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Interim treatment: Bridging delays to opioid treatment access

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ABSTRACT

Objective. Despite the undisputed effectiveness of agonist maintenance for opioid dependence, individuals can remain on waitlists for months, during which they are at significant risk for morbidity and mortality. To mitigate these risks, the Food and Drug Administration in 1993 approved interim treatment, involving daily medication + emergency counseling only, when only a waitlist is otherwise available. We review the published research in the 20 years since the approval of interim opioid treatment.

Methods. A literature search was conducted to identify all randomized trials evaluating the efficacy of interim treatment for opioid-dependent patients awaiting comprehensive treatment.

Results. Interim opioid treatment has been evaluated in four controlled trials to date. In three, interim treatment was compared to waitlist or placebo control conditions and produced greater outcomes on measures of illicit opioid use, retention, criminality, and likelihood of entry into comprehensive treatment. In the fourth, interim treatment was compared to standard methadone maintenance and produced comparable outcomes in illicit opioid use, retention, and criminal activity.

Conclusions. Interim treatment significantly reduces patient and societal risks when conventional treatment is unavailable. Further research is needed to examine the generality of these findings, further enhance outcomes, and identify the patient characteristics which predict treatment response.

Introduction

Opioid abuse and dependence are reaching epidemic proportions in the United States, resulting in drug overdoses, premature death, criminal activity, lost workdays, and other consequences that cost over $56 billion annually (Becker et al., 2008; Birnbaum et al., 2011; Clausen et al., 2009; Jones et al., 2013; Substance Abuse and Mental Health Services Administration, 2010; Wisniewski et al., 2008). Opioid maintenance treatment, typically involving the agonist medications methadone or buprenorphine, is the most efficacious and widely-used treatment for opioid dependence and dramatically reduces morbidity, mortality and spread of infectious disease (Ball and Ross, 1991; Johnson et al., 2000; Stotts et al., 2009).

However, demand for maintenance treatment remains consistently above available capacity in many areas of the country (Friedmann et al., 2003; Harlow et al., 2013; Sigmon, 2014; Wenger and Rosenbaum, 1994). An alarming number of methadone clinics have extensive waitlists, due in part to inadequate public funding and unfavorable zoning regulations (Des Jarlais et al., 1995; Fountain et al., 2000; Gryczynski et al., 2009; Peles et al., 2012, 2013; Peterson et al., 2010). Municipal governments in areas across North America, for example, have attempted to restrict the establishment of methadone treatment programs through zoning bylaws (e.g., Bernstein and Bennett, 2013). Federal regulations also require that methadone programs include comprehensive services (e.g., on-site psychosocial counseling, urinalysis testing, medical management) and, while beneficial to many patients, this also can increase programs' cost and prohibit rapid expansion. Furthermore, while approval of buprenorphine (Suboxone®) extended maintenance treatment into general medical practices, many areas of the country have an insufficient number of willing providers, due to physicians' concerns about induction logistics, reimbursement challenges, potential for medication diversion, lack of support for providers, and lack of psychosocial services for patients (Barry et al., 2009; Becker and Fiellin, 2006; Kissin et al., 2006; Netherland et al., 2009; Sigmon, 2015). The result is that many opioid-dependent individuals needing treatment may remain on waitlists for weeks or months, particularly those who must await admission to a subsidized program (Schwartz et al., 2009, 2011; Sherba et al., 2012). During this delay to treatment, they are at significant risk for continued illicit drug use, criminal activity, infectious disease, overdose, and mortality (Adamson and Sellman, 1998; Clausen et al., 2009; Cooper, 1989; Darke and Hall, 2003; Schwartz et al., 2009; Warner-Smith et al., 2001; Wenger and Rosenbaum, 1994). Prolonged waits are also associated with reduced likelihood of eventual treatment entry (Donovan et al., 2001; Festinger et al., 1995; Hser et al., 1998; Kaplan and Johri, 2000).

One effort to mitigate these risks during the delay to treatment has been to offer interim treatment to those awaiting enrollment into a

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traditional methadone program. Methadone programs are generally required to pair medication with comprehensive treatment plans that include regular counseling, vocational rehabilitation and urine toxicology testing. However, in recognition of the growing waitlists and delays in treatment access, in 1993 the Food and Drug Administration (FDA) and the Substance Abuse and Mental Health Services Administration (SAMHSA) granted permission for methadone clinics to provide medication without accompanying psychosocial services on a temporary basis when only a waiting list would be otherwise available (Institute of Medicine (IOM), 1995; Nightingale, 1993). The rationale behind this initial approval of interim methadone treatment was largely based on reducing human immunodeficiency virus (HIV) risk and transmission among intravenous drug abusers who could not be placed in comprehensive methadone treatment programs within 14 days of seeking admission (Dole, 1991; Nightingale, 1993). Under this ruling, the FDA authorized interim methadone treatment to be provided only by existing programs already licensed as a specialty methadone treatment clinic. The regulations mandated that interim methadone patients ingest all medication doses under direct staff observation, thus requiring daily clinic visits (Institute of Medicine (IOM), 1995). They also limited the duration of interim treatment to no more than 120 days, with clinics required to discharge patients at that time or admit them to standard methadone treatment if a slot has become available. Finally, the clinic was required to notify their state's public health officer when interim treatment begins and ends for each patient.

We review here the published controlled studies conducted over the past two decades evaluating the efficacy of the interim treatment approach for patients awaiting admission to standard opioid maintenance programs. Our aim is to characterize what is known empirically about interim opioid treatment, as well as to discuss the strengths and limitations associated with this treatment approach.

Methods

Study selection

Literature searches were conducted using PubMed, MEDLINE, PsychINFO, PREMEDLINE, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews using the terms 'interim methadone' and 'interim buprenorphine', both alone and paired with the term 'treatment'. Relevant references from retrieved articles were also evaluated. The search was conducted in November 2014 and did not restrict the timeframe for eligible studies.

Studies were included provided that they met the following criteria: (1) involved interim methadone or buprenorphine treatment with opioid-dependent individuals awaiting entry into comprehensive treatment; (2) were published in a peer-reviewed journal; (3) included randomization to an experimental comparison condition; and (4) used a research design wherein treatment effects could be attributed to the interim treatment condition.

Findings

Four randomized trials have evaluated interim treatment for opioid dependence using experimental designs wherein effects on treatment outcome could be attributed to the interim treatment condition. A summary of their methods and results is presented in Table 1.

The first study on this topic was published just prior to the FDA's formal approval of interim treatment. In that trial, heroin-dependent adults were recruited from the waitlists of 23 Beth Israel methadone maintenance clinics throughout New York City (Yancovitz et al., 1991). Participants had been on these waitlists for an average of 3 months. The investigators randomly assigned participants to either an interim methadone (N = 149) or control (N = 152) condition. Interim methadone participants visited the clinic 6 days per week for dosing, received take-homes on Sundays, and received an approximate methadone dose of 80 mg/day. Their participation in the interim methadone condition extended from the time of study enrollment until an opening occurred in the clinic to which they had originally applied. Interim methadone participants received only minimal counseling or support services, free condoms and HIV education, and biweekly urinalysis. Control participants remained on their waitlist and visited the clinic biweekly for urinalysis, free condoms and a follow-up assessment. This control condition lasted for one month, after which participants were transferred into the interim methadone condition for the remaining time until a treatment slot became available. Comparison between the two groups on the primary outcome (i.e., heroin use) was limited to this 1-month period. Urinalysis data showed significantly less heroin use among participants assigned to the interim methadone vs. control condition, with 29% vs. 60% testing positive for heroin at 1-month follow-up, respectively ($p < .001$). Also examined was the number of participants who had entered conventional drug treatment programs 16 months after the interim treatment program had begun. More interim methadone participants had entered treatment by that timepoint compared to controls (72% vs. 56%, respectively; $p < .005$). Taken together, this study provided an initial demonstration of the feasibility and

Table 1
Randomized trials evaluating interim treatment with opioid-dependent patients.

Reference	Experimental intervention	Comparison intervention	Illicit opioid abstinence	Additional outcomes
Yancovitz et al., 1991	Interim methadone; 6 clinic visits/week; biweekly urinalysis; N = 149	Continued waitlist for 1 month; biweekly visits for urinalysis; N = 152	Fewer IM participants tested positive for heroin at 1-month FU than controls (29% vs. 60%, respectively; p < .001)	More IM participants eventually entered comprehensive treatment than controls (72% vs. 56%, respectively; p < .005)
Krook et al., 2002	Interim buprenorphine for 3 months; 6 visits/week; N = 55	Double-blind placebo treatment for 3 months; 6 visits/week; N = 51	IB participants reported greater reductions in heroin use on experimenter-developed VAS (p < .0001)	IB participants retained longer than controls (42 vs. 14 days, respectively; p < .001)
Schwartz et al., 2006	Interim methadone for 4 months; 7 visits/week; N = 199	Continued waitlist for 4 months; no contact other than 4-month FU assessment; N = 120	Fewer IM participants tested positive for heroin at end of study than controls (56.6% vs. 79.2%, respectively; p < .001) IM participants reported fewer days of heroin use in past 30 at end of study (4.2 vs. 26.4 days, respectively; p < .001)	More IM participants eventually entered comprehensive treatment than controls (75.9% vs. 20.8%, respectively; p < .001) IM participants reported less illegal income in past 30 at end of study ($36 vs. $412, respectively; p < .02)
Schwartz et al., 2011	Interim methadone for 4 months; 7 visits/week; N = 99	1) Standard methadone; ~2 counseling sessions/month; daily dosing visits + some take-homes; N = 104 2) Restored methadone; ~4 counseling sessions/month with counselor with reduced caseload; daily dosing visits + some take-homes; N = 27	IM, SM, and RM groups showed similar reduction from baseline in heroin use, with 54%, 58%, and 56% of patients heroin-positive at 4-month follow-up, respectively (p = .98) IM, SM, and RM groups showed similar reduction from baseline in self-reported heroin use (2.6, 3.6 and 2.8 days in past month at 4-month follow-up, respectively; p = .21)	4-month retention rates were similar for IM, SM and RM groups (91.9%, 80.8% and 88.9% respectively; p = .06) IM, SM, and RM groups showed similar reductions from baseline in criminal activity, money spent on drugs, and illegal income (p's < .001), with the IMT group showing greater reductions than SM at 2-month follow-up (p's < .05)

efficacy of offering basic medication services to opioid-dependent patients awaiting access to full treatment. Study limitations included the brief duration (i.e., 1 month) of the interim treatment being evaluated, as well as a lack of details presented on the overall duration of treatment or longer-term outcomes in the interim methadone group.

The second study was published over a decade later by Krook et al. (2002) in Oslo, Norway. The authors sought to evaluate the efficacy of interim treatment with buprenorphine, rather than methadone. Participants were 106 heroin-dependent adults awaiting methadone maintenance treatment. They were randomly assigned to receive buprenorphine (N = 55) or placebo (N = 51) without psychosocial support or other services and under double-blind conditions for the 12-week study. Participants visited the clinic for dosing 6 days per week, with either sublingual buprenorophine (16 mg) or placebo tablets given under staff supervision. They received a double dose on Saturdays and no dose on Sundays. On the primary outcome of retention, interim buprenorphine participants were retained significantly longer than those in the placebo condition (42 vs. 14 days, respectively, $p < .001$). Self-reported heroin use, assessed via a visual analogue scale ranging from 0 (drug free) to 10 (daily heavy drug abuse), was also significantly lower in the buprenorphine vs. placebo group. This study provided promising initial support for the use of buprenorphine in an interim treatment approach and used a double-blind approach, which is uncommon for studies of this type. That said, while the buprenorphine group demonstrated superior retention, attrition was still high with two-thirds of patients having dropped out by Week 12. The authors also used no objective measure of opioid abstinence, relying instead on patients to rate their recent drug use via visual analogue scales.

In the third study, participants were 319 heroin-dependent adults awaiting methadone maintenance in Baltimore, MD (Schwartz et al., 2006). Participants were randomly assigned to either interim methadone treatment (n = 199) or a waitlist control (n = 120). Interim methadone participants visited the clinic daily to receive methadone (approximately 80 mg/day) without psychosocial support or other services for up to 4 months, consistent with federal regulations. All participants completed a follow-up assessment when they entered regular methadone treatment or at the 4-month timepoint. Those randomized to the waitlist condition had no further contact with clinic staff after completing the baseline assessment. Interim methadone participants provided significantly fewer heroin-positive urines at follow-up compared to waitlist controls (56.6% vs. 79.2%, respectively; $p < .001$). A similar pattern was seen with self-reported heroin use, with interim methadone participants reporting fewer days of past-month heroin use than controls (4.2 vs. 26.4 days, respectively; $p < .001$). Benefits of interim methadone treatment also extended beyond illicit opioid use. More interim methadone participants eventually entered comprehensive treatment than controls (75.9% vs. 20.8%, respectively; $p < .001$), and they reported less past-month illegal income ($36 vs. $412, respectively; $p < .02$). The authors also evaluated the outcomes from this trial 6 months following the end of the 4-month initial study period (e.g., 10 months after study intake; Schwartz et al., 2007). At the time of this second follow-up, 64.8% and 27.5% of interim methadone and control participants were enrolled in comprehensive opioid treatment ($p < .001$). Interim methadone participants provided significantly fewer heroin-positive urine samples at the 10-month timepoint (48.1% vs. 72.3%, respectively; $p = .001$). They also had significantly lower ASI Legal composite scores ($p < .001$) and they reported spending less money on drugs ($p < .001$), obtaining less money from illegal activity ($p = .002$), and engaging in fewer days of illegal activity ($p < .001$). Taken together, this randomized trial and its 10-month follow-up evaluation provided a strong demonstration that interim methadone treatment produces robust and sustained benefits over simply placing individuals on waitlists.

The fourth and final study on this topic was also conducted by Schwartz et al. (2011). Interim methadone was compared to conventional methadone maintenance rather than a waitlist control, with the aim of examining whether opioid-dependent individuals receiving medication alone may fare poorly compared to those who receive immediate entry into more traditional, comprehensive methadone treatment. Participants were 230 heroin-dependent adults awaiting methadone maintenance treatment in Baltimore, MD. They were randomly assigned to one of three treatment conditions: interim methadone treatment (n = 99), standard methadone treatment with regular counseling (n = 104), or 'restored' methadone treatment involving regular counseling with a clinician who had a limited caseload (n = 27). Interim methadone participants visited the clinic daily to receive methadone for up to 4 months, a minimum of three urine toxicology tests and emergency counseling only if deemed necessary. Standard methadone participants visited the clinic regularly for dosing but could also earn take-home doses. They received regular counseling, treatment planning and other psychosocial treatment as needed as well as more frequent urine toxicology testing than the interim methadone group. Restored treatment was similar to the standard group, except that participants in this group met with a counselor who carried a reduced caseload of patients and they could meet with this counselor as frequently as they wished. By the 4-month assessment, the interim methadone group had received virtually no counseling, the standard group had averaged 2 sessions per month, and the restored group approximately 4 sessions per month. All groups showed significant reductions in heroin use from baseline, with no differences in heroin-positive urines at 4-month follow-up between the interim, standard and restored treatment groups (54%, 58% and 56%, respectively; $p = .98$). The three groups also showed significant reductions from baseline in self-reported heroin use that did not differ at follow-up (2.6, 3.6 and 2.8 days in past month, respectively; $p = .21$), and their 4-month retention rates were similar as well (91.9%, 80.8% and 88.9% respectively; $p = .06$). Finally, the interim, standard and restored methadone groups reported significant reductions from baseline in criminal activity, money spent on drugs, and illegal income. These reductions in risk behavior were generally comparable across groups, with one exception: the interim treatment group showed greater reductions in criminal activity than the standard methadone group at the 2-month timepoint ($p < .05$). Finally, the authors conducted a subsequent 12-month follow-up assessment, which translated to 8 months after the interim group had been transitioned to standard methadone treatment (Schwartz et al., 2012). At this second evaluation, there were no differences between the interim, standard and restored methadone groups in treatment retention (60.6%, 54.8% and 37.8%, respectively; $p = .09$) or percent of heroin-positive urine specimens (46%, 48% and 51%, respectively; $p = .91$). The groups were also generally comparable on measures of past-month criminal activity as well as ASI scores. In summary, there was no evidence that receiving medication only, at least for several months, undermined patients' drug abstinence and clinical stability at later timepoints.

Conclusions

Despite the demonstrated effectiveness and continued expansion of agonist maintenance for treatment of opioid dependence, concerns persist about the underutilization and limited availability of these treatments (Volkow et al., 2014). For opioid abusers who cannot gain immediate entry into agonist maintenance, the probability of continued criminal activity, infectious disease, overdose, and premature death is high. Interim opioid treatment represents one important approach to help reduce the consequences associated with treatment delays. In the two decades that have passed since the FDA approval of interim treatment, a small but compelling number of randomized trials have demonstrated its efficacy in reducing illicit opioid use and criminality, as well as increasing patients' likelihood of subsequent treatment entry. The benefits of interim treatment have been shown to persist through at least one year following enrollment into conventional treatment. Additional secondary analyses of data from these randomized trials have demonstrated the ability of interim treatment to reduce criminal (Schwartz et al., 2009) and HIV-risk (Wilson et al., 2010) behavior, as well as demonstrated its general cost-effectiveness (Schwartz et al., 2014). Taken together, when delays to treatment entry are unavoidable, the benefits of bridging these delays with daily medication and barebones clinical support are clear.

Despite these promising outcomes, however, it is important to consider several potential limitations of interim opioid treatment as it has been used thus far. First, this approach has primarily involved methadone as the pharmacological tool. Methadone treatment in the United States is limited to licensed specialty clinics, it requires frequent clinic visits, and the medication itself has risks of diversion, abuse and overdose (Luty et al., 2005). As noted earlier, interim methadone treatment regulations mandate that patients ingest all doses under direct observation, thus requiring daily clinic visits (Institute of Medicine (IOM), 1995). They also limit the duration of interim methadone treatment to 120 days, after which clinics are required to discharge patients at that time if a slot has not yet become available. As a result, these regulatory and pharmacological features may constrain the ability of interim methadone treatment to significantly expand access to much-

needed agonist treatment. The promising data thus far might warrant a reevaluation of the current federal restrictions on interim methadone treatment (Newman, 2014). However, it is also possible that the partial opioid agonist buprenorphine, which is available without the rigid dosing regulations and 120-day interim-dosing limit required for methadone, may be especially compatible with an interim treatment approach. It is this direction — developing an interim buprenorphine treatment for waitlisted opioid abusers — that our research group is currently pursuing (Sigmon et al., submitted for publication).

Second, while the above studies produced clear evidence of the efficacy of interim treatment in reducing illicit opioid use, a meaningful subset of patients continued to use heroin. In the three studies that reported urinalysis results, the percent of participants testing heroin-positive was 30% after one month of interim treatment (Yancovitz et al., 1991) and approximately 55% after four months (Schwartz et al., 2006, 2011). While urine results were not reported for the interim buprenorphine trial by Krook et al. (2002), 71% of participants had dropped out by the end of the 4-month study. These data suggest that efforts to further improve interim treatment outcomes are warranted, though they will still need to be mindful of the resource-constrained settings in which this approach is likely to be implemented.

Third, we must extend our scientific knowledge about interim treatment to new populations and settings. The interim treatment studies to date, for example, have been conducted with heroin-dependent patients (Krook et al., 2002; Schwartz et al., 2006, 2011; Yancovitz et al., 1991). Given the recent increases in abuse of prescription opioids (e.g., oxycodone, hydrocodone, hydromorphone), efforts to evaluate the effects of this approach in individuals dependent on prescription opioids are crucial (Centers for Disease Control and Prevention (CDC), 2011, 2012; Compton and Volkow, 2006). Similarly, the above studies took place in predominantly urban areas (i.e., New York City; Baltimore, Maryland; Oslo, Norway). It is important to examine the efficacy of interim treatment in the rural and suburban areas where access to maintenance can be especially limited (Fortney and Booth, 2001; Havens et al., 2007; Lenardson and Gale, 2007; Rosenblum et al., 2011; Rounsaville and Kosten, 2000; Sigmon, 2014).

Finally, we must learn more about the baseline characteristics that may predict a patient's response to interim opioid treatment. While Yancovitz et al. (1991) noted that ongoing cocaine use predicted poorer response to interim treatment, which is consistent with prior studies in more traditional methadone maintenance settings (e.g., Preston et al., 1998), other efforts have failed to identify predictors of interim treatment response (Highfield et al., 2007). The ability to distinguish those who will likely need more intensive psychosocial services in order to succeed (e.g., McLellan et al., 1993) from those who may fare well receiving medication alone (e.g., Gruber et al., 2008; Schwartz et al., 2011) is important, especially under conditions of limited resources.

Taken together, providing interim opioid treatment as opposed to a waitlist when a formal treatment slot is unavailable reduces drug-related risks and consequences to the patient and for society more generally. Future research efforts should expand on these promising outcomes in several ways, including examining the generality of these findings, improving upon the treatment outcomes observed thus far, and identifying the patient characteristics which may predict treatment response.

Conflict of interest statement

The authors declare that there are no conflicts of interests.

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