone induction. Using one of the rapid withdrawal methods described earlier can shorten the waiting period. Mild symptoms of precipitated withdrawal can usually be treated with clonidine and clonazepam. If sufficient abstinence is unclear, a test dose of a small amount of IM naloxone (eg, 0.2 mg) can be used.[157-159] Any withdrawal produced will be short-lived. Naltrexone should be initiated with a dose of 25 mg and, if that produces no withdrawal, the second 25-mg dose can be given 1 hour later. If depot naltrexone is to be used, it is useful to have 1 to 2 days of a well-tolerated 50 mg oral dose.

For oral naltrexone, virtually 100% adherence is needed because the blockade wears off around 24 to 48 hours after the last dose. Missed doses often eventuate in relapse, after which another detoxification and naltrexone induction is needed. Behavioral treatments have been found to be helpful in improving naltrexone adherence and treatment retention, doubling retention rates at 12 to 24 weeks. Approaches have included voucher incentives contingent on pill-taking adherence and involvement of family in monitoring such adherence.[160-165]

When possible, all doses should be monitored either by a family member or a health professional. Three times per week dosing (100 mg, 100 mg, 150 mg) may be useful if daily monitoring is difficult to arrange. Individuals doing monitoring should be trained to look for "cheeking" and other ways to avoid ingestion. Involvement in self-help groups such as Alcoholics Anonymous or (AA) or Narcotics anonymous (NA) should be encouraged. While such groups usually oppose agonist maintenance, naltrexone is often tolerated because of its lack of psychoactive effects. Urine tests should be carried out, if possible on a random basis, to see if the individual is using opioids, suggesting missing naltrexone doses, or has switched to drugs such as cocaine or benzodiazepines.

Side effects

Nausea, headache, and dysphoria have been reported, especially during the first 4 weeks of naltrexone administration. These symptoms resemble mild protracted opioid withdrawal and usually go away on their own or can be ameliorated by clonidine. Elevated liver enzymes, especially transaminases, were noted decades ago in patients given high doses (eg, 300 mg/day) as experimental obesity treatment. They reversed when the drug was halted, as they have when occasionally observed in patients taking normal doses.[166] If the enzymes are not reduced, brief hospitalization to stop excess alcohol intake or tests for such excessive drinking can be diagnostic.[167,168] Patients should be evaluated for viral hepatitis, which is very common among former IV users. Because of the possibility of hepatic effects, baseline liver function tests should be carried out. If abnormal (greater than 3 to 5 times normal), naltrexone should not be started. Monthly lab retests for the first 3 months can be a useful precaution.

Although naltrexone affects a variety of endocrine functions,[169-172] such effects have not been associated with particular problems. Likewise, although upregulation of opioid receptors has been reported in rodents, it was not found in a human study. Thus, the main risk of heroin overdose post naltrexone appears to be from loss of tolerance.[148]

Treatment of pain

When patients on naltrexone need analgesia, such as after surgery or in emergency situations, nonsteroidal anti-inflammatory drugs (NSAIDs, eg, Ketorolac) should be tried. If not adequate, the blockade can be surmounted by large doses of full agonists but this should only be done in an environment where emergency ventilation is available as in a hospital or emergency room because of the danger of overdose.

Duration of maintenance

There are no clear guidelines on the duration of naltrexone maintenance although, in general, 6 to 12 months are probably a minimum depending on the circumstances. Careful clinical evaluation of relapse risk should be done prior to the decision to discontinue naltrexone. The 30-day depot injection may improve compliance. Because naltrexone is an antagonist, it can be stopped abruptly without withdrawal symptoms. The high dropout rates and patient preference for agonist treatments will probably continue to keep antagonists in a secondary role and in select populations unless agonist maintenance is not available.[173,174]

Conclusion

Compared with other drugs of abuse, opioid dependence benefits from a wider range of available pharmacological tools for treatment. In spite of this, the large majority of the 1 million heroin addicts and 2 to 3 million prescription opioid abusers are not receiving treatment, and those who enter often only seek detoxification, from which early relapse is the most common outcome. The most successful treatment is long-term maintenance on agonists such as methadone and buprenorphine, but a variety of obstacles, including government regulations, cost, availability, and stigma, combine to diminish their use. The death rate among heroin addicts is approximately 2% to 3% per year, significantly higher than among their age- and socioeconomically matched cohorts. In addition to dealing with the obstacles above, what is needed to decrease this are new approaches that deal with the brain changes produced by chronic dependence and could reverse the intracellular changes related to addiction and craving. ❑

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Pharmacological aspects

Tratamientos farmacológicos para la dependencia de opioides: opciones para la detoxificación y el mantenimiento

Aun cuando la dependencia de opioides tiene más agentes terapéuticos disponibles que otras drogas de abuso, ninguno de ellos resulta curativo. Sin embargo, estos agentes pueden disminuir marcadamente los síntomas de abstinencia y el craving, y bloquear los efectos de los opioides debidos a las recaídas. El método más efectivo para tratar la abstinencia es la sustitución y disminución progresiva con metadona o buprenorfina. Los agentes alfa-2 adrenérgicos pueden reducir los síntomas no tratados o reemplazar a los agonistas si no se dispone de ellos. Se ha estudiado la reducción del período de abstinencia utilizando antagonistas narcóticos, pero los temas de seguridad o de la persistencia de síntomas han dificultado su desarrollo. La mejor evolución a largo plazo no se relaciona ni con los métodos ni con los agentes usados para manejar la abstinencia, sino que se asocia con el tratamiento post-detoxificación. Excluyendo a aquellos pacientes que cambian de hábito en el corto plazo, la mejor evolución ocurre cuando se mantiene metadona o buprenorfina a largo plazo, junto con adecuadas intervenciones psicosociales. En aquellos pacientes con una fuerte motivación externa puede ser útil el uso del antagonista naltrexona. Actualmente no hay claridad respecto a la duración de los tratamientos de mantenimiento. Se requiere de mejores agentes para combatir los cambios cerebrales relacionados con la adicción.

Traitements pharmacologiques de la dépendance aux opioïdes : détoxification et traitement d'entretien

Les traitements de la dépendance aux opioïdes, bien que plus nombreux que ceux des autres substances addictogènes, ne sont pas curatifs. Ils peuvent néanmoins diminuer notablement les symptômes de sevrage et la compulsion de consommation et bloquer les effets opioïdes dus aux récidives.
La méthode de sevrage la plus efficace est celle de la substitution et de la réduction progressive par la méthadone et la buprénorphine. Les agents α-2 adrénergiques peuvent améliorer les symptômes non traités ou remplacer les agonistes s'ils ne sont pas disponibles. On a cherché à raccourcir la période de sevrage en la déclenchant par des antagonistes narcotiques mais des problèmes de tolérance ou de persistance des symptômes en ont gêné le déroulement. L'amélioration à long terme n'est liée ni aux produits de sevrage ni aux méthodes mais plutôt au traitement qui suit la détoxification.
En excluant les produits avec lesquels l'accoutumance survient à court terme, les meilleurs résultats sont obtenus avec le maintien au long cours de la méthadone ou de la buprénorphine accompagné d'interventions psychosociales adaptées. Les patients dont la motivation externe est forte pourront préférer l'antagoniste naltrexone. Actuellement, la durée optimale de maintien de l'un ou de l'autre n'est pas bien définie. De meilleurs produits sont attendus pour traiter les modifications cérébrales liées à la dépendance.

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A randomized pilot clinical trial to evaluate the efficacy of Community Reinforcement and Family Training for Treatment Retention (CRAFT-T) for improving outcomes for patients completing opioid detoxification*

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Abstract

Background—Detoxification with psychosocial counseling remains a standard opioid-use disorder treatment practice but is associated with poor outcomes. This study tested the efficacy of a newly-developed psychosocial intervention, Community Reinforcement Approach and Family Training for Treatment Retention (CRAFT-T), relative to psychosocial treatment as usual (TAU), for improving treatment outcomes.

Methods—A randomized, 14-week trial with follow-up visits at 6 and 9 months post-randomization conducted at two substance use disorder (SUD) treatment programs. Opioid-dependent adults (i.e., identified patient - IP) enrolled in a residential buprenorphine-detoxification program and their identified concerned significant other (CSO) were randomized to CRAFT-T (n=28 dyads) or TAU (n=24 dyads). CRAFT-T consisted of 2 sessions with the IP and CSO together and 10 with the CSO alone, over 14 weeks. TAU for the CSOs was primarily educational

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Dr. Brigham lead the design and implementation of the study in collaboration with Drs. Somoza and Slesnick. Mr. Lewis and Dr. Guo conducted the analyses and provided critical review of the manuscript. Dr. Brigham drafted the manuscript and Drs. Winhusen, Slesnick, and Somoza contributed to the interpretation of the findings and critically revised the manuscript for intellectual content. All authors have approved the final manuscript.

Conflict of Interest
The authors have no conflicts to declare.

and referral to self-help. All IPs received treatment as usually provided by the SUD program in which they were enrolled. The primary outcome was time to first IP drop from treatment lasting 30 days or more. Opioid and other drug use were key secondary outcomes.

Results—CRAFT-T resulted in a moderate but non-significant effect on treatment retention ($p = 0.058$, hazard ratio = 0.57). When the CSO was parental family, CRAFT-T had a large and significant effect on treatment retention ($p < 0.01$, hazard ratio = .040). CRAFT-T had a significant positive effect on IP opioid and other drug use ($p<0.0001$).

Conclusion—CRAFT-T is a promising treatment for opioid use disorder but replication is needed to confirm these results.

Keywords

addiction; dependence; family; treatment

1. Introduction

In 2009, there were an estimated 2.3 million Americans with an opioid-dependence disorder (Substance Abuse and Mental Health Services Administration, 2010). Over four decades of research indicates that agonist maintenance therapy (AMT) utilizing methadone (a full opioid agonist) and, more recently, buprenorphine (a partial opioid agonist) is the most effective treatment for opioid dependence (Kleber, 2008; Kreek et al., 2010; Mattick et al., 2008). Social, economic and regulatory barriers limit access to AMT and consequently detoxification followed by psychosocial counseling, with accompanying high relapse rates, is the most common approach to opioid dependence treatment (Mattick et al., 2009; Mayet et al., 2005). Availability of buprenorphine has improved the effectiveness of opioid detoxification (Brigham et al., 2007; Ling et al., 2005) however, without AMT, treatment drop-out and relapse rates are high and potentially lethal (Strang et al., 2003). Interventions are needed to increase retention in treatment and prevent relapse.

Community Reinforcement and Family Training (CRAFT), developed by Robert Meyers, works with concerned significant others (CSOs) to motivate treatment-refusing persons with a substance use disorder to volunteer for treatment. CRAFT has demonstrated a robust effect in several randomized clinical trials (Kirby et al., 1999; Meyers et al., 1998, 2003; Miller et al., 1999).

Between April of 2009 and November of 2010 fifteen dyads, each consisting of an opioid dependent adult identified patient (IP) and their respective CSO, were enrolled in stages 1a and 1b of a therapy development study (Rounsaville, 2001) to modify CRAFT. The new manualized treatment, Community Reinforcement and Family Training for Treatment Retention (CRAFT-T), works with the CSOs of IPs already in treatment, to increase the IP's retention in treatment and recovery support. This report presents the results of a randomized clinical pilot evaluating CRAFT-T.

2. METHODS

2.1 Participants

We enrolled 104 participants into an intent to treat (ITT), 2-group randomized clinical trial at two Ohio locations: Site 1, in a metropolitan county, with 1.2 million residents, and Site 2, in a smaller county, with 178,000 residents. The study was IRB approved and sponsored by the National Institute on Drug Abuse. A detailed study protocol is available (Brigham et al., 2009).

Participants enrolled as dyads consisting of an IP and a CSO. IPs were approached during a detoxification program and, if interested, provided contact information for a CSO. CSOs and IPs were consented and screened separately. IPs were adults who: met DSM-IV-TR criteria for opioid dependence; planned to transfer from detoxification to outpatient; and had a CSO willing to participate. CSOs were relatives, spouses, or intimate partners, or planned to live with the IP following randomization. IPs and CSOs were ineligible if they had: a history of violence with each other; current suicide or homicide intent; a medical or psychiatric condition that would make participation difficult; or were court ordered to complete treatment.

2.2 Procedures

Participants were randomized to CRAFT-T or TAU using urn randomization balanced on site (1 or 2), race (Black or other), and CSO type (parent or other). The study treatment phase was 14 weeks during which there were 2 weekly research assessment visits for IPs and 12 for CSOs. The follow-up phase extended to 38 weeks with research visits for IPs and CSOs at weeks 14, 26, and 38. Randomization began in January of 2011 and follow-up was completed in June of 2012. Participants were compensated for research visits by gift cards ($20 for baseline and screening, $10 for each weekly treatment assessment, and $20 each for the end of treatment assessment and two follow-ups).

2.2.1 Treatments

2.2.1.1 Treatment as usual (TAU) for IPs: All IPs received the usual services offered at the treatment program which began with a 13-day BUP taper detoxification (Brigham et al., 2007). At Site 1 the taper was initiated in a residential sub-acute medical detoxification setting followed by step-down to ambulatory detoxification. At Site 2 the entire taper was completed in an ambulatory setting. At both sites IPs transferred to outpatient treatment following detoxification.

2.2.1.2 Treatment as usual (TAU) for CSOs: The TAU for CSOs was minimal consisting of an invitation to attend a volunteer-facilitated support group and an informal referral to self-help (Al-Anon or Nar-Anon).

2.2.1.3 Community Reinforcement and Family Training for Treatment Retention (CRAFT-T): This unilateral family intervention worked primarily with the CSO with the goal of influencing the IP's behavior. CRAFT-T used a cognitive behavioral approach to assist the CSO in using behavioral principles to increase the IP's treatment retention and

reduce their drug use. CRAFT-T departed from the CRAFT model in five important ways: it worked with the CSO's of IP's who were in treatment; CSOs were identified by the IP; it targeted retention in treatment; the IP participated in two initial sessions; and it targeted reduction of HIV risk behavior.

CRAFT-T consisted of twelve weekly one-hour sessions. The IP and CSO attended the first two sessions together and the remaining ten sessions were attended by the CSO alone. Two optional sessions were also available. The CRAFT-T manual was designed to supplement the book *"Motivating Substance Abusers to Enter Treatment"* (Smith and Meyers, 2004).

2.2.2 CRAFT-T Therapist, Training, and Fidelity—Four therapists were recruited. Two had master's degrees with less than one year of post-graduate experience and two were non-degreed licensed drug abuse counselors with over ten years of experience. Therapists attended a two-day training followed by training cases. Prior to the start of the trial eleven participant dyads were enrolled to serve as training cases. All therapist training case sessions were audio-recorded and rated for fidelity. Therapists were certified to see trial participants after ratings of two training cases reached a criterion threshold. During the treatment phase of the study all CRAFT-T sessions were audio-recorded and 25% were rated by the study PI [G.B.]. All therapists maintained acceptable fidelity with an overall compliance rating of 87%.

2.3 Measures

The primary outcome was days to the IP's first drop of 30 days or more from all treatment as recorded in the clinic's electronic health record. Secondary outcomes included days of opioid use and any drug use. A Timeline Follow-back (TLFB) procedure (Robinson et al., 2012; Sobell et al., 1988), was used to record the IP's day-to-day use of alcohol, opioids, cocaine, marijuana, benzodiazepines, methamphetamine, and other illicit drugs. Urine samples were collected at each of the IPs research visits (weeks 1, 2, 14, 26, and 38) and were analyzed for opioids, cocaine, marijuana, benzodiazepines, methamphetamine using the Redi Test rapid screen system from Redwood Toxicology Laboratory. The Structured Clinical Interview for DSM-IV (First et al., 1996) was used with the IP to obtain the opioid-dependence diagnosis.

2.4 Data Analysis

Baseline measures are summarized in Table 1. Each measure was tested for between-treatment-arm differences using the Pearson Chi Square, Fisher Exact, Wilcoxon Rank Sum or Student's t.

Each outcome analysis was performed twice: grouping participants by treatment arm, and then by CRAFT-T participants with parental family CSO (parent, aunt, grandparent or sibling) vs. all others. This second grouping resulted from previous indication of CSO relationship as a potential moderator (Meyers et al., 1998; Miller et al., 1999), and from the small, pilot study sample size which precluded all but the simplest regression models.

The primary outcome variable was treated as survival data and tested for group differences using Cox Proportional Hazard regressions. There were no missing data on the primary

outcome. Daily TLFB IP opioid and drug use indicators, were assessed using random intercept mixed-model logistic regressions testing for both group effects and group-by-time interaction effects over weeks 1–2 (IP study treatment), over weeks 3–14 (CSO treatment after IP study treatment), and finally over the remaining follow-up weeks. No attempt was made to account for multiple analyses or missing data (on the drug use outcomes).

Urine drug screens (UDS) were too sparse for meaningful between-group comparisons. Instead, the Cohen Kappa was used to compare the UDS opioid indicators to TLFB results compiled over three-day periods ending with respective UDS days.

3. RESULTS

3.1 Participants

A total of 136 potential participants were pre-screened, 108 consented and screened, and 104 (52 dyads) randomized (Supplementary Figure S1[1]). For weeks 14, 28 and 38 respectively, follow-up rates were 52%, 56% and 62% for IP, and 62%, 54%, and 79% for CSO. No reported baseline characteristics indicated significant between-treatment differences. IP participants averaged 29 years old and were 79% male, 94% white, and 73% unemployed (Table 1.). Based on the Risk Assessment Battery (RAB) self-reports, the CSO's substance use appeared minimal (data not shown).

3.2 Study Treatment Exposure

IPs attended an average of 1.78 (median of 2) of their 2 scheduled CRAFT-T sessions. CSOs attended an average of 7.62 (median of 9.5) of their 12 scheduled study treatment sessions. Three CRAFT-T dyads dropped out before their first session. Of the two optional CSO sessions, 8 CSOs attended at least one session, and 2 attended both.

3.3 Primary Outcome

The primary outcome measure had 3 censored participants (2 for early withdrawal and one for outlasting the 38-day assessment period) and no missing data. CRAFT-T participants showed a longer time-to-dropout which approached significance with $p = 0.058$ and a hazard ratio of 0.57 indicating they were 57% as likely as TAU participants to dropout at any given point in time. CRAFT-T participants with parental-family CSOs showed a longer time-to-dropout with $p < 0.01$ and hazard ratio = 0.40 (Figure 1).

3.4 Daily Drug Use Outcomes

For both of the participant groupings, week 3–14 regressions and follow-up regressions demonstrated significant time-by-treatment interaction effects for both opioid and drug use TLFB indicators ($p < 0.0001$). The corresponding graphs in Figure 1 suggest divergence during weeks 3–14 favoring CRAFT-T and CRAFT-T-with-parental-family-CSO respectively, with differences diminishing during follow-up. A Cohen Kappa of 0.54 resulted from testing the TLFB opioid results for agreement with UDS results: disagreement balanced between positive and negative urines.

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:…

4. DISCUSSION

The goal was to determine if adding CRAFT-T to opioid detoxification followed by outpatient, would improve treatment retention and drug use outcomes. The primary outcome was days to the IP's first drop of 30 days or more from treatment. Compared to TAU, CRAFT-T resulted in a moderate-sized effect that approached significance. We also evaluated the effect of type of CSO and found that when dyads with both CRAFT-T and CSOs from parental family were compared to all others, the effect on retention was large (Hazard Ratio = 0.4, Cohen's d = 0.95) and significant. This is consistent with previous CRAFT research by Meyers (1998) who found parents were significantly more effective than spouses. Retention in treatment is important as it is consistently associated with improved drug use outcomes (Mertens et al., 2012; Simpson et al., 1997).

We also examined effects on drug use and found that assignment to CRAFT-T resulted in significant reductions in both opioid and drug use days reported on the TLFB. While this observed effect on drug use is encouraging, the overall rates of relapse and drug use were high. These outcomes should be interpreted with caution due to the relatively low follow-up rates.

CSOs attended an average of 8 of the 12 planned sessions, which is low compared to previous CRAFT research. In CRAFT research the CSO initiates involvement. In CRAFT-T, IPs invite a specific CSO and the relationships often appeared strained with a sense that the CSO was being engaged with reluctance.

This study had numerous strengths: the ITT randomized trial design, a manual guided treatment, and no missing data on the primary outcome measure. Some limitations resulted from the small sample size: lack of generalizability, lack of power to evaluate therapist effects and to fully evaluate the effects of CSO relationship type, and possibly distorted estimates of effect sizes (Kraemer et al., 2006). CSO's utilization of CRAFT-T skills was not measured and therefore we cannot conclude that use of these skills caused the observed effects.

In conclusion, these preliminary results suggest that CRAFT-T is a promising intervention for improving treatment retention and drug use outcomes in adults with opioid use disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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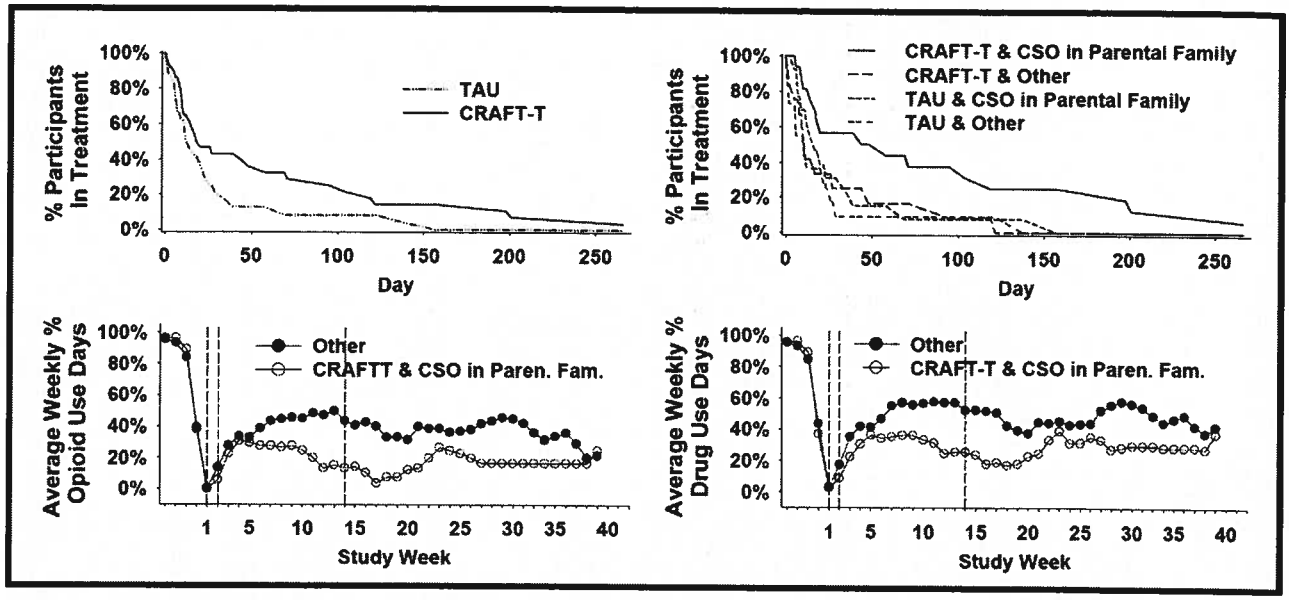

Figure 1.

(a,b) Survival curves for IP retention in drug abuse treatment are shown. Time point 0 is baseline and 1 – 250 are days in drug abuse treatment following randomization. (c,d) Comparison of treatments on TLFB reports of weekly percentage of opioid use and any drug use days are shown. Weeks 1 – 2 are treatment weeks in which both the CSO and IP attend CRAFTT sessions, 3 –14 are the weeks in which only the CSO attends CRAFT-T sessions, and weeks 15–40 are follow-up.

Table 1

Participant Comparison at Baseline by Treatment Group

	TAU (N=24)	CRAFT-T (N=28)	Total (N=52)
Site (n, %):			
Site 1	16, 66.7%	20, 71.4%	36, 69.2%
Site 2	8, 33.3%	8, 28.6%	16, 30.8%
IP:			
Age in yrs. (mean, std.dev.)	28.7, 6.7	29.5, 9.2	29.2, 8.1
Males (n, %)	18, 75.0%	23, 82.1%	41, 78.8%
Race (n,%):			
Black	1, 4.2%	1, 3.6%	2, 3.8%
White	22, 91.7%	27, 96.4%	49, 94.2%
Other	1, 4.2%	0, 0.0%	1, 1.9%
CSO:			
Age in yrs. (mean, std.dev.)	40.3, 14.8	28 44.3, 12.1	42.5, 13.4
Males (n, %)	5, 20.8%	4, 14.3%	9, 17.3%
Race (n,%):			
Black	2, 8.3%	1, 3.6%	3, 5.8%
White	21, 87.5%	26, 92.9%	47, 90.4%
Other	1, 4.2%	1, 3.6%	2, 3.8%
CSO Relation (n, %):			
Parent/Aunt/Grandparent	11, 45.8%	15, 53.6%	26, 50.0%
Spouse/Common Law	2, 8.3%	5, 17.9%	7, 13.5%
Girlfriend/Boyfriend/Fiancee	8, 33.3%	5, 17.9%	13, 25.0%
Sibling	2, 8.3%	1, 3.6%	3, 5.8%
Friend	1, 4.2%	2, 7.1%	3, 5.8%
CSO in Parental Family* (n, %)	13, 54.2%	16, 57.1%	29, 55.8%
IP Secondary SUD Diagnosis (n, %):			
None	19, 79.2%	23, 82.1%	42, 80.8%
Sedative-Hyp-Anx Abuse	1, 4.2%	0, 0.0%	1, 1.9%
Cannabis Abuse	0, 0.0%	2, 7.1%	2, 3.8%
Cannabis Dependence	1, 4.2%	1, 3.6%	2, 3.8%
Stimulant Dependence	0, 0.0%	1, 3.6%	1, 1.9%
Cocaine Abuse	1, 4.2%	0, 0.0%	1, 1.9%
Cocaine Dependence	1, 4.2%	1, 3.6%	2, 3.8%
Poly Drug Dependence	1, 4.2%	0, 0.0%	1, 1.9%

None of these variables showed significant between-treatment differences.

*CSO is parent, aunt, grandparent, or sibling

905 Court Street • Lynchburg • Virginia • 24504
www.lynchburgva.gov/police

April 17, 2023

Virginia Opioid Abatement Authority

RE: Cooperative Projects Involving Cities and Counties

Dear Sir or Madam:

This letter is to express the strong support of the Lynchburg Police Department for the implementation of Horizon Behavioral Health's Crisis Receiving Center (CRC). This includes the detoxification program for individuals with an opioid use disorder (OUD) or other substance use disorder which will be supported through funding from the Virginia Opioid Abatement Authority.

Through collaboration with Horizon, the Central Virginia localities will support the development of an eight-bed detoxification unit for individuals with an opioid use disorder and/or other substance use disorder, to provide a needed level of care in our community. This project will aim to divert individuals with an OUD away from emergency departments and residential facilities toward addiction-specific services locally in the community.

The Lynchburg Police Department and our community have benefited from a long-standing relationship with Horizon Behavioral Health through a variety of programs that provide impactful services to our residents in greatest need. The CRC and its affiliated programs will offer a readily available level of service that currently doesn't exist, while also reducing the demand for law enforcement services.

Together we will leverage strengths with other local organizations to make a greater difference in our community and the future of our community members. This will be done by instilling hope, empowerment, and recovery through funding for the detoxification unit at the CRC for individuals with an opioid use disorder or other substance use disorder.

Sincerely,

Ryan M. Zuidema
Chief of Police
Lynchburg Police Department

MIRIAM'S HOUSE

SOLUTIONS TO HOMELESSNESS

Est. 1994

April 18, 2023

Virginia Opioid Abatement Authority

RE: Cooperative Projects Involving Cities and Counties

To Whom It May Concern:

This letter is to express the firm support of name of Miriam's House to the implementation of Horizon Behavioral Health's Crisis Receiving Center (CRC) including the detoxification program for individuals with an opioid use disorder (OUD) or other substance use disorder which will be supported through funding from the Virginia Opioid Abatement Authority.

Through collaboration with Horizon, the Central Virginia localities will support the development of an eight bed detoxification unit for individuals with an opioid use disorder and/or other substance use disorder, to provide a needed level of care in our community. This project will aim to divert individuals with an OUD away from emergency departments and residential facilities toward addiction-specific services locally in the community.

For 30 years, Miriam's House has worked to end homelessness in the Central Virginia region. We recognize that a critical component in fulfilling our mission is the existence of recovery services in the community. A detoxification program is vital in ensuring housing stability for formerly homeless households and we look forward to continued collaboration with Horizon as we serve the community.

I am happy to answer any questions regarding our support of this project and can be reached at *sarah@miriamshouse.org* or 434.847.1101.

Sincerely,

Sarah Quarantotto, MSW
Executive Director