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Randomized controlled trial of MICBT for co-existing alcohol misuse and depression: Outcomes to 36-months

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Abstract

Integrated psychological treatment addressing co-existing alcohol misuse and depression has not been compared with single-focused treatment. This trial evaluates changes over 36 months following randomization of 284 outpatients to one of four motivational interviewing and cognitive-behavior therapy (MICBT) based interventions: (1) a brief integrated intervention (BI); or BI plus 9 further sessions with (2) an integrated-, (3) alcohol-, or (4) depression-focus. Outcome measures: changes in alcohol consumption, depression (BDI-II: Beck Depression Inventory) and functioning (GAF: Global Assessment of Functioning). There were overall improvements at each timepoint relative to baseline (e.g., average improvement: 21.8 drinks per week; 12.6 BDI-II units; 8.2 GAF units). Longer interventions tended to be more effective in reducing depression and improving functioning, but not alcohol consumption, except during the initial treatment phase. Integrated treatment was at least as good as single-focused MICBT, with alcohol-focused treatment being relatively more effective in reducing alcohol misuse. The best approach seems to be an initial focus on both conditions followed by additional integrated- or alcohol-focused sessions.

Keywords: Depression, Alcohol dependence, Comorbidity, Cognitive behavior therapy, Motivational Interviewing, Long-term outcomes, Randomized controlled trial.

1. Introduction

Alcohol misuse and depression frequently co-occur (Teesson, Slade, & Mills, 2009), especially in clinical settings (Rush & Koegl, 2008; Weaver et al., 2003), and adverse clinical and health care utilisation outcomes are common (Sullivan, Fiellin, & O'Connor, 2005). Depressive symptoms are associated with poorer alcohol treatment outcomes (Burns, Teesson, & O'Neill, 2005) and heavy drinking, especially binge drinking, has been found to produce depressive symptoms (Paljärvi et al., 2009). Remission of problem drinking has also been found to significantly and strongly increase the chances of remission in depression (Hasin et al., 1996). Thus, it has been suggested that treatment for mood disorder should not be withheld from people who misuse alcohol (Grant et al., 2004).

Relatively few trials have focused on the treatment of co-existing alcohol misuse and depression (e.g., Kay-Lambkin, Baker, Lewin, & Carr, 2009; Markowitz, Kocsis, Christos, Bleiberg, & Carlin, 2008; Satre, Delucchi, Lichtmacher, Sterling, & Weisner, 2013) and, as several reviews have noted, further research in this area is needed (e.g., Baker, Thornton, Hiles, Hides, & Lubman, 2012; Hides, Samet, & Lubman, 2010; Kelly, Daley, & Douaihy, 2012; Richardson, 2012; Tiet & Mausbach, 2007). There have also been calls for more targeted approaches to pharmacological treatments for comorbid substance use and mood disorders, which go beyond evidence based on single disorders (Pettinati, O'Brien, & Dundon, 2013).

While it seems reasonable to develop integrated interventions for co-existing alcohol misuse and depression (versus parallel or sequential treatments), the evidence base supporting integrated interventions is mixed. Cornelius and colleagues (2011) reported that adolescents with comorbid alcohol use disorder and major depression, who had participated in a manual guided nine session intervention

of cognitive-behavior therapy (CBT) and motivational enhancement therapy (MET) addressing both alcohol misuse and depression, showed greater improvement in the number of criteria for alcohol use disorder and depressive symptoms at a two-year follow-up assessment compared to a naturalistic comparison group who had not received CBT and MET. On the other hand, Brown and colleagues (2011) recently failed to replicate findings from their 1997 pilot trial (Brown, Evans, Miller, Burgess, & Mueller, 1997), which had found positive outcomes among partially hospitalized alcohol-dependent individuals with elevated depressive symptoms who received eight individual sessions of CBT for depression compared with a relaxation training control. They reported significant improvements in alcohol use and depression outcomes over time for all participants.

As far as we are aware, no trials have compared integrated treatment with traditional, single-focused treatment programs for alcohol misuse or depression. We aimed to address this need in the DAISI trial (Depression and Alcohol Integrated and Single-focused Interventions). We have previously reported patterns and predictors of early change (from screening to session 10) and described short-term (18-week) results (Baker et al., 2010; Baker et al., 2013). The current paper reports longer-term outcomes from this trial and includes all follow-up timepoints, from 18-weeks to 36-months post-baseline. We predicted that: (a) compared with a brief intervention (BI) control condition, 10 treatment sessions would produce greater reductions in alcohol consumption and depression and greater improvement in global functioning; (b) integrated treatment would have greater impacts on these variables than single-focused treatment; and (c) alcohol-focused and depression-focused treatments would have greater impacts on their corresponding domains.

2. Materials and methods

2.1. Design

A multi-site randomised controlled trial (RCT) was conducted comparing several manualised motivational interviewing and cognitive-behavior therapy based psychological interventions (MICBT) for adults with co-existing alcohol misuse and depression. Participants provided written informed consent for the study. Following baseline assessments, all participants were offered a single session of BI (described later), after which they were randomized to no further treatment (*n* = 70) or to 9 further sessions of integrated- (*n* = 75), alcohol- (*n* = 68), or depression-focused (*n* = 71) treatment; original power calculations were based on projected retention rates of 80 participants per condition. Randomization was stratified by study site, gender, and presence of concurrent antidepressant or anti-craving medication. Independent psychologists, blind to treatment allocation, completed follow-up assessments either face-to-face or by telephone. Participants were assessed at baseline, 18-weeks, 6-, 12-, 24-, and 36-months. The treatment phase of the study was implemented between October 2005 and April 2007 across two east-coast Australian cities (Newcastle and Brisbane). Participants attended sessions in research clinics, community mental health, or alcohol and other drug centers. Follow-up data collection finished in August 2010. This trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: www.anzctr.org.au) – Trial acronym: DAISI (Depression and Alcohol Integrated and Single-focused Interventions); registered: 18th January, 2007 (identifier: ACTRN12607000057482).

2.2. Participants

Inclusion criteria were: (i) aged over 16 years; (ii) a BDI-II (Beck, Steer, & Brown, 1996) score ≥ 17; and (iii) hazardous alcohol consumption in the month before baseline (≥ an average of 4 10gm ethanol drinks per day for men, ≥ 2 per day for women) (Lau-Barraco, Skewes, & Stasiewicz, 2009; Stockwell, 2001). Potential participants were excluded if they: (i) were currently diagnosed with a psychotic disorder; (ii) reported a history of traumatic brain injury; (iii) lacked fluency in English; or (iv) lived too far away to attend sessions. Most participants self-referred, after seeing television advertisements or media stories (76%) or hearing about the study from others (7%), while 14% were referred by health agencies. Although participants were not excluded on the basis of current pharmacotherapy, entry to the study was delayed until 4 weeks after commencing any new medications or changing treatment regimens. Thus, at entry to the study some participants were already engaged in treatment for alcohol misuse and/or depression, while others were community members receiving no formal treatment. Participants were not discouraged from engaging in treatments other than the DAISI project, but that involvement was tracked.

2.3. Measures

Primary outcome measures. Since different elements of alcohol consumption and functioning could potentially be impacted by the interventions, and given our interest in comorbid conditions, 5 primary outcome measures were identified, each expressed as change from baseline (i.e., follow-up minus baseline score). Three self-report alcohol consumption indices were included: 1) change in estimated standard drinks per day, based on Q-scores for alcohol from the Opiate Treatment Index (OTI) (Darke, Hall, Wodak, Heather, & Ward, 1992), which estimates average use

occasions per day for a range of substances in the previous month (limited results for baseline tobacco and cannabis are also reported); 2) change in total standard drinks per week, based on a 2-week timeline follow back (TLFB) procedure (Sobell & Sobell, 1992); and 3) change in percent of days heavy drinking, derived from TLFB responses, for which the daily threshold for heavy drinking was set at ≥ 6 standard drinks for men and ≥ 4 standard drinks for women (Sobell, Sobell, Connors, & Agrawal, 2003); the validity of relatively short TLFB assessment timeframes has been demonstrated (Toll, Leeman, McKee, & O'Malley, 2008).

The other primary outcome indices were: change in depressive symptoms, assessed using the 21-item Beck Depression Inventory - II (BDI-II) (Beck et al., 1996), for which higher total scores (0-63) indicate greater severity; and change in Global Assessment of Functioning (GAF) (APA, 1994) scores, a clinician-rated indicator of psychological, social and occupational functioning (on a single 0-100 anchored scale), which has been found to be more reliable in research settings than in routine clinical use (Aas, 2011; Startup, Jackson, & Bendix, 2002; Vatnaland, Vatnaland, Friis, & Opjordsmoen, 2007).

Other measures. In addition to questions about socio-demographic characteristics, a range of measures were used at baseline to quantify the duration and severity of existing conditions. The Structured Clinical Interview for DSM-IV-TR (SCID) (First, Gibbon, Spitzer, & Williams, 1995) provided current and lifetime diagnoses of a major depressive episode, alcohol abuse and dependence. Alcohol consumption was assessed at baseline using the Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Aasland, Babor, De La Fuente, & Grant, 1993). A Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell, Sitharthan, McGrath, & Lang, 1994) also assessed degree of dependence on alcohol over the preceding 6

months at baseline. Additional measures (e.g., therapeutic alliance, craving, neurocognitive assessments) are reported elsewhere (Baker et al., 2010; Baker et al., 2013; Connolly et al., 2013; Hunt, Baker, Michie, & Kavanagh, 2009).

2.4. Interventions

The intervention manual (Kay-Lambkin, Baker, Hunt, Kavanagh, & Bucci, 2005) was adapted from that evaluated in the study by Kay-Lambkin *et al.* (2002; 2011; 2009) and the interventions have previously been described (Baker et al., 2010); the DAISI treatment manual is also included in the supplementary documentation. Each weekly session was conducted individually and commenced with a review of the previous week, including homework completion, a suicide risk assessment, and negotiation of the session agenda. In order to consolidate commitment to change, motivational interviewing (MI; Miller & Rollnick, 2002) was thematically employed throughout therapy.

Session 1 (the content of which did not differ between treatment conditions), was received by all participants and comprised assessment feedback, case formulation (covering the development and maintenance of co-existing depression and alcohol problems), MI, planning for behavior change, and education about hazardous alcohol use and depression. In three of the treatment conditions (integrated-, alcohol-, and depression-focused), nine weekly one-hour sessions followed. These three treatments were designed to be identical in their MICBT structure and duration, while differing in the focus of the content. For example, in session 2, participants received a rationale for CBT, and then those in the alcohol-focused treatment began monitoring cravings, those in the depression-focused treatment did mood monitoring, and those in the integrated treatment monitored both

mood and cravings. Activity scheduling and mindful walking were covered in all three treatment conditions.

In Session 3, there was an introduction to thought monitoring, assessment of change, and mindful listening, again, with a focus on alcohol, depression or both, as dictated by treatment allocation. Session 4 included development of an activity list, clarification of the change plan, information about cravings (for the alcohol-focused treatment) or coping with impulsive thoughts (for the depression-focused treatment) or both (for the integrated treatment), and mindfulness of pleasant activities. In Session 5, there was a focus on identifying and managing unhelpful automatic thoughts and application of mindful breathing, while in Session 6, problem solving and mindful visual experiences were introduced.

Session 7 saw participants identify and examine evidence for problematic schema and core beliefs, and practice using a 3-minute breathing space. In Session 8, participants continued cognitive therapy, incorporating ‘allowing and letting be’, practiced alcohol refusal skills (for the alcohol-focused treatment) or assertiveness (for the depression-focused treatment) or both (for the integrated treatment), and developed an emergency plan. Relapse prevention techniques based on work of Marlatt and Gordon (1998) and further mindfulness practice were covered in Session 9. In Session 10, participants applied MI to relapse prevention and wrote a management plan for relapse risk.

Baseline assessment and therapy were conducted by intern psychologists, psychologists or clinical psychologists, who met weekly for supervision, where selected audiotaped sessions and issues in applying treatments were discussed. Therapists worked across the 4 intervention conditions.

2.5. Procedures

Approval for this project was obtained from relevant regional Ethics Committees (Hunter New England, the University of Newcastle, the University of Queensland and the Queensland University of Technology Ethics Committees). Following informed consent, baseline assessments were typically completed over two 1.5 hour sessions a week apart, and reimbursement of up to $AUS20 was given for travel and other costs. Participants were informed that if they failed to attend three consecutive treatment sessions, without adequate explanation, they would be considered to have discontinued treatment. Reimbursement was not provided for treatment sessions. Future contact details for participants and an alternative contact person were sought at baseline to enable re-contact for the follow-up assessment.

Randomization was generated at the beginning of the study by the Research Manager at the Newcastle site, and linked to a unique identification code. Allocations were concealed in individual sealed envelopes labeled with the code, which were opened by participants at the end of Session 1, ensuring that the content and experience of the initial session would be unaffected by knowledge of the allocation.

Collateral reports were obtained on at least 1 of the 6- or 12-month assessment occasions for 150 participants (58%; 150/258 of the post-treatment sample). Partners (51%), relatives (28%), or friends (21%) completed a subset of five AUDIT items about the participant's recent alcohol consumption (frequency of use, typical consumption, binge drinking, associated injuries, and concerns expressed). Total scores derived from these items were compared with the equivalent scores from participants. At both the 6- and 12-month follow-up assessments, participant and collateral agreement was reasonable (6-month: $r = 0.579$, $p < 0.001$; 12-month: $r = 0.460$, $p < 0.001$), with no instances of substantial under-reporting.

2.6. Statistics

All analyses were conducted using SPSS software (Version 19.0; SPSS, Chicago, IL, USA). The major analyses comprised a series of generalized linear models (and, where appropriate, generalized estimating equations), with change scores from baseline as the dependent variables, whilst controlling for gender, 'other treatment' status during the focal timeframe, and baseline values for the outcome of interest. Participants without any follow-up assessments were excluded from these analyses (n = 26), however, they were included in the linear regression analyses used to assess potential retention biases. 'Other treatment' during the preceding 12 months (for each timeframe) was coded using three dummy variables, reflecting any self-reported usage of antidepressant medication, receipt of any mental health related treatment, or any substance misuse treatment (excluding study based interventions).

In the major analyses, three planned orthogonal (Helmert) contrasts were used to assess treatment effects: a) BI *vs* 10 sessions; b) integrated- *vs* single-focused; and c) alcohol- *vs* depression-focused. A separate analysis was conducted for each outcome measure at each follow-up timepoint, as well as overall (i.e., across the five timepoints, controlling for the within-subject elements). Parameter estimates and their associated 99% confidence intervals (CI) are reported for each of the contrasts examined (i.e., estimated mean differences in change scores, see Tables 2 and 3), while changes from baseline for the total sample are reported in the supplementary documentation (see Tables S2 and S3).

The approach described above provides analogous results to an analysis of covariance with baseline scores as a covariate (by controlling for some of the

variance in change due to differences in baseline levels), but with the added benefit of using a reporting metric that is easier to interpret and to compare across successive timepoints (i.e., change from baseline). All analyses were conducted using the intention-to-treat (ITT) principal (i.e., treatment as allocated, regardless of the number of sessions attended), although individuals with missing data at a given follow-up timepoint were not included in the analysis of that timepoint. The criterion for statistical significance was $p \leq 0.01$, with statistical trends also noted at $p \leq 0.05$; an alpha level of 0.01 is the equivalent of a Bonferroni-adjusted 0.05 level family-wise error rate, controlling for the 5 primary outcome measures.

3. Results

Tables S1 to S6, and Figure S1 are presented in the supplementary documentation.

3.1. Participation patterns and characteristics

Recruitment and attrition profiles are summarized in Figure 1. In total, 284 participants completed the baseline assessment and were randomized to treatment. Baseline demographic and clinical characteristics were similar across treatment conditions for the 258 participants (91%) who completed at least 1 follow-up assessment (see Table 1, and Table S1 for additional baseline characteristics); presenting characteristics for the full sample are reported elsewhere (Baker et al., 2010). On average, participants (n = 258) were aged 45.6 years (SD = 10.8) and 47% were female. The majority met SCID (DSM-IV) diagnostic criteria for alcohol dependence (89%) or depression (75%) during the last 12 months. Alcohol consumption averaged 61.1 (SD = 42.4) standard drinks per week at baseline, while the mean BDI-II score was 31.2 (SD = 8.8), falling within the “severe depression”

range (≥ 29) (Beck et al., 1996). Just over half the sample reported taking antidepressants (137/258; 53%), with a mean duration of 2 years (102.1 weeks, SD = 126.3, range 4-520). Likewise, almost three-quarters of participants (190/258; 74%) reported receiving any mental health treatment during the preceding 12 months, while one-fifth (54/258; 21%) reported any substance misuse treatment.

Figure 1 and Table 1 about here

On average, those offered 10 sessions attended 5.8 sessions (SD = 4.1, median 6.0), with participants in the integrated-, alcohol-, and depression-focused groups attending a mean (median) of 6.3 (10.0), 5.3 (4.5) and 5.6 (6.0) sessions, respectively (p = 0.305). For participants allocated to the BI, 86% attended the single treatment session that was offered. To assess potential retention biases, participants were allocated a score indicating the number of follow-up phases with outcome data available (range 0 to 5, mean 3.6, SD = 1.7, median 4.0). These scores were regressed onto 15 predictor variables, including selected baseline demographic characteristics, assessment location, 'other treatment' status, treatment condition contrasts, and baseline scores for the outcome measures. Modest associations were identified (R^2 = 0.134, p = 0.002), with 4 predictors each making marginal contributions (gender, β = -0.14, p = 0.037; assessment location, β = -0.15, p = 0.018; single-focus intervention type, β = -0.13, p = 0.035; and baseline GAF, β = 0.16, p = 0.041). In short, more follow-up datapoints tended to be available for males (3.7 *vs* 3.4), Newcastle participants (3.8 *vs* 3.2), those in the depression- *vs* alcohol-focus condition (3.9 *vs* 3.3), and those with higher baseline GAF scores.

3.2. Alcohol consumption

Mean change scores from baseline for the alcohol consumption measures are reported in Table S2. As detailed in the right-hand column of this table, there was a significant difference from baseline on each follow-up assessment occasion, with an average reduction of 3.4 standard drinks per day (OTI Q-score), 21.8 standard drinks per week (TLFB), and a 24.3 percent reduction in days heavy drinking (TLFB).

Table 2 reports selected comparisons (orthogonal contrasts) between the treatment conditions in the mean change from baseline, separately for each follow-up timepoint and overall; these are parameter estimates from generalized linear models controlling for gender, baseline score (for the relevant alcohol outcome) and 'other treatment' status for the focal timeframe. There was a trend for the longer interventions to be more effective in the short-term relative to the BI condition; namely, a differential benefit at 18-weeks on the two TLFB measures, of 11.1 drinks per week (p = 0.031) and 10.5 percent for days heavy drinking (p = 0.034). However, for the average follow-up timepoint, the longer interventions were not significantly better. Likewise, within the longer interventions, the integrated-intervention did not differ from the single-focus conditions (collectively) at any follow-up timepoint. However, for the average follow-up timepoint, there tended to be a relative advantage for the alcohol- versus depression-focus intervention, which equated to a differential benefit for the alcohol-focus intervention of 2.1 drinks per day (OTI Q-score, p = 0.012), and an 11.2 percent difference in days heavy drinking (TLFB, p = 0.021). There was some supporting evidence for this relative advantage across the 6- to 24-months timepoints in particular (i.e., 4 statistically significant differences or trends), with the direction of difference consistently favoring the alcohol-focus intervention across all timepoints (see Table 2); the impact of the alcohol-focus

intervention on days heavy drinking was notably stable across timepoints, with an average 24.3 percent reduction (see Table S2).

Table 2 about here

3.3. Depression (BDI-II) and global functioning (GAF)

Mean change scores from baseline for the depression and global functioning measures are reported in Table S3. As detailed in the right-hand column of this table, there was a significant difference from baseline on each follow-up assessment occasion, with an average improvement of 12.6 BDI-II units and 8.2 GAF units.

Table 3 reports selected comparisons between the treatment conditions in the mean change from baseline, separately for each follow-up timepoint and overall, using comparable generalized linear models to those reported for changes in alcohol consumption. For the average follow-up timepoint, the longer interventions (collectively) tended to produce greater improvement relative to the BI condition, equating to a differential benefit of 2.4 GAF units (p = 0.022). Longer interventions were particularly effective across the 12- to 36-months timepoints (i.e., 3 statistically significant differences or trends); however, the direction of difference consistently favored the longer interventions across all timepoints (see Table 3).

There was also a trend for the integrated intervention to be more effective in the short-term relative to the single-focus interventions (collectively), with a differential improvement of 3.8 BDI-II units at 18-weeks (p = 0.036); however, for the average follow-up timepoint, the integrated-intervention was not significantly better (see Table 3). Likewise, there were no significant differences in depression or global functioning changes between the alcohol- and depression-focus conditions for the average follow-up timepoint.

Table 3 about here

3.4. Other analyses

The majority of participants in the current trial reported 'other treatment' during the preceding 12 months across all of the timeframes investigated; see Table S4 for details. For example, for the 12 months preceding baseline, 71.1% reported receiving mental health treatment (with 51.8% using antidepressant medication), while 19.4% reported receiving substance misuse treatment. At 36-months, the corresponding values were 64.5% (51.0%) and 18.7%, respectively. Across the major follow-up timeframes (12-, 24- and 36-months), 81.8% of those reporting involvement in other mental health treatments (and 79.6% of those reporting antidepressant usage) during the preceding 12 months had reported similar involvement at baseline; the corresponding value for substance misuse treatments was 51.9%. Within each timeframe, there were no statistically significant associations between study treatment condition and self-reported other treatment profiles.

As expected, the primary outcome measures were not independent, with moderate overall correlations between change scores for the alcohol consumption measures (ranging from 0.39 to 0.66) and between change scores for BDI-II and GAF (-0.53), with only small cross-correlations between the alcohol and non-alcohol measures (ranging from -0.21 to 0.20); see Table S5 for details.

A useful method for evaluating the overall magnitude and clinical relevance of the observed changes is to re-apply the study inclusion criteria to the outcome data. Based on combined data from 24- and 36-months (324 assessments), 31% would have still met study inclusion criteria (BDI-II score ≥ 17 and hazardous alcohol consumption during the last month), with a significant overall difference between treatment conditions (BI: 48%; integrated: 24%; alcohol-focus: 23%; depression-focus: 30%; $p = 0.004$); see Table S6 for details by follow-up phase.

4. Discussion

Regardless of potential explanatory factors (e.g., natural recovery, initial engagement/feedback, ongoing assessment effects, regression to the mean, actual intervention effects, concurrent treatments, or some combination of these), there were clinically significant overall improvements across all of the outcome measures (see Tables S2 and S3), despite the severity of the current sample's baseline alcohol misuse and depressive symptomatology. The average standardized change profile (across all follow-up timepoints) was: 0.43 for estimated drinks per day (OTI Q-score); 0.53 for drinks per week (TLFB); 0.63 for percent of days heavy drinking (TLFB); 1.03 for depression (BDI-II); and 0.68 for global functioning (GAF). From our earlier analyses, it is also worth noting that over one-third of the change that occurred by session 10 did so *before* the first treatment session (Baker et al., 2013).

4.1. Support for hypotheses

Our first hypothesis, that the 10 session interventions would produce greater improvement compared with the BI, received only modest support for the alcohol consumption outcomes. While more effective in the short-term (see Table 2, TLFB measures), the longer interventions produced only marginal differential benefits overall (e.g., for drinks per week, standardized change: 0.55 *vs* 0.47 for the BI). Thus, our findings neither support nor contradict other studies showing positive differential impacts on drinking from alcohol-focused BI's among inpatients with severe mental disorders (Baker et al., 2002; Hulse & Tait, 2003; Kay-Lambkin et al., 2009). Comparisons between the BI condition and the longer interventions for the depression and global functioning outcomes tended to mirror one another across the

follow-up timepoints (see Table 3). Among our study sample, 10 session interventions tended to be associated with better improvement in depression and global functioning (i.e., all differences were in a consistent direction). We have previously found longer interventions to be more effective than BIs for depression among amphetamine users (Baker & Dawe, 2005) and that 10 sessions of MICBT resulted in better global functioning than BI among people with psychotic disorders and substance misuse (Baker, Turner, Kay-Lambkin, & Lewin, 2009).

There was limited support for the second hypothesis, that integrated treatment would have greater impacts than single-focused treatment. On the other hand, there was no evidence that the single-focus interventions were collectively better than the integrated approach. Only 1 of the 30 comparisons between integrated- and single-focus interventions reported in Tables 2 and 3 approached statistical significance; for the BDI-II at 18-weeks, the integrated-intervention achieved a standardized change from baseline of 1.12, compared with 0.83 for the single-focus conditions (see Table S3), with a parallel but non-significant differential effect for percent of days heavy drinking (see Table S2, standardized change: 0.91 *vs* 0.63).

In regard to the hypothesis that alcohol- and depression-focused treatments would have greater impacts on their corresponding domains, the alcohol-focus condition was demonstrably better than the depression-focus intervention for the alcohol consumption outcomes, particularly between 6- and 24-months (see Table 2). The two single-focus conditions produced reasonably comparable depression and general functioning outcomes (see Table 3).

If we had to recommend one program based on the current study's findings, then it would either be the integrated- or the alcohol-focus intervention; since the depression-focus intervention was consistently less effective for the alcohol

outcomes (see Table 2) and the BI condition was consistently less effective for the non-alcohol outcomes (see Table 3). The integrated-intervention had the additional benefit of a more rapid short-term improvement in depression (with a clinically important differential of 3.8 BDI-II units at 18-weeks), and a tendency for higher attendance and retention rates. On the other-hand, the alcohol-focus intervention produced a stable benefit with respect to days heavy drinking in particular (see Tables 2 and S2) and may be perceived as particularly relevant for the current sample (cf., Gastfriend, Garbutt, Pettinati, & Forman, 2007), among whom 89% met diagnostic criteria for alcohol dependence at baseline and 81% were identified by their study therapist as having a primary alcohol problem (see Table S1).

In any event, the longer interventions were all preceded by a common 90-minute integrated BI, which drew attention to alcohol and depression problems and their interrelationship, as did the screening, assessment and engagement strategies used in this study (Baker et al., 2013). Notwithstanding, at the longer-term follow-up assessments, the proportion of BI only participants who would have still met study inclusion criteria was twice that of the integrated- and alcohol-focus interventions (see Table S6) – suggesting that a BI alone was not sufficient for most participants.

To help synthesise the study's findings, Figure 2 presents a standardised change profile for the integrated treatment condition, which highlights the different improvement trajectories across the primary outcome measures. Improvements peaked around 18-weeks on the alcohol consumption measures (standardised change: 0.56 to 0.91), diminished somewhat by 12-months (standardised change: 0.51 to 0.62), and were then maintained at 36-months (standardised change: 0.47 to 0.66). While the change trajectories for the other measures were also steeper during the active treatment phase (prior to 18-weeks), there were modest ongoing

improvements till 36-months (depression standardised change: 1.39; global functioning standardised change: 1.26). The improvement trajectories for the alcohol-focus treatment condition were reasonably similar, but less marked during the active treatment phase (see Figure S1).

Figure 2 about here

4.2. Broader clinical research context

Given the diversity of everyday clinical presentations by those with co-existing alcohol misuse and depression, pharmacological treatments are likely to be an active component of treatment for many individuals (Kelly et al., 2012). In the current study, we chose to focus predominantly on psychological interventions, but with limited study inclusion/exclusion criteria and no constraints on ongoing involvement in other treatments. At baseline, 74.3% of participants reported that they had received mental health or substance misuse treatment in the preceding 12 months, with 51.8% reporting usage of antidepressant medication (for an average of 2 years). From our perspective, it is preferable to include such participants in clinical trials, as the results will be generalizable to a broader range of community and clinical settings; however, the potential implications for data analysis and interpretation also need to be addressed.

Across the follow-up phases, approximately two-thirds of participants reported ongoing involvement in ‘other treatment’, with around half of the overall sample continuing to report usage of antidepressant medication. However, the four intervention conditions within the study reported similar patterns of involvement across these timeframes (see Table S4), which lessens the likelihood of biased findings. Moreover, reported participation in other treatments during the preceding 12 months was included as a dynamic covariate in the major analyses (i.e., potentially

varying with the focal timeframe), together with gender and baseline scores for the selected outcomes.

Consequently, it would probably be appropriate to frame the current study as a four-armed clinical trial of MICBT interventions that were supplementary to ongoing treatment as usual (TAU) – but with the added dimension that TAU was broadly monitored and accounted for in the analysis; which is reasonably similar to '*Design 3*' in the classification system for multisite randomized (effectiveness) trials described by Nunes and colleagues (2010). While this is a positive research design feature (which enhances the generalizability of efficacy study findings), it is difficult to know whether such an approach strengthens or weakens any given study's ability to detect differential effects (e.g., BI *vs* longer interventions, both within a TAU setting). For the moment, we simply identify the 'clinical research context' within which the current study was conducted and flag this as a potential research limitation.

4.3. Other limitations

Potential recruitment and retention biases also need to be considered. By design, recruitment was based on concurrent hazardous alcohol use and depressive symptoms, rather than formal diagnostic criteria or other severity indices, which may result in the inclusion of individuals below the typical threshold for treatment in some clinical settings; however, at baseline, 96% (272/284) of the current sample met DSM-IV diagnostic criteria for *either* alcohol dependence or depression in the preceding 12 months.

Across the short-term follow-up timepoints (i.e., ≤ 12 months), the average retention rate was 80%, which dropped to 57% for the longer-term follow-up timepoints; however, 91% of the sample were included in the major generalized

linear model analyses. Furthermore, other analyses suggested that retention biases were likely to be minor, with some possible links to socio-demographic (gender, location), clinical (baseline GAF scores) and intervention characteristics (depression-focus condition).

Although several of the reported findings were based on statistical trends ($p < .05$), we have focused primarily on lessons drawn from consistent patterns and trajectories within the overall dataset, as opposed to individual effects and timeframes. However, all of these statistical trends were associated with standardized treatment differences in excess of one-quarter of a standard deviation, suggesting that they may be worthy of consideration in future studies. To the extent that we have examined change scores over five timeframes using orthogonal contrasts, while statistically controlling for gender, baseline outcome scores, and concurrent involvement in other treatments during the preceding 12 months, it could also be argued that we have made a reasonable effort to reduce the likelihood of Type 1 errors.

Despite the observed improvements, there is considerable room for further change, with 31% still meeting study inclusion criteria at the longer-term follow-up timepoints (see Table S6). Across the longer interventions, the median number of sessions attended was 6, so it is possible that better treatment attendance might have been associated with further improvement (and with greater differentiation from the BI condition). As efficacious CBT for depression has often been much longer (Beck, Rush, Shaw, & Emery, 1979), it might be worth investigating contingent reinforcement for attendance in future studies among this comorbid group. On the other hand, the magnitude of the depression improvement was similar to that achieved by Watson and Nathan (2008) among people with long histories of alcohol

and depression problems. Remaining symptomatology may be difficult to shift without substantial improvements in other domains, such as finances, social situation and employment, as addressed in some community reinforcement approaches (Meyers & Smith, 1995).

4.4. Conclusions

In everyday practice, clinicians regularly combine treatments that are likely to be effective, often employing higher intensity interventions for more severe conditions, with comorbidity being one of the factors impacting on severity (Baker et al., 2012; Kelly et al., 2012). Consequently, comorbidity research needs to identify both the treatment elements and combinations that should be considered, and the treatment settings and processes that are likely to be optimal.

Based on the current study's findings, manualised psychological interventions such as MICBT clearly contribute to sustained improvement by individuals with co-existing alcohol misuse and depression. Moreover, given the pattern of results, there is currently no reason to rule out an integrated intervention strategy addressing both conditions. However, variations in the improvement trajectories for the different outcomes that were assessed reinforce the need for more creative, multifaceted and longer-term treatment plans (cf., Kelly et al., 2012). We also need more sophisticated strategies for monitoring outcomes, adjusting treatments and evaluating changes within routine treatment settings. This includes greater attention to adjunctive treatments (Satre et al., 2013) and staged or stepped-care approaches (Hides et al., 2010; Kay-Lambkin, Baker, & Lewin, 2004; Scogin, Hanson, & Welsh, 2003), more comprehensive assessment of the predictors and moderators of treatment engagement and outcomes (Connolly et al., 2013; Hunt et al., 2009), and closer

examination of the value of booster sessions aimed at maintaining those outcomes (Hides et al., 2010).

One specific implication of the present study is that an integrated BI should be considered as a useful (but often not sufficient) first step, to help contextualize possible associations between alcohol misuse and depressive symptomatology. Thereafter, for those with continuing problems, the best approach seems to be further sessions of MICBT with either an integrated- or an alcohol-focus. The choice of intensive intervention may also depend on a range of other factors, including the therapist's training, expertise and confidence, as well as the interplay with client characteristics, such as severity and primacy, treatment acceptability and expectations, preparedness for change, and the likelihood of developing a satisfactory therapeutic alliance (Kay-Lambkin, Baker, Lewin, & Carr, 2011).

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Table 1
Selected baseline characteristics of participants who completed at least 1 follow-up assessment (*n* = 258)

Characteristic	Statistic or category	*Treatment condition*				*Total sample (n = 258)*	*p-value*[a]
		Brief (*n* = 64)	Integrated (*n* = 66)	Alcohol focus (*n* = 60)	Depression focus (*n* = 68)		
Age (years)	Mean (SD)	44.8 (10.3)	46.2 (11.5)	45.8 (10.6)	45.4 (10.9)	45.6 (10.8)	0.884
Gender	Female	28 (44%)	29 (44%)	31 (52%)	32 (47%)	120 (47%)	0.796
Marital status	Married/de facto	25 (39%)	24 (36%)	22 (37%)	15 (22%)	86 (33%)	0.361
	Previously married	23 (36%)	24 (36%)	25 (42%)	35 (52%)	107 (42%)	
SCID alcohol diagnosis – lifetime (*n* = 245)	Abuse only	0	0	3 (5.2%)	5 (7.8%)	8 (3.3%)	0.220
	Dependence	57 (96%)	62 (97%)	52 (90%)	58 (91%)	229 (94%)	
SCID alcohol diagnosis – last 12 months (*n* = 245)	Abuse only	1 (1.7%)	0	3 (5.2%)	6 (9.4%)	10 (4.1%)	0.106
	Dependence	55 (93%)	59 (92%)	50 (86%)	56 (88%)	220 (89%)	
SCID depression diagnosis – lifetime (*n* = 256)	Yes	55 (87%)	49 (74%)	48 (80%)	58 (87%)	210 (82%)	0.435
SCID depression diagnosis – last 12 months (*n* = 256)	Yes	49 (78%)	46 (70%)	45 (75%)	51 (76%)	191 (75%)	0.839
Pharmacotherapy status (antidepressant or anticraving medication)	Yes	33 (52%)	35 (53%)	36 (60%)	37 (54%)	141 (55%)	0.799
Key outcome measures: (Baseline)							
OTI alcohol Q-score (estimated drinks per day)	Mean (SD)	9.8 (7.6)	10.7 (7.4)	9.6 (8.0)	9.6 (6.2)	9.9 (7.3)	0.808
TLFB drinks per week (*n* = 257)	Mean (SD)	63.3 (50.3)	67.0 (41.9)	52.0 (30.6)	61.5 (43.5)	61.1 (42.4)	0.241
TLFB percent of days heavy drinking (*n* = 257)	Mean (SD)	67.0 (33.5)	69.5 (32.2)	63.4 (32.4)	68.3 (32.5)	67.1 (32.5)	0.749
Beck Depression Inventory II	Mean (SD)	29.9 (8.2)	31.5 (8.6)	31.8 (8.8)	31.7 (9.7)	31.2 (8.8)	0.596
Global Assessment of Functioning (*n* = 240)	Mean (SD)	56.5 (11.2)	57.4 (8.3)	58.6 (10.0)	55.3 (10.1)	56.9 (9.9)	0.330

Abbreviations: SCID, Structured Clinical Interview for DSM-IV; OTI, Opiate Treatment Index – alcohol subscale; TLFB, drinking assessment based on 2-week timeline follow back.
[a] Statistical significance of overall test (one-way analysis of variance, or chi-square test).

Table 2
Selected comparisons between treatment conditions in the mean change from baseline: alcohol consumption measures

Measure	*Follow-up time*	*Differences between groups in change from baseline (parameter estimates from generalized linear models and 99% CI)*[a]		
		Brief intervention vs 10 sessions	*Integrated vs Single focus*	*Alcohol focus vs Depression focus*
OTI alcohol Q-score (estimated drinks per day)	18-weeks	0.96 (-1.69, 3.61)	-0.89 (-3.69, 1.92)	-0.14 (-3.52, 3.24)
	6-months	1.13 (-1.07, 3.33)	1.11 (-1.18, 3.40)	-2.41 (-5.15, 0.33)[#]
	12-months	-0.44 (-2.56, 1.68)	0.12 (-2.04, 2.28)	-1.72 (-4.31, 0.88)
	24-months	1.40 (-1.61, 4.40)	-0.34 (-3.28, 2.61)	-3.90 (-7.51, -0.29)*
	36-months	1.51 (-1.69, 4.70)	0.53 (-2.46, 3.52)	-1.92 (-5.63, 1.80)
	Overall	0.83 (-0.90, 2.56)	0.08 (-1.76, 1.92)	-2.06 (-4.18, 0.05)[#]
TLFB drinks per week	18-weeks	11.14 (-2.19, 24.47)[#]	-8.31 (-22.56, 5.94)	-1.75 (-18.71, 15.21)
	6-months	5.47 (-7.17, 18.10)	-1.02 (-14.15, 12.11)	-6.20 (-21.86, 9.47)
	12-months	-2.47 (-16.20, 11.29)	-2.94 (-16.94, 11.06)	-7.15 (-24.04, 9.75)
	24-months	5.87 (-13.72, 25.45)	-2.29 (-21.56, 16.97)	-20.92 (-44.68, 2.84)[#]
	36-months	-0.59 (-17.07, 15.89)	0.73 (-14.90, 16.37)	-6.01 (-25.30, 13.29)
	Overall	4.35 (-5.38, 14.07)	-2.92 (-13.29, 7.45)	-8.45 (-20.29, 3.39)
TLFB percent of days heavy drinking	18-weeks	10.52 (-2.26, 23.31)[#]	-9.43 (-23.00, 4.13)	-7.81 (-24.07, 8.46)
	6-months	1.99 (-11.68, 15.66)	-6.99 (-21.17, 7.19)	-11.96 (-28.88, 4.96)
	12-months	-2.96 (-17.10, 11.19)	-2.92 (-17.34, 11.50)	-16.14 (-30.34, 4.40)
	24-months	5.38 (-10.98, 21.74)	0.06 (-15.98, 16.10)	-16.50 (-36.29, 3.28)[#]
	36-months	-5.39 (-24.30, 13.53)	4.33 (-13.56, 22.23)	-6.04 (-28.12, 16.03)
	Overall	2.59 (-7.18, 12.36)	-3.52 (-13.67, 6.63)	-11.23 (-23.75, 1.29)[#]

Abbreviations: OTI, Opiate Treatment Index – alcohol subscale; TLFB, drinking assessment based on 2-week timeline follow back.
[a] Estimated mean differences in change scores from baseline for selected orthogonal (Helmert) contrasts and associated 99% Confidence Intervals, controlling for gender, baseline score, and 'other treatment' during the preceding 12 months (for each timeframe); see Table S2 for group means and overall phase comparisons with baseline;
* statistically significant difference (Wald chi-square, $p < .01$); [#] statistical trend (Wald chi-square, $p < 0.05$).

Table 3
Selected comparisons between treatment conditions in the mean change from baseline: depression and global functioning measures

		Differences between groups in change from baseline (parameter estimates from generalized linear models and 99% CI)[a]		
Measure	*Follow-up time*	*Brief intervention vs 10 sessions*	*Integrated vs Single focus*	*Alcohol focus vs Depression focus*
Beck Depression Inventory II	18-weeks	1.60 (-2.76, 5.96)	-3.75 (-8.34, 0.85)[#]	-0.50 (-6.05, 5.04)
	6-months	0.59 (-3.99, 5.17)	-0.52 (-5.26, 4.22)	-0.42 (-6.09, 5.25)
	12-months	3.77 (-0.74, 8.29)[#]	-0.64 (-5.23, 3.96)	-2.38 (-7.92, 3.17)
	24-months	2.23 (-2.72, 7.18)	0.66 (-4.19, 5.51)	-1.00 (-6.95, 4.96)
	36-months	4.00 (-1.37, 9.38)	-1.75 (-6.82, 3.33)	-.08 (-6.34, 6.19)
	Overall	2.35 (-1.08, 5.78)	-1.37 (-4.71, 1.97)	-0.75 (-4.84, 3.34)
Global Assessment of Functioning	18-weeks	-0.98 (-5.33, 3.37)	-0.15 (-4.71, 4.40)	0.66 (-4.85, 6.16)
	6-months	-0.43 (-5.08, 4.23)	2.04 (-2.75, 6.83)	-0.04 (-5.88, 5.80)
	12-months	-4.24 (-8.77, 0.29)[#]	0.64 (-3.93, 5.21)	2.65 (-2.96, 8.25)
	24-months	-1.31 (-6.17, 3.56)	-0.06 (-4.77, 4.66)	3.85 (-1.96, 9.66)
	36-months	-5.68 (-11.10, -0.25)*	2.54 (-2.58, 7.65)	-2.93 (-9.50, 3.65)
	Overall	-2.41 (-5.13, 0.30)[#]	1.07 (-2.03, 4.17)	0.78 (-3.19, 4.74)

[a] Estimated mean differences in change scores from baseline for selected orthogonal (Helmert) contrasts and associated 99% Confidence Intervals, controlling for gender, baseline score, and 'other treatment' during the preceding 12 months (for each timeframe); see Table S3 for group means and overall phase comparisons with baseline; * statistically significant difference (Wald chi-square, $p < .01$); [#] statistical trend (Wald chi-square, $p < 0.05$).

Fig. 1. Recruitment and attrition profiles

Follow-up participation patterns (with useable outcome data): 18-weeks: 84%; 6-months: 82%; 12-months: 74%; 24-months: 60%; and 36-months: 55%; with 91% completing at least 1 follow-up. On average, these follow-up assessments were completed, respectively, at 17.5 weeks (SD = 3.3), 30.2 weeks (SD = 5.1), 57.5 weeks (SD = 6.1), 111.7 weeks (SD = 8.2) and 162.3 weeks (SD = 7.4) after the baseline assessment.

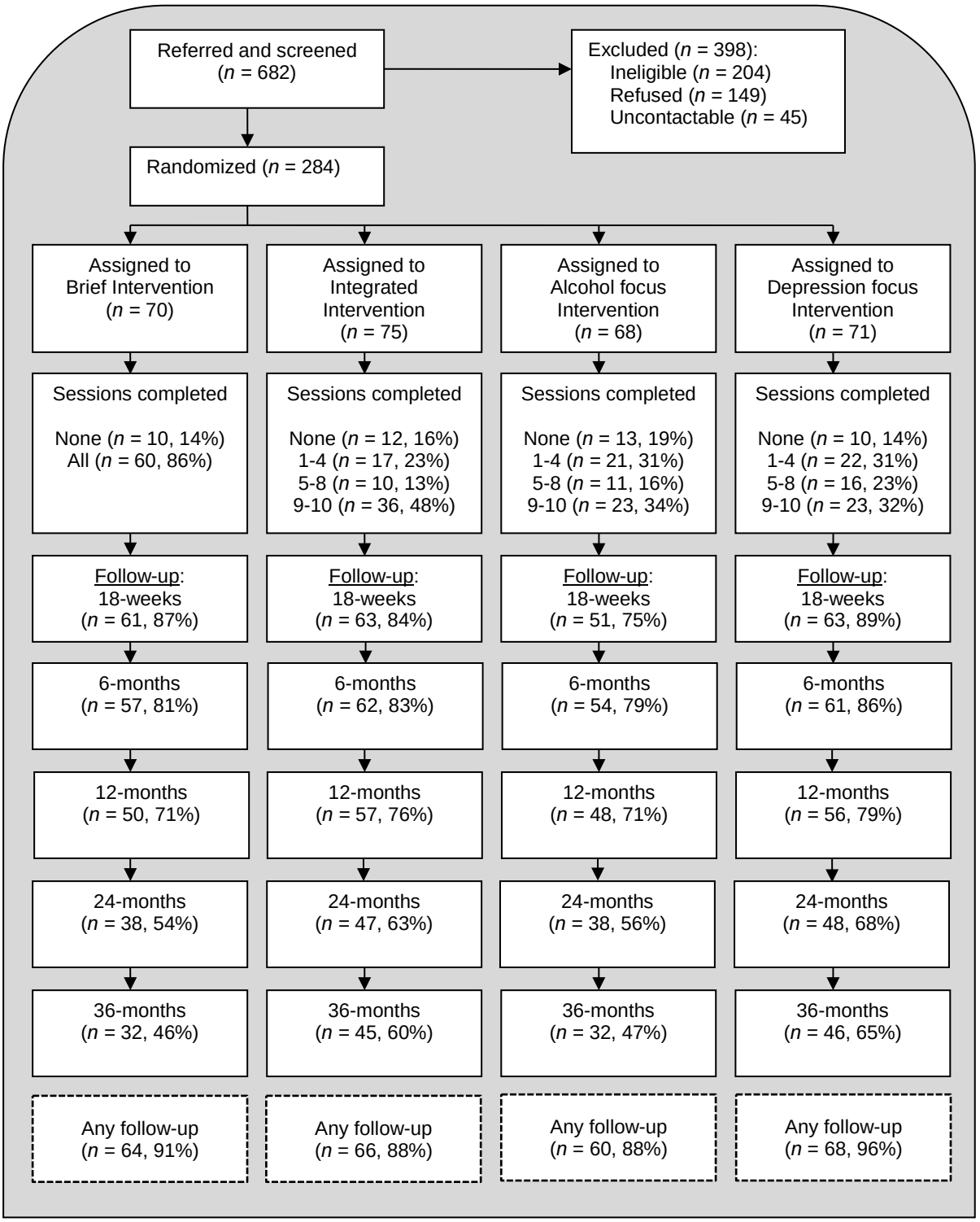

Fig. 2. Standardised change profile for the integrated treatment condition

Abbreviations: OTI, Opiate Treatment Index – alcohol subscale; TLFB, drinking assessment based on 2-week timeline follow back. Standardised scores utilised the grand SD of change scores for the total sample for each outcome measure, with reversed scoring for the Global Assessment of Functioning; see Tables S2 and S3 for means (SD).