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RESEARCH REPORT

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The efficacy of an internet-based cognitive behavioral program added to treatment-as-usual for alcohol-dependent patients in primary care: a randomized controlled trial

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Abstract

Background and Aims: Most alcohol-dependent people have a moderate level of dependence. General practitioners (GPs) hesitate to engage in this area, and need to have access to treatment they find applicable and feasible to use. The aim of this present study was to test if an open-ended internet-based cognitive–behavioral therapy (iCBT) program added to treatment-as-usual (TAU) is more effective than TAU-only for alcohol-dependent patients in primary care.

Design, Setting and Participants: The present study was a two-group, parallel, randomized controlled superiority trial comparing iCBT+TAU versus TAU-only at 3- and 12-month follow-ups. TAU was delivered at 14 primary care centers in Stockholm, Sweden. A total of 264 patients (mean age 51 years, of whom 148 were female and 116 were male) with alcohol dependence and hazardous alcohol consumption were enrolled between September 2017 and November 2019.

Measurements: Participants were randomized at a ratio of 1:1 to iCBT, as a self-help intervention added to TAU (n = 132) or to TAU-only (n = 132). The GPs gave participants in both treatment arms feedback on the assessments and biomarkers and offered TAU at the primary care center. Primary outcome was weekly alcohol consumption in g/week at 12-month follow-up, analyzed according to intention-to-treat (n = 132 + 132). The per-protocol analysis included participants who completed at least one module of iCBT (n = 102 + 132).

Findings: There was no significant difference in weekly alcohol consumption between iCBT+TAU and TAU in the intention-to-treat (ITT) analysis at 12-month follow-up [iCBT +TAU = 133.56 (95% confidence interval, CI = 100.94–166.19) and TAU = 176.20 (95% CI = 144.04–208.35), P = 0.068, d = 0.23]. In the per-protocol analysis, including only those who initiated iCBT, the iCBT+TAU group showed lower mean weekly alcohol consumption compared with TAU [iCBT+TAU = 107.46 (95% CI = 71.17–143.74), TAU = 176.00 (95% CI = 144.21–207.80), P = 0.010, d = 0.42].

Conclusions: In Sweden, an internet-based cognitive–behavioral program added to treatment-as-usual to reduce alcohol consumption showed weak evidence of a benefit at 12 months in the intention-to-treat analysis and good evidence of a benefit in the per-protocol analysis.

KEYWORDS
Alcohol dependence, AUD, efficacy, internet-based CBT added to TAU, primary care, randomized controlled trial

INTRODUCTION

Alcohol is a leading risk factor for several major health problems and is estimated to cause nearly 10% of global deaths among populations aged 15–49 years [1]. The risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption and the level of consumption that minimizes health loss is zero [1]. Alcohol use disorders (AUD) have the second highest burden of disease of all mental disorders after depression, with the highest burden in men [2].

Alcohol dependence is highly prevalent world-wide, but most individuals with alcohol dependence do not engage in treatment [3]. Only approximately 10–20% seek help, and treatment-seekers tend to have more severe dependence with comorbid disorders and unstable social situation [4–7]. Most alcohol-dependent people have a moderate level of dependence [8]. The major part of morbidity and mortality, as well as community costs related to alcohol consumption, occurs in this large group with moderate dependence that is reluctant to seek treatment in specialized care, mainly due to stigma [9, 10]. Studies indicate that people with alcohol dependence are positive with regard to seeking treatment in primary care [10–12], and many individuals with alcohol dependence are already present due to health problems other than alcohol dependence [3, 7]. In a recent qualitative study, patients found alcohol acceptable to discuss in primary care, particularly those experiencing co-occurrent health problems [13].

Heavy alcohol use causes or complicates many diseases and conditions and is consequently relevant to discuss in many primary care consultations [5, 14]. General practitioners (GPs) are, at present, reluctant to engage in this, mainly due to time constraints and uncertainty regarding their competence in this field [15, 16]. To lessen the morbidity associated with alcohol dependence and encourage health-care providers in primary care to raise questions about alcohol, they need to have access to treatment alternatives they find applicable and feasible to use. In primary care, fewer than one in five of individuals with hazardous consumption are identified and fewer than one in four with alcohol dependence are offered treatment [3, 17]. Pharmacotherapy for AUD is underutilized, and somatic comorbidity is associated with lower odds of prescription of AUD medications [18].

Previous studies with positive results in primary care have mainly involved screening and brief intervention (SBI) for hazardous drinkers, but implementation in practice remains low [19, 20]. However, a recent study comparing treatment for alcohol dependence in primary care to treatment in specialized care found specialized care to be superior to primary care only for participants with a high severity of dependence [21]. In this study, a stepped-care program, including brief interventions and pharmacological treatment, was tailored to the primary care setting and the participating GPs were given a 1-day training session prior to the study. An alternative approach is to complement existing treatment in primary care with internet-based interventions, which have been shown to be attractive for, and to reach, individuals with alcohol problems [22, 23]. Internet-based interventions have the potential to increase access to evidence-based treatment, to reduce stigma, overcome geographical barriers, to be cost-effective and to broaden the base for treatment-seeking [24–27]; they have often included student populations and participants with hazardous use. Individuals with AUD or alcohol dependence are studied to a lesser extent [28, 29]. A meta-analysis has reported a significant effect of therapist-guided internet interventions for problem drinkers, with a reduction of 10 weekly standard units compared with controls [30]. A recent randomized trial that included patients with AUD in specialized care found that internet treatment was non-inferior to face-to-face treatment in reducing alcohol consumption [31]. Internet-based cognitive behavioral therapy (iCBT) could be used as a treatment option, which would not increase the work-load for the GPs. To our knowledge, there have been no previous studies on internet treatment for alcohol dependence or AUD in a primary care setting.

The overall objective of the present study was to test the efficacy of an open-ended iCBT program for alcohol-dependent patients in primary care. The main hypothesis was that iCBT, when added to treatment-as-usual (TAU), will reduce weekly alcohol consumption at 12-month follow-up more than TAU-only for alcohol-dependent patients in primary care.

METHODS

Study design

The present study was a two-group, parallel, randomized controlled superiority trial. Alcohol-dependent participants from 14 primary care centers in Stockholm, Sweden were randomly assigned to iCBT+TAU or to TAU-only with a 1:1 allocation, and were followed-up at 3 and 12 months.

Participants

Potential participants were informed about the study via advertisements in local newspapers and on websites, leaflets at the primary care study sites or at a primary care consultation. Using the study website, interested individuals accessed more information regarding the study, provided their informed consent and completed screening assessment in the on-line platform. If inclusion criteria were fulfilled (> 18 years of age, three or more criteria for alcohol dependence according to the ICD-10 [32] and > 6 points for women/> 8 points for men for hazardous consumption according to the AUDIT [33]), eligible individuals were automatically invited to create a personal account and complete baseline assessment. The assessment was kept brief to minimize the risks of assessment reactivity [34]. Hereafter, eligible individuals were contacted via telephone by the study coordinator, who was a nurse clinically trained in the field of addiction and psychiatry, to ensure data quality and completeness and to advise individuals who met exclusion criteria to seek appropriate care. The exclusion criteria were serious mental illness, substance-use disorder other than alcohol and nicotine, need of specialized treatment in psychiatry or addiction care, cognitive impairment and lack of Swedish language skills.

Randomization and blinding

Participants who gave informed consent and completed assessments in the on-line platform were randomized to treatment with either iCBT+TAU or TAU-only. The randomization was conducted in blocks of 20, according to a fully automated procedure in the on-line platform that was programmed in the content management system Drupal (drupal.org) by the fourth author. As we expected that the recruitment of participants would take place gradually over time, we used blocks to obtain even groups at regular intervals. The blocks were pre-programmed on the study website and hidden from both participants and research staff. The study was not designed to stratify based on unit. The study included both larger and smaller units, and the number of participants per unit was expected to vary greatly. The study coordinator randomized the participants by activating a link only he/she had access to. All patients were informed by the study coordinator about their group allocation, were asked to provide a blood test for biomarkers and were scheduled for an appointment with their GP at their primary care center. The primary care staff were not blinded to the allocations. None of the authors had access to the codes concerning which experimental condition the participants were randomized to until after completion of data collection.

Interventions

TAU

TAU was delivered at 14 primary care centers in Stockholm, which were selected based on their interest in participating when approached by the research team. In both treatment arms, the GPs gave participants feedback on the assessments and biomarkers and designed a treatment plan based on current routines on treating alcohol problems at the primary care center. Clear guidelines for treating alcohol dependence are lacking in Swedish primary care, hence TAU will vary. All GPs were offered a short training session in providing feedback on assessments and biomarkers and pharmacotherapy (acamprosate, disulfiram, naltrexone, nalmefene) prior to the study. Written instructions, including contact details to the first author in case of questions, were provided to the primary care centers to also administer to colleagues who could not take part in the training. The GPs were instructed to refer patients they usually refer; for example, when addiction was assessed as too severe to treat in primary care, when liver enzymes were heavily raised or with other somatic or psychiatric conditions requiring specialized care.

iCBT

The iCBT+TAU group was offered iCBT in addition to TAU. The iCBT was delivered on-line at the same platform that was used for assessment in the study. It was an extended self-help intervention with automated e-mails, with feedback and reminders to start and complete the assignments that were given to the participants. The iCBT program was based on self-help material used in previous trials of iCBT in specialized care [31, 35, 36]. The content and exercises in the program were based on motivational interviewing, relapse prevention and behavioral self-control training. The program was divided into five main modules: (1) motivation to change, (2) drinking-goal and self-control strategies, (3) behavioral analysis of drinking and risk-situations, (4) general problem-solving and (5) - preventing relapse. There were also three optional problem-solving modules (handling feelings, drink-refusal skills and handling cravings). iCBT was an open-ended intervention, meaning that participants could log on to the treatment platform as often and for as long as they wanted. For each assignment, an informational text was provided and a home assignment was included, but all assignments were possible to use in the order preferred by the participants. The treatment was fully automated; that is, no therapist contact was provided.

Follow-up

At 3 and 12 months after randomization, participants were sent automated reminders and were contacted by the study coordinator to complete the follow-up questionnaires (see 'Measures' below). The same questionnaires that were used at baseline assessment were used at the follow-ups. At the 3-month follow-up, the client satisfaction questionnaire (CSQ) [37] was added. The study coordinator also reminded the participants to provide blood tests at 3- and 12-month follow-ups and collected the results from the patient records.

Measures

Primary outcome

The primary outcome variable was alcohol consumption in mean grams per week at 12-month follow-up. Consumption was self-reported using the time-line follow-back (TLFB) [38] during the last 30 days. A drink contains 12 g of alcohol. The primary comparison statistic was the difference between mean consumption per group.

Secondary outcomes

Questionnaires

Alcohol consumption in mean grams per week at 3-month follow-up and mean number of days with heavy drinking (≥ 4/5 drinks for women and men) per month were measured with TLFB [38]. Problematic alcohol use was assessed with the AUDIT total score [33]. Severity of dependence was assessed by the self-reported number of ICD-10 criteria for alcohol dependence [32]. Symptoms of anxiety and depression were assessed with the Hospital Anxiety and Depression Scale (HADS) [39]. Health-related quality of life was assessed with the Equation 5D-5L questionnaire [40]. Based on TLFB, we also explored the number of alcohol-free days during the last 30 days using TLFB; note that this was not a pre-registered outcome. As mentioned above, CSQ was used to assess satisfaction with treatment [37].

Biomarkers

Blood was analyzed for standard biomarkers of heavy drinking and liver pathology, levels of phosphatidylethanol (PEth), gamma-glutamyl transferase (GGT), aspartate amino transferase (AST) and alanine amino transferase (ALT).

The primary and secondary outcomes were assessed on-line at baseline and at 3 and 12 months post-randomization.

Analyses

Sample size

The study was designed to demonstrate statistical superiority. An effect-size of $g = 0.61$ has been shown in previous internet studies on high consumers in the general population [41]. Due to a lack of studies on alcohol-dependent patients, our estimate was based on a more conservative effect-size of $d = 0.4$, corresponding to a difference between groups of 65 g/week, which required a sample size of 100 participants in each arm to achieve a power of 80% with an alpha of 0.05 and using an independent-samples *t*-test for weekly alcohol consumption at 12-month follow-up. Given an estimated dropout in iCBT of 30%, 264 participants were included in the study [42].

Analytical plan and statistical procedure

As per the trial protocol [43], the change in the primary outcome (weekly alcohol consumption at 12-month follow-up) was modeled using linear mixed effects models, according to the intention-to-treat (ITT) principle and with missing data estimated (per model, with no additional predictors) using restricted maximum likelihood estimation, under the missing at random (MAR) assumption. As in similar research [35, 44, 45], this missing mechanism was deemed clinically plausible and reasonable [46]: measures were collected independent of treatment adherence (i.e. not only those who remained in treatment continued to contribute data), on-line administration of measures made it convenient to contribute data and provided data had no impact on continued treatment. Multiple imputations were not run prior to mixed effects modeling, as simulations and empirical findings suggest no additional benefits of this approach [47, 48]. Sensitivity analyses, with a missing not at random (MNAR) assumption and first observation carried forward (FOCF) imputation, was run on significant mixed models [49–52].

Due to difficulties in modeling a trajectory with so few data points and no obvious grounds for equidistance [53], we opted to include only random intercepts and to treat time as a factor (rather than numeric), with the 3-month follow-up (mid-study measurement) as reference, in interaction with group. This mid-study reference was chosen to reflect observed (and assumed) trajectories, with marked differences between slopes on either side of the reference. Factorial time made time-coding intervals for blood test outcomes necessary (as blood tests could not be administered with the same precision as on-line self-ratings), requiring balancing maximization of sample size with avoiding misclassification bias. The coding intervals settled upon coded blood tests < 31 days subsequent to on-line sign-up as baseline; those between > 75 and < 181 days were coded as 3-month and those between < 330 and > 457 days were coded as 12-month. Analysis of secondary variables (weekly alcohol consumption at 3-month follow-up and heavy drinking days per month, alcohol-free days per month, ICD-10 criteria, AUDIT total score, HADS scale depression, HADS scale anxiety, EQ-5D-5L questionnaire, PEth, GGT, AST, ALT at 3- and 12-month follow-up) followed the same strategy as described above for the primary outcome.

From these mixed models, estimated marginal means (with confidence intervals) were calculated for each arm and time-point (with degrees of freedom using the Satterthwaite method), with pairwise contrasts at each time-point. ITT analyses was complemented with per-protocol (PP) analyses. PP analyses included all participants in the iCBT+TAU arm that completed at least one module of iCBT. PP analyses included all participants in the TAU arm, as all participants were scheduled for an appointment with their GP per study arm. Cohen's effect sizes were calculated using estimated marginal means and observed standard deviations. Analyses were conducted in the R version 3.6.3 statistical environment using the lme4 [54], lmerTest [55] and emmeans [56] packages.

RESULTS

Participants

Participants were enrolled between September 2017 and November 2019. A total of 768 individuals were screened for participation. A total of 264 participants were randomly allocated to the two study arms (see flow-chart in Figure 1). The sample had a mean age of 51 years, and included 148 female and 116 male participants. The participants overall had a moderate level of dependence. They were highly educated, employed and cohabiting, which is in line with previous studies on the large group with moderate alcohol dependence [8]. Full demographic and clinical variables at baseline are presented in Table 1. There were no significant differences between the groups in any variables at baseline.

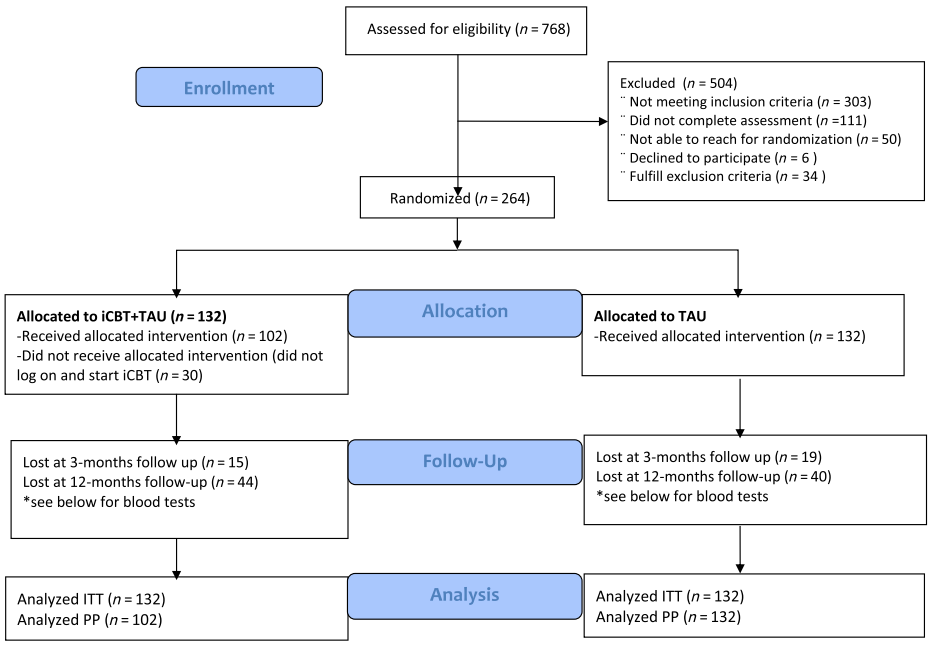
Lost to follow-up

Attrition rate was 12.9% (n = 34) at the 3-month follow-up and 31.8% (n = 84) at the 12-month follow-up. There was no difference in attrition rate between treatment conditions at either 3 months (χ^2 = 0.540, P = 0.462) or 12 months (χ^2 = 0.279, P = 0.597). A total of 44 participants were lost to follow-up for the primary outcome in the iCBT+TAU group and 40 participants in the TAU group. There was no difference in attrition rate between treatment conditions for the primary outcome (χ^2 = 0.279, P = 0.597). Participants who completed the 12-month follow-up reported a higher baseline weekly alcohol consumption (291.6 versus 231.6 g, t = −2.552, P = 0.011) and more days with heavy drinking compared with participants who were lost to follow-up (11.7 versus 9.2, t = −2.420, P = 0.016). Participants who completed the 3-month follow-up reported a lower baseline ICD-10 score than those who were lost to follow-up (4.11 versus 4.59, t = 2.523, P = 0.012). No differences in any other baseline variables were found between those lost to follow-up at 3 or 12 months and those who completed both follow-ups.

A minority of participants provided blood tests at follow-ups (for details see Figure 1).

Primary outcome analysis

The ITT analysis showed no significant difference in the reduction of mean weekly alcohol consumption between groups at the 12-month follow-up. In the PP analysis, including only those who completed at least one module of iCBT in the allocated treatment (n = 102), the results showed less alcohol consumption in the iCBT+TAU group compared with TAU (n = 132) (see Table 2). The significant between-group difference in alcohol consumption at 12 months in the PP analysis remained significant in MNAR (FOCF) analysis of covariance (ANCOVA) sensitivity analysis (F = 5.82, P = 0.017). As random allocation was independent of recruitment site, there was no



*Number of individuals providing blood tests at follow-up (%), see table:

Analysis	iCBT+TAU, 3-months	iCBT+TAU, 12-months	TAU, 3-months	TAU, 12-months
PEth	56 (42.4)	20 (15.5)	59 (44.7)	23 (17.4)
GGT	55 (41.7)	22 (16.7)	59 (44.7)	24 (18.2)
AST	55 (41.7)	23 (17.4)	60 (45.5)	24 (18.2)
ALT	55 (41.7)	22 (16.7)	60 (45.5)	24 (18.2)

FIGURE 1 Flow-chart. iCBT = internet-based cognitive behavioral treatment; ITT = intention-to-treat; PP = per-protocol; TAU = treatment-as-usual.

TABLE 1 Demographic and baseline values.

	iCBT+TAU (*n* = 132)	TAU (*n* = 132)
Gender (*n*, %)		
Male	54 (40.9)	62 (47.0)
Female	78 (59.1)	70 (53.0)
Age [mean (range)]	52 (28–80)	50 (23–77)
Education (*n*, %)		
Not completed compulsory education	0 (0.0)	1 (0.8)
9 years of education	6 (4.5)	6 (4.5)
12 years of education	35 (26.5)	41 (31.1)
Higher education	88 (66.7)	82 (62.1)
Other	3 (2.3)	2 (1.5)
Source of income (*n*, %)		
Employment	106 (80.3)	97 (73.5)
Pension	24 (18.2)	23 (17.4)
Other	2 (1.5)	12 (9.1)
Marital status (*n*, %)		
Married/cohabiting	80 (60.6)	84 (63.6)
Live alone	49 (37.1)	45 (34.1)
Widowed	3 (2.3)	3 (2.3)
AUDIT risk-level (*n*, %)		
≤ 15	19 (14.4)	26 (19.7)
16–19	22 (16.7)	31 (23.5)
20–40	91 (68.9)	75 (56.8)
Weekly alcohol consumption (g) [mean (SD)]	263.77 (137.09)	284.45 (184.89)
Heavy drinking days per month [mean (SD)]	10.96 (7.45)	10.89 (8.38)
Alcohol-free days per month [mean (SD)]	9.86 (7.51)	9.41 (7.25)
ICD-10 criteria dependence [mean (SD)]	4.03 (0.99)	4.32 (1.07)
AUDIT total score [mean (SD)]	21.17 (5.07)	21.00 (5.64)
HADS scale anxiety [mean (SD)]	10.40 (3.37)	9.79 (3.20)
HADS scale depression [mean(SD)]	6.12 (3.68)	5.57 (3.65)
Equation 5D 5 L VAS [mean (SD)]	62.89 (20.18)	65.43 (20.68)
PEth [mean (SD)]	0.65 (1.03) *n* = 93	0.58 (0.68) *n* = 100
GGT [mean (SD)]	0.68 (0.75) *n* = 95	0.62 (0.93) *n* = 100
AST [mean (SD)]	0.49 (0.25) *n* = 95	0.49 (0.28) *n* = 102
ALT [mean (SD)]	0.50 (0.30) *n* = 95	0.46 (0.28) *n* = 101

Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; AUDIT = Alcohol Use Disorders Identification Test; EQ-5D-5L = EuroQol-5 dimension; GGT = gamma-glutamyl transferase; HADS = Hospital Anxiety and Depression Scale; iCBT = internet-based cognitive behavioral therapy; ICD = International Classification of Disease; Peth = phosphatidylethanol; TAU = treatment-as-usual.

expectation of within-site clustering of outcomes. Congruently, preliminary analyses revealed no evidence of such clustering effects, and a study site parameter was therefore not included in the final models.

Secondary outcome analysis

Regarding the secondary outcomes, there was a reduction in all symptom scores in both groups at the 3- and 12-month follow-ups compared with baseline. The results from the ITT analysis showed no significant differences between the groups in any of the secondary outcomes at the 3- and 12-month follow-ups (Table 4).

In the PP analysis on the secondary outcomes, including only those who completed at least one module of iCBT in the allocated treatment (n = 102), the results showed a greater increase in number of alcohol-free days and a decrease in symptoms of depression for the iCBT+TAU group compared to TAU at the 12-month follow-up (Tables 3 and 4). The significant between-group differences at 12 months in the PP-analysis remained significant in MNAR (FOCF) ANCOVA sensitivity analysis (F = 5.53, P = 0.020) and (F = 7.17, P = 0.08).

Treatment utilization

In both study arms, all participants were offered a scheduled appointment to a GP for feedback on the assessments and biomarkers and to design a treatment plan. In the iCBT+TAU group, 11 participants (8.3%) never attended the GP visit compared with 14 participants (10.3%) in the TAU group (χ^2 = 0.398, P = 0.528). Participants in the iCBT+TAU group had, on average, as many visits at the primary care center as the TAU group (3.29 versus 3.55, t = 0.573, P = 0.567).

For participants randomized to iCBT+TAU, the mean number of assignments completed in iCBT was 4.67 of eight possible completed. Approximately 36.4% (n = 48) of the participants completed all assignments in iCBT, 40.9% (n = 54) partially completed the assignments and 22.7% (n = 30) did not log on and start iCBT. Nine of the 30 participants who did not start the program were lost to follow-up at 3 months, and 12 of 30 were lost at 12 months.

In both groups, pharmacological treatment was prescribed by the GPs. In total, 161 participants received prescriptions from their GP, 69 (52%) participants in the iCBT+TAU group and 92 (70%) participants in the TAU group (χ^2 = 8.42, P = 0.004).

Three participants randomized to iCBT+TAU received additional alcohol treatment in specialized care during the 12-month course. The corresponding number randomized to TAU was six. Thus 97%, the vast majority of participants, did not receive additional specialized treatment.

TABLE 2 Primary outcome; estimated means and pointwise between-group differences with 95% CI for primary outcome at 12-month follow-up (ITT and PP analysis data set).

	iCBT+TAU	TAU	Difference in drinking quantities	*P*-value	Cohen's *d*
ITT (MAR)	133.56 (100.94–166.19)	176.20 (144.04–208.35)	42.64	0.068	0.23
ITT (MNAR)	172.80 (150.00–196.80)	195.60 (171.60–219.60)	22.80	0.205	0.16
PP (MAR)	107.46 (71.17–143.74)	176.00 (144.21–207.80)	68.54	0.010	0.42
PP (MNAR)	153.60 (128.40–178.80)	194.40 (171.60–216.00)	40.80	0.019	0.31

Note: In missing at random (MAR) analyses, the minor difference in estimated (MAR) values of the TAU arm between ITT and PP analyses reflects that missing data were estimated per model, not per model and arm. Estimated means for the TAU arm from last observation carried forward (LOCF) [missing not at random (MNAR)] models also differ between ITT and PP, due to covariate adjustment being based on whole-sample mean.
Abbreviations: iCBT = internet-based cognitive behavioral therapy; ITT = intention-to-treat; PP = per-protocol; TAU = treatment-as-usual; CI = confidence interval.

Clinical outcomes

Low-risk alcohol consumption according to AUDIT was reported by 58 of 117 (49.6%) of follow-up participants in the iCBT+TAU group and 62 of 113 (54.9%) in the TAU group at 3 months, with no significant differences found between the groups ($\chi^2 = 0.646$, $P = 0.422$). Low-risk alcohol consumption was reported by 52 of 91 (57.1%) in the iCBT+TAU group and 51 of 89 (57.3%) in the TAU group at 12 months, with no significant differences found between the groups ($\chi^2 = 0.0005$, $P = 0.983$).

Satisfaction with treatment

No significant differences in treatment satisfaction as measured with the CSQ were seen between the groups. Mean total score in the iCBT +TAU group ($n = 118$) was 23.0, and the mean score in the TAU group ($n = 114$) was 21.6 ($t = -1.86$, $P = 0.065$).

DISCUSSION

The objective of this study was to investigate if iCBT, when added to TAU, was more effective than TAU-only in treating alcohol-dependent patients in primary care. In the ITT analysis, no statistically significant effect favoring iCBT+TAU was found compared with TAU. The participants in the iCBT+TAU group, who completed at least one module of iCBT in the allocated treatment, continued to reduce their alcohol consumption from 3 to 12 months significantly more compared with the TAU group. They also reported a higher number of alcohol-free days and a greater reduction of symptoms of depression compared with the TAU group. As a considerable number of the participants never initiated iCBT, it is difficult to draw conclusions about the reason for the improvement for the completers. Given the ease of administration of iCBT and that the intervention does not increase the work-load for the GP, iCBT may be a viable treatment complement to usual care. This conclusion is based on the fact that time constraints and perceived lack of competence in managing alcohol problems constitute barriers for treating alcohol dependence in primary care [15, 57, 58]. In a recent qualitative study, we interviewed GPs involved in this present study [59]. They believed that iCBT might facilitate raising questions about alcohol use, and iCBT was viewed as an attractive treatment option to some patients [59].

Participants in both groups reduced their average weekly consumption and their heavy drinking days at follow-up compared with baseline. The effect sizes for both groups are in line with previous internet studies among high consumers in communities and primary care [30, 60] and also in line with other studies on psychosocial interventions [61]. The main reduction of alcohol consumption occurred during the first 3 months after the start of treatment, with effects of the treatment sustained at the 12-month follow-up. That treatment effects were mainly accomplished during the period of active treatment is in line with previous studies treating alcohol dependence face-to-face in primary care [62, 63]. Participants who completed the 12-month follow-up reported a higher average alcohol consumption and more days with heavy drinking at baseline compared with those lost to follow-up.

Pharmacological treatment was prescribed to a far greater extent (52% of the participants in the iCBT+TAU group and 70% in the TAU group) in this study compared with prior studies on alcohol-dependent patients in primary care [64]. Participating practitioners were offered a 1-hour training session including information regarding how to provide feedback on assessments and biomarkers and pharmacotherapy prior to this study. The short training session seems to have contributed towards increasing the use of pharmacological treatment compared with prior studies, where training was not provided [64], and is in line with prior studies where training was provided [21]. The training may also have contributed to reducing differences in outcome between study arms, where TAU unintentionally became better-than-usual treatment in primary care.

The large gap between prevalence and treatment-seeking indicates that changes in clinical practice are needed to reach alcohol-dependent people and reduce the morbidity and mortality associated with this disorder. As the majority of individuals with alcohol dependence are reluctant to seek treatment in specialized care, but more positive to seeking treatment in primary care, the results from this study are encouraging [8, 11]. We see several venues for future research. Given the fairly limited resources required by the iCBT provided in this study this may be a feasible and cost-effective treatment, even if the effects compared

TABLE 3 Secondary outcomes; estimated means and pointwise between-group differences with 95% CI for secondary outcomes at 3-month follow-up (3MFU) and 12-month follow-up (12MFU) (ITT analysis data set).

Variable (mean)	iCBT+TAU, 3MFU (95% CI)	iCBT+TAU, 12MFU (95% CI)	TAU, 3MFU (95% CI)	TAU, 12MFU (95% CI)	Difference 3MFU	*P*-value 3MFU	Cohen's *d*	Difference 12MFU	*P*-value 12MFU	Cohen's *d*
Weekly alcohol consumption (g)	157.79 (128.13–187.45)	See Table 2	181.58 (151.56–211.61)	See Table 2	23.794	0.269	0.15	See Table 2	See Table 2	See Table 2
Heavy drinking days per month	5.63 (4.30–6.97)	4.79 (3.32–6.26)	5.93 (4.58–7.28)	5.93 (4.48–7.38)	0.298	0.758	0.045	1.141	0.279	0.15
Alcohol-free days	14.93 (13.51–16.35)	17.17 (15.61–18.73)	15.08 (13.65–16.52)	15.24 (13.71–16.78)	0.155	0.880	0.018	−1.925	0.084	0.23
ICD-10 criteria dependence	2.70 (2.44–2.96)	2.16 (1.86–2.45)	2.86 (2.60–3.13)	2.31 (2.02–2.60)	0.163	0.389	0.11	0.150	0.474	0.079
AUDIT total score	15.15 (14.08–16.23)	12.98 (11.80–14.16)	15.28 (14.19–16.36)	13.75 (12.59–14.92)	0.122	0.875	0.023	0.774	0.360	0.11
HADS scale anxiety	8.05 (7.48–8.63)	7.42 (6.80–8.05)	8.18 (7.60–8.76)	7.64 (7.02–8.26)	0.130	0.754	0.040	0.222	0.621	0.068
HADS scale depression	4.01 (3.38–4.64)	3.29 (2.60–3.98)	3.87 (3.24–4.50)	4.14 (3.47–4.82)	−0.139	0.759	0.041	0.858	0.082	0.25
Equation 5D 5 L VAS	71.85 (68.33–75.37)	71.71 (67.76–75.66)	71.95 (68.38–75.53)	73.03 (69.15–76.91)	0.103	0.968	0.0054	1.321	0.639	0.068
PEth	0.52 (0.35–0.70)	0.59 (0.35–0.82)	0.51 (0.34–0.68)	0.46 (0.23–0.68)	−0.008	0.948		−0.129	0.436	
GGT	0.75 (0.53–0.97)	0.72 (0.40–1.04)	0.67 (0.46–0.89)	0.73 (0.43–1.03)	−0.081	0.605		0.007	0.976	
AST	0.48 (0.39–0.58)	0.48 (0.33–0.63)	0.58 (0.48–0.67)	0.44 (0.29–0.58)	0.093	0.173		−0.043	0.684	
ALT	0.47 (0.40–0.55)	0.49 (0.37–0.60)	0.54 (0.47–0.62)	0.50 (0.40–0.61)	0.07	0.193		0.016	0.842	

Note: Effect sizes for biomarkers are not shown due to few blood samples provided at follow-ups.

Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; AUDIT = Alcohol Use Disorders Identification Test; EQ-5D-5L = EuroQol-5 dimension; HADS = Hospital Anxiety and Depression Scale; iCBT = internet-based cognitive behavioral therapy; ICD = International Classification of Diseases; Peth = phosphatidylethanol; TAU = treatment-as-usual; CI = confidence interval; VAS = visual analog scale; ITT = intention-to-treat.

TABLE 4 Per-protocol analysis of estimated means and between group differences with 95% CI for secondary outcomes at 3-month follow-up (3MFU) and 12-month follow-up (12MFU).

Variable (mean)	iCBT+TAU 3MFU	iCBT+TAU 12MFU	TAU 3MFU	TAU 12MFU	Difference baseline	*P*-value baseline	Difference 3MFU	*P*-value 3MFU	Cohen's *d*	Difference 12MFU	*P*-value 12MFU	Cohen's *d*
Weekly alcohol consumption (g)	145.72 (112.93–178.52)	See Table 2	181.55 (151.80–211.29)	See Table 2	28.96	0.18	35.82	0.11	0.23	See Table 2	See Table 2	See Table 2
Heavy drinking days per month	5.20 (3.75–6.66)	4.01 (2.39–5.63)	5.93 (4.61–7.25)	5.93 (4.51–7.35)	0.06	0.95	0.73	0.47	0.11	1.92	0.08	0.27
Alcohol free days per month	15.71 (14.16–17.26)	18.47 (16.74–20.19)	15.07 (13.66–16.48)	15.22 (13.70–16.73)	−0.77	0.46	−0.64	0.55	0.080	−3.25	**0.01**	**0.40**
ICD-10 criteria dependence	2.58 (2.29–2.87)	2.02 (1.69–2.35)	2.86 (2.60–3.13)	2.31 (2.02–2.60)	0.26	0.18	0.28	0.16	0.20	0.29	0.20	0.15
AUDIT total score	14.76 (13.60–15.93)	12.07 (10.77–13.37)	15.27 (14.21–16.34)	13.75 (12.61–14.89)	0.11	0.89	0.51	0.53	0.090	1.68	0.06	0.25
HADS scale anxiety	8.03 (7.39–8.68)	7.37 (6.66–8.07)	8.18 (7.60–8.76)	7.64 (7.03–8.26)	−0.86	0.04	0.15	0.74	0.046	0.28	0.56	0.085
HADS scale depression	3.93 (3.23–4.63)	3.01 (2.24–3.79)	3.87 (3.24–4.51)	4.15 (3.47–4.82)	−0.66	0.16	−0.06	0.91	0.018	1.13	**0.03**	**0.35**
Equation 5D 5 l VAS	73.13 (69.28–76.97)	72.08 (67.73–76.43)	71.95 (68.44–75.47)	73.03 (69.22–76.84)	3.72	0.14	−1.17	0.66	0.066	0.95	0.75	0.051
PEth	0.52 (0.33–0.71)	0.53 (0.28–0.79)	0.51 (0.34–0.69)	0.46 (0.23–0.68)	−0.02	0.86	−0.01	0.94		−0.08	0.66	
GGT	0.60 (0.39–0.81)	0.64 (0.37–0.91)	0.66 0.47–0.85)	0.74 (0.49–0.98)	−0.04	0.75	0.06	0.70		0.10	0.61	
AST	0.45 (0.35–0.55)	0.45 (0.30–0.60)	0.58 (0.49–0.67)	0.46 (0.32–0.60)	0.01	0.79	0.13	0.06		0.01	0.94	
ALT	0.44 (0.36–0.52)	0.48 (0.36–0.60)	0.54 (0.47–0.61)	0.51 (0.40–0.61)	−0.04	0.64	0.10	0.07		0.03	0.74	

Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; AUDIT = Alcohol Use Disorders Identification Test; EQ-5D-5L VAS = EuroQol-5 Dimension visual analog scale; GGT = gamma-glutamyl transferase; HADS = Hospital Anxiety and Depression Scale; iCBT = internet-based cognitive behavioral therapy; ICD = International Classification of Diseases; Peth = phosphatidylethanol.

with TAU are similar. Further clinical trials with larger sample sizes would be one step to increase the evidence base for this treatment. Another approach would be to investigate if the effects of iCBT are further strengthened by adding on-line therapist contact, which has been shown to be associated with larger effects in internet-based treatments [30]. In a previous published qualitative study based on interviews with GPs working in the current randomized trial, the GPs believed that one method to increase patients' motivation to engage in iCBT would be to add a chat forum where patients could support each other [59]. This is also a possible venue for future research. Further, facilitated access by GPs to iCBT has been evaluated in a project in Italy [65]. Collaboration with researchers within primary care might be a way to gain more access to GPs and to increase their motivation to support patients to initiate iCBT.

Limitations

Outcomes, except biomarkers in blood, were based on self-reported data. A recent systematic review suggests that inconsistencies between self-reported consumption and biomarkers occur, yet the extent was found to differ widely [66]. In the present study it was difficult to motivate participants to provide blood tests at follow-ups. This makes it difficult to draw conclusions concerning the biomarkers and their association to the self-reported data. Another limitation was that the study was conducted in a large group of socially stable individuals with moderate dependence seen in primary care. The level of dependence was similar to a recent Swedish study comparing treatment outcomes in primary care with specialized care but lower than in regular specialized care, and the results may therefore not be generalizable to people with more severe alcohol dependence [21]. Furthermore, the participants were self-selected, and the findings are not generalizable to the untreated population of alcohol-dependent individuals. Pharmacotherapy was more often prescribed in the TAU group. Access to iCBT might have had a negative influence on the willingness to prescribe or to take pharmacotherapy for the participants in the iCBT+TAU group.

Conclusions

The ITT analysis failed to demonstrate improved outcomes when iCBT was provided in addition to TAU for alcohol dependence. Greater use of pharmacotherapy in the TAU group may have confounded this comparison. The PP analysis showed that when including only patients who actually initiated iCBT, the combination of iCBT and TAU resulted in an additionally reduced alcohol consumption. As a considerable number of participants randomized to iCBT+TAU never initiated iCBT, it is difficult to draw firm conclusions about this result.

The participants included in this study had obvious problems with alcohol and mental health and a majority reduced their alcohol use considerably, as well as symptoms of dependence, anxiety and depression at follow-ups.

Access to a treatment method that does not take time or require expertise might increase the likelihood that questions about alcohol are asked in primary care and contribute to the development of a treatment system where primary care is the base of treatment for AUD.

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DECLARATION OF INTERESTS

All authors declare no competing interests.

AUTHOR CONTRIBUTIONS

Karin Hyland: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); writing — original draft (lead); writing — review and editing (equal). **Anders Hammarberg:** Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); validation (equal); writing — review and editing (equal). **Erik Hedman-Lagerlöf:** Conceptualization (equal); funding acquisition (equal); methodology (equal); supervision (equal); validation (equal); writing — review and editing (equal). **Magnus Johansson:** Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); software (equal); validation (equal); writing — review and editing (supporting). **Philip Lindner:** Data curation (lead); formal analysis (lead); software (lead); writing — review and editing (equal). **Sven Andreasson:** Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); supervision (lead); validation (equal); writing — review and editing (equal).

CLINICAL TRIAL REGISTRATION

The study was approved by the Regional Ethics Board in Stockholm, no. 2016/1367–31/2. The study protocol was published in Trials 30 December 2019. The trial identifier is ISRCTN69957414, available at http://www.isrctn.com, assigned 7 June 2018.

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