

Interim Buprenorphine Treatment During Delays to Comprehensive Treatment: Changes in Psychiatric Symptoms

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Prevalence of depression, anxiety, and mood disorders among individuals with opioid use disorder far exceeds that of the general population. While psychiatric symptoms often improve upon entry into opioid treatment, this has typically been seen with treatments involving psychosocial counseling. In this secondary analysis, we examined changes in psychiatric symptoms during a randomized clinical trial evaluating an interim buprenorphine treatment without counseling among individuals awaiting entry into comprehensive treatment. Waitlisted adults with opioid use disorder ($N = 50$) were randomized to one of two 12-week conditions: interim buprenorphine treatment (IBT; $n = 25$) consisting of buprenorphine maintenance using a computerized medication dispenser, with bimonthly clinic visits and technology-assisted monitoring, or waitlist control (WLC; $n = 25$), wherein participants remained on the waitlist of their local clinic. All participants completed assessments of psychiatric symptoms at intake and Study Weeks 4, 8, and 12. We examined changes on the Beck Anxiety Inventory (BAI), Beck Depression Inventory–II (BDI-II), Brief Symptom Inventory (BSI), and Psychiatric subscale of the Addiction Severity Index (ASI). Significant group-by-time interactions were observed for all measures of psychiatric severity examined: BAI ($p < .05$), BDI-II ($p < .01$), 5 BSI subscales ($ps < .05$), and the ASI Psychiatric subscale ($p < .05$). On all measures, IBT participants reported significantly reduced psychiatric severity at the 4-, 8-, and 12-week assessments relative to baseline. In contrast, there were no significant changes in psychiatric symptoms among WLC participants. IBT without counseling may improve psychiatric distress among waitlisted individuals with opioid use disorder.

Public Health Significance

Interim buprenorphine treatment was associated with an improvement in psychiatric symptoms among waitlisted individuals with opioid use disorder. These data provide further support for the use of interim opioid treatment approaches for reducing individual and societal risks when only a waiting list is available.

Keywords: opioid use disorder, buprenorphine, psychiatric symptoms, depression, interim treatment

Opioid abuse and dependence represent a serious public health epidemic in the United States, with over 2.5 million Americans meeting criteria for opioid use disorder (OUD) related to heroin or prescription opioid abuse (Substance Abuse and Mental Health Services Administration, 2015). OUD is associated with a host of adverse consequences, including infectious disease, overdoses, and premature death, as well as significant economic costs (Birnbaum et al., 2011; Clausen, Waal, Thoresen, & Gossop, 2009; Hser,

Hoffman, Grella, & Anglin, 2001; Jones, Mack, & Paulozzi, 2013). Psychiatric comorbidities, particularly mood, anxiety, and personality disorders, are also highly prevalent among individuals with OUD (Strain, 2002), with prevalence of psychiatric disorders in this group nearly fourfold that of the general population (Calhoun, Trauer, Munro, & Whelan, 2001; González-Saiz et al., 2011; Kessler, Chiu, Demler, Merikangas, & Walters, 2005; Kidorf et al., 2004). Concurrent opioid dependence and psychiatric distress also

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The primary outcomes from the parent trial were published in December 2016 (Sigmon et al., 2016). Preliminary versions of this secondary analysis were included in poster presentations at two national scientific conferences in October 2016 and June 2017. [ClinicalTrials.gov NCT02360007](https://clinicaltrials.gov/ct2/show/study/NCT02360007).

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likely confer additive vulnerabilities. For example, while OUD itself is associated with a suicide risk 14 times that of the general population, a concurrent psychiatric diagnosis further increases opioid-dependent patients' risk of suicidality, poor physical health, and decreased quality of life (Cacciola, Alterman, Rutherford, McKay, & Mulvaney, 2001; Carpentier et al., 2009; Darke & Ross, 2002).

Maintenance treatment with opioid agonist medications (e.g., methadone, buprenorphine) represents the most widely used and efficacious approach for treating OUD (Johnson et al., 2000; Mattick, Breen, Kimber, & Davoli, 2014; Stotts, Dordill, & Kosten, 2009). Methadone and buprenorphine treatments have been consistently shown to reduce illicit drug use, morbidity, mortality, criminality, and the spread of infectious disease (Ball & Ross, 1991; Marsch, 1998; Mattick, Breen, Kimber, & Davoli, 2009). Patients also often experience a reduction in psychiatric symptoms upon entering treatment (Fingleton, Matheson, & Jaffray, 2015). With depression, for example, the incidence and severity of depressive symptoms reliably decrease during opioid maintenance (Darke et al., 2009; Dean, Bell, Christie, & Mattick, 2004; Havard, Teesson, Darke, & Ross, 2006; Pani et al., 2011).

It is important to note, however, that methadone and buprenorphine treatments typically include some form of psychosocial counseling, generally in the form of individual or group therapy (Ball & Ross, 1991; Clark, 2001; Johnson, Strain, & Amass, 2003). Indeed, the studies demonstrating improvements in psychiatric symptoms during opioid maintenance have generally done so in the context of treatments involving counseling. We are aware of only three studies that have examined psychiatric symptoms as secondary outcomes during medication-only treatment for OUD. The primary focus of those studies was whether administration of methadone (Gruber, Delucchi, Kielstein, & Batki, 2008; Schwartz, Kelly, O'Grady, Gandhi, & Jaffe, 2012) or buprenorphine (Krook et al., 2002) alone, without counseling, on an interim basis, could reduce illicit drug use and other risks among individuals with OUD awaiting entry into traditional, more comprehensive opioid maintenance treatment. While those studies provided some evidence that psychiatric symptoms may improve during methadone or buprenorphine treatment without counseling, they did not examine within-group changes in symptoms over time. Those studies also used limited assessments of psychiatric severity.

We recently developed a novel interim buprenorphine regimen for reducing illicit opioid use and other risk behaviors among waitlisted adults with OUD and demonstrated its initial efficacy in a 12-week randomized trial (Sigmon et al., 2016). In the present secondary analyses, we examine between- and within-group changes in psychiatric symptoms during interim buprenorphine treatment (IBT) without counseling, while employing a waitlist control (WLC) condition and evaluation of symptoms before and repeatedly throughout the trial.

Method

Participants

Participants were recruited via flyers posted in the community, distributed through treatment providers and mailed to waitlisted individuals between November 2014 and February 2016. Eligible participants had to be ≥ 18 years old, be in good health, meet

DSM-5 (American Psychiatric Association, 2013) criteria for OUD, provide an opioid-positive urine, and be waitlisted for methadone or buprenorphine treatment. Individuals who were pregnant or nursing were excluded, as were those who had a significant and unstable psychiatric (e.g., active psychosis) or medical (e.g., acute cardiovascular disease) illness that could interfere with consent or participation. Individuals who were physically dependent on sedative-hypnotics or alcohol were also excluded. All participants provided written informed consent. The study was approved by the University of Vermont Institutional Review Board, and participants provided written informed consent prior to participating.

Parent Trial Design

Participants were enrolled in a randomized clinical trial evaluating the initial efficacy of an IBT regimen for waitlisted adults with OUD (Sigmon et al., 2016). They were randomized to one of two 12-week conditions: IBT ($n = 25$) or continued WLC ($n = 25$). IBT participants received buprenorphine maintenance, visiting the research clinic bimonthly to ingest their dose under observation of research staff. They received the remaining doses for the upcoming 2-week interval in a portable, disk-shaped computerized medication dispenser (Med-O-Wheel Secure; Addoz, Forssa, Finland) for ingestion at home. No formal counseling or psychosocial support was provided. Participants received nightly calls from an automated interactive voice response (IVR) system, which was developed by our group for this study. The IVR system assessed any opioid use, other illicit drug or alcohol use, and opioid craving and withdrawal, and participants entered responses via the phone keypad. These daily calls averaged 1.24 ± 0.40 min in duration. Reports of drug use prompted additional follow-up questions (e.g., amount, route of administration), as well as encouragement to attend support meetings in the community. The IVR system also permitted immediate connection with staff if a participant had any urgent concerns or questions. Finally, IBT participants were contacted via IVR twice monthly (generally once per 2-week dosing interval) and instructed to return to the clinic within a specified timeframe (typically 12 hr) for a random call-back visit. They were instructed to refrain from taking that day's dose and instead bring their Med-O-Wheel to the clinic. At each of these random call-backs, participants presented their device for inspection and pill count. They ingested that day's dose under nurse observation and provided a urine specimen.

WLC participants remained on the waitlist of their local clinic. Participants in both conditions completed 4-, 8-, and 12-week follow-up assessments involving completion of participant- and staff-administered assessments (described below) and provision of urine specimens under same-sex staff observation. Research staff also provided all participants with handouts of community resources (e.g., mental health, medical and dental care, housing, employment).

Measures

As the intake assessment has been described in full previously (Sigmon et al., 2016), we focus here on the measures evaluating psychiatric symptoms. At study intake, participants completed the Beck Anxiety Inventory (BAI; Beck & Steer, 1993), Beck Depres-

sion Inventory–II (BDI-II; Beck, 1996), Brief Symptom Inventory (BSI; Derogatis, 1993), and the Addiction Severity Index (ASI; McLellan et al., 1992). The BAI is a 21-item self-report instrument that measures the severity of anxiety in the past week. On the BAI, cutoff scores of 10 and 19 reflect mild and moderate anxiety, respectively (Beck & Steer, 1993; Kabacoff, Segal, Hersen, & Van Hasselt, 1997). The 21-item BDI-II assesses severity of depressive symptomatology in the past 2 weeks using *DSM–IV* depressive disorder criteria (American Psychiatric Association, 2000), with scores of 17 or greater indicating clinically significant depression (Beck, 1996; Sprinkle et al., 2002). The BSI is a 53-item self-report inventory that assesses psychiatric symptoms and has been normed to both psychiatric and nonpsychiatric patients (Derogatis, 1993). It consists of nine subscales and three indices (i.e., Global Severity Index [GSI], Positive Symptom Distress Index, Positive Symptom Total), with the GSI representing a widely used indicator of distress. Participants can also be dichotomized using the established clinical cutoff score on the GSI (i.e., t score ≥ 63) based on t scores adjusted to a normative sample (Derogatis, 1993). Finally, the ASI is a semistructured interview assessing lifetime and past-month problems in seven areas of psychosocial functioning. The ASI Psychiatric composite score was the focus of present analyses and ranges from 0 to 1, with higher values indicating greater severity. A cutoff of 0.27 has been used to identify individuals in need of mental health services (Drymalski & Nunley, 2016). In addition to study intake, all participants completed follow-up assessments at Weeks 4, 8, and 12 that included the above measures as well as provision of a staff-observed urine specimen. They received \$30 for completing each assessment, independent of urinalysis results.

Statistical Method

IBT and WLC groups were compared on baseline psychiatric subscales using t tests for continuous outcomes and chi-square tests for categorical measures. Outcome measures consisted of mean scores on the BAI, BDI-II, BSI, and ASI Psychiatric subscale, assessed at intake and postrandomization Weeks 4, 8, and 12. Mixed-model repeated-measures analyses based on restricted estimated maximum likelihood estimation procedures and compound symmetry covariance structure were used to compare temporal changes between IBT and WLC groups. Linear contrasts were used to compare time-specific changes within and between groups. Means reported are least square means, which adjust for missing data. Generalized estimating equations were used to examine within- and between-group differences on the percentage of

subjects above the clinical cutoff of the GSI. All analyses were performed using SAS Statistical Software, Version 9.4 (SAS Institute, Cary, NC).

Results

Participants

A full description of participants' demographic and drug use characteristics has been reported previously (Sigmon et al., 2016). Briefly, participants had used opioids regularly for 7.2 ± 6.1 years, and 78% reported a lifetime history of intravenous drug use. Fifty-two percent endorsed heroin as their current primary drug of abuse and 48% prescription opioids. Participants had been on a treatment waitlist for 3.3 ± 2.5 months. The two groups did not significantly differ on any measured baseline characteristic.

Retention rates for the 12-week study were favorable for both groups and did not significantly differ (92% and 80% for the IBT and WLC conditions, respectively). In terms of the primary outcome in the randomized parent study (i.e., abstinence from illicit opioids), participants randomized to IBT submitted a higher percentage of specimens testing negative for illicit opioids than those in the WLC group at the 4-week (88% vs. 0%), 8-week (84% vs. 0%), and 12-week (68% vs. 0%) follow-up timepoints ($ps < .001$; Sigmon et al., 2016). Additionally, adherence to buprenorphine administration was high (99%). With regard to the psychiatric measures that were the focus of this report, intake characteristics for the full sample and each experimental group are presented in Table 1. There were no significant differences on these measures between experimental conditions.

BAI

Participants presented with a mean BAI score of 15.56 ± 14.5 at study intake. Mixed-model repeated-measures analyses resulted in a significant group-by-time interaction, $F(3, 126) = 3.33$, $p = .021$ indicating changes over time were different between the two groups (Figure 1, upper left panel). IBT and WLC participants were significantly different on the mean change in BAI scores from study intake to Week 4 ($p = .015$) and from intake to Week 8 ($p = .005$). Group differences were not statistically significant for the change from intake to Week 12 ($p = .054$). Within-group comparisons showed that mean BAI scores in the IBT group were significantly lower at Weeks 4, 8, and 12 compared to the intake assessment ($ps < .01$). There was no evidence of change in mean BAI scores among WLC participants, $F(3, 127) = 0.97$, $p = .41$.

Table 1
Participants' Psychiatric Characteristics at Study Intake

Variable	Full sample	IBT ($n = 25$)	WLC ($n = 25$)	p value
Beck Anxiety Inventory	15.6 ± 14.5	17.6 ± 16.6	13.5 ± 11.9	.23
Beck Depression Inventory	20.2 ± 13.1	21.6 ± 13.9	18.9 ± 12.4	.45
Brief Symptom Inventory				
Global Severity Index	$.97 \pm .93$	1.10 ± 1.10	$.84 \pm .73$	.26
Addiction Severity Index				
Psychiatric subscale	$.28 \pm .21$	$.32 \pm .24$	$.23 \pm .18$	.16

Note. Values represent mean $\pm$ SD unless otherwise indicated. IBT = interim buprenorphine treatment; WLC = waitlist control.

BDI-II

Participants' mean BDI-II score was 20.20 ± 13.1 at intake. There was a significant group-by-time interaction, $F(3, 125) = 11.26$, $p < .001$, indicating changes over time were different between groups (Figure 1, upper right panel). IBT and WLC participants were significantly different on their mean change in BDI-II scores from study intake to Week 4 ($p < .001$), intake to Week 8 ($p < .001$), and intake to Week 12 ($p < .001$). BDI-II scores significantly decreased over time within IBT participants, $F(3, 125) = 26.62$, $p < .001$, with scores significantly lower than intake at the 4-, 8-, and 12-week assessments ($ps < .001$). No significant changes in mean BDI-II scores were observed in WLC participants, $F(3, 126) = 1.29$, $p = .28$.

BSI

On the GSI subscale of the BSI, participants' mean score at intake was 0.97 ± 0.93 . There was a significant group-by-time interaction, $F(3, 125) = 6.13$, $p < .001$, indicating changes over time were different between groups (Figure 1, lower left panel). Mean changes from study intake to Week 4 ($p < .001$), intake to Week 8 ($p < .001$), and intake to Week 12 ($p = .002$) were significantly different between IBT and WLC participants. GSI scores significantly decreased over time within IBT participants, $F(3, 125) = 18.58$, $p < .001$, and were significantly lower than intake at the 4-, 8-, and 12-week assessments ($ps < .001$). There were no significant changes in mean GSI scores in WLC participants, $F(3, 126) = 0.92$, $p = .43$.

Global Severity Index

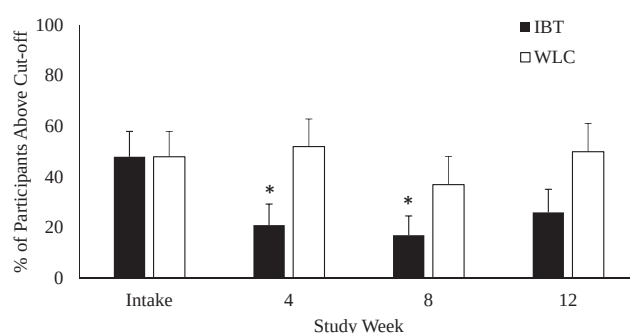


Figure 2. The percentage of participants at study intake and each assessment whose Global Severity Index score exceeds the clinical cutoff (t score ≥ 63). The differences between groups were not statistically significant. Asterisks indicate a significant difference between intake and assessment timepoint within the interim buprenorphine treatment (IBT) group. Error bars represent SEM. WLC = waitlist control.

As an additional measure of clinical significance, we examined the percentage of participants in each group whose GSI scores exceeded the established clinical cutoff (t score ≥ 63). Prior to randomization, 48% of both IBT and WLC participants presented with GSI scores above the cutoff (see Figure 2). At the 4-, 8-, and 12-week assessments, 21%, 17%, and 26% of IBT participants remained above the clinical cutoff, respectively, compared to 52%, 37%, and 50% of WLC participants. There was not sufficient

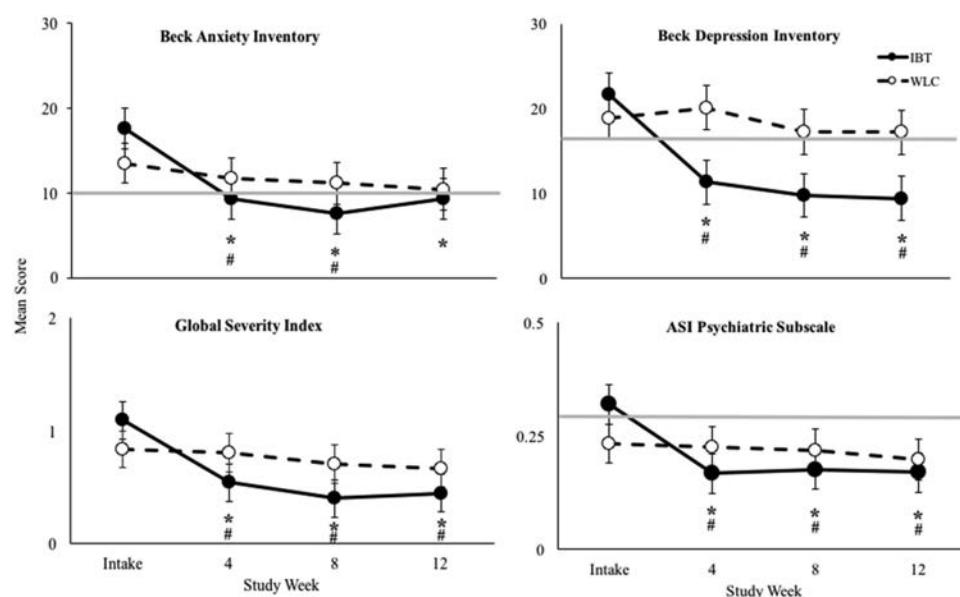


Figure 1. Changes over time in Beck Anxiety Inventory (BAI), Beck Depression Inventory–II (BDI-II), Global Severity Index (GSI), and Addiction Severity Index (ASI) Psychiatric scores for interim buprenorphine treatment (IBT) and waitlist control (WLC) conditions. Some y-axes are presented on a smaller scale to permit detailed inspection of data. The gray horizontal lines represent established clinical cutoff scores for the BAI (≥ 10), BDI-II (≥ 17), and ASI (0.27). For all panels, error bars represent SEM, asterisks indicate a significant difference between intake and the assessment timepoint within the IBT group, and hash marks indicate that the change from intake to assessment timepoint significantly differed between IBT and WLC groups ($p < .05$).

evidence of a group-by-time interaction (Wald $\chi^2 = 5.96$, $df = 3$, $p = .11$). Within-group comparisons showed a significant decrease in the percentage of IBT participants above this clinical cutoff at Weeks 4 ($p = .006$) and 8 ($p = .003$) but not at Week 12 ($p = .055$). No significant decreases were observed within WLC participants ($ps > .30$).

BSI Subscales. There were significant group-by-time interactions on five of the BSI subscales: Interpersonal Sensitivity, $F(3, 125) = 4.92$, $p < .01$; Depression, $F(3, 125) = 5.36$, $p < .01$; Anxiety, $F(3, 124) = 3.46$, $p < .05$; Obsessive–Compulsive, $F(3, 124) = 4.40$, $p < .01$; and Paranoid Ideation, $F(3, 126) = 4.41$, $p < .01$ (data not shown). The change from study intake to Weeks 4, 8, and 12 in IBT participants was significantly different from the change in WLC participants ($ps < .01$). Mean scores on these subscales decreased significantly over time among participants in the IBT group ($ps < .01$) with mean scores lower at 4-, 8-, and 12-week assessments compared to intake ($ps < .01$). In contrast, there was no evidence of temporal changes on these subscales among WLC participants.

ASI

Finally, a similar pattern was seen on the ASI Psychiatric subscale. Participants presented at study intake with a mean score of 0.28 ± 0.21 . There was a significant group-by-time interaction, $F(3, 126) = 3.56$, $p = .016$ (Figure 1, lower right panel). The changes from study intake to Weeks 4, 8, and 12 were significantly different between IBT and WLC participants ($ps < .05$). Scores significantly decreased over time among IBT participants, $F(3, 125) = 9.25$, $p < .01$, and were significantly lower than intake at Weeks 4, 8, and 12 ($ps < .01$). No changes were observed among WLC participants, $F(3, 127) = 0.32$, $p = .81$.

Discussion

Baseline levels of anxiety and depression among adults with opioid use disorder waitlisted for methadone or buprenorphine treatment were elevated, with scores on psychiatric measures at intake exceeding established clinical cutoffs. This is consistent with prior studies reporting elevated baseline psychiatric severity prior to enrollment in opioid treatment (Dean et al., 2004; Griffin et al., 2014; Nunes, Sullivan, & Levin, 2004). Participants randomly assigned to receive IBT experienced significant reductions in psychiatric severity. In contrast, no changes in psychiatric symptoms were seen among participants assigned to the continued WLC condition. Improvements in the IBT group were observed across all measures examined (e.g., depression, anxiety, global psychiatric distress) and occurred relatively early in treatment, with symptom severity decreasing markedly in the initial weeks following intake and remaining significantly lower than baseline throughout the 12-week study. These data align with prior studies demonstrating reductions in psychiatric symptom severity upon entry into opioid maintenance (Dean et al., 2004; Fingleton et al., 2015). Unlike the previous studies, however, the reductions in psychiatric distress seen here occurred in the absence of any formal psychosocial counseling.

These findings build upon the existing literature in several ways. This investigation is the first to our knowledge to examine within- and between-groups changes in psychiatric symptoms among

adults with OUD receiving medication alone. Additionally, the inclusion of a WLC condition provided a unique opportunity to document the persistent psychiatric distress among individuals who remain on waitlists. Considering that 96% of states in the United States have OUD rates that exceed their medication-assisted treatment capacity, waitlists are an all too common reality, and an improved understanding of the individual and societal consequences of these treatment delays is important (Jones, Cam-piano, Baldwin, & McCance-Katz, 2015).

Several limitations should also be noted. First, this secondary analysis reported on data from a relatively small pilot study, and additional studies should seek to evaluate this question in larger samples. Second, as no formal diagnostic psychiatric interviews were included in the parent study, it is unclear whether participants' psychiatric symptoms were associated with an underlying clinical disorder or rather stemmed from distress related to their illicit drug use or inability to access treatment in a timely manner (Callaly et al., 2001; Strain, 2002). Third, it is unclear whether the observed improvements in psychiatric symptoms were moderated by illicit opioid abstinence, although this is an empirical question we hope to examine in a subsequent study on this topic with a larger sample size and greater heterogeneity in abstinence outcomes than was seen in the parent trial (Sigmon et al., 2016). Nonetheless, the marked reductions in psychiatric severity seen in the IBT group suggest clinically meaningful improvements in symptoms over time, regardless of their underlying cause. Fourth, it is impossible to evaluate the contribution of the individual IBT components (i.e., buprenorphine, daily IVR calls, brief study visits) to the outcomes observed. For example, while we do not anticipate that a 1-min call from a computerized IVR system likely contributed to the pronounced improvements in psychiatric symptoms observed, this too is an empirical question that should be addressed in future studies. The extent to which IBT participants' psychiatric improvements may be related to potential antidepressant effects of buprenorphine, for example, is also unknown but warrants further research (Fava et al., 2016; Karp et al., 2014). Fifth, future studies should examine changes in psychiatric symptoms over longer periods, as the present 12-week study is brief relative to the durations of opioid maintenance treatment that patients typically receive. Finally, changes in psychiatric distress during IBT should also be examined relative to changes in symptoms during more comprehensive treatment that involves counseling.

In summary, the prevalence of depression, anxiety, and general psychiatric distress among individuals with OUD far exceeds that of the general population. IBT, without formal counseling, may attenuate psychiatric distress in this vulnerable population while they await entry into comprehensive treatment. These results lend additional support for the potential utility of interim treatment approaches for reducing the individual and societal risks during treatment delays.

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