Internet-based therapy versus face-to-face therapy for alcohol use disorder, a randomized controlled non-inferiority trial

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ABSTRACT

Background and aims Most people with alcohol use disorder (AUD) are never treated. Internet-based interventions are effective in reducing alcohol consumption and could help to overcome some of the barriers to people not seeking or receiving treatment. The aim of the current study was to compare internet-delivered and face-to-face treatment among adult users with AUD. Design Randomized controlled non-inferiority trial with a parallel design, comparing internet-delivered cognitive–behavioural therapy (ICBT) (n = 150) with face-to-face CBT (n = 151), at 3- and 6-month follow-ups. Setting A specialized clinic for people with AUD in Stockholm, Sweden. Participants were recruited between 8 December 2015 and 5 January 2018. Participants A total of 301 patients [mean age 50 years, standard deviation (SD) = 12.3] with AUD, of whom 115 (38%) were female and 186 (62%) were male. Intervention and comparator Participants were randomized in blocks of 20 at a ratio of 1 : 1 to five modules of therapist-guided ICBT or to five modules of face-to-face CBT, delivered over a 3-month period. The same treatment material and the same therapists were used in both groups. Measurements The primary outcome was standard drinks of alcohol consumed during the previous week at 6-month follow-up, analysed according to intention-to-treat. The pre-specified non-inferiority limit was five standard drinks of alcohol and d = 0.32 for secondary outcomes. Results The difference in alcohol consumption between the internet and the face-to-face group was non-inferior in the intention-to-treat analysis of data from the 6-month follow-up [internet = 12.33 and face-to-face = 11.43, difference = 0.89, 95% confidence interval (CI) = −1.10 to 2.88]. The secondary outcome, Alcohol Use Disorder Identification Test score, failed to show non-inferiority of internet compared with face-to-face in the intention-to-treat analysis at 6-month follow-up (internet = 12.26 and face-to-face = 11.57, d = 0.11, 95% CI = −0.11 to 0.34). Conclusions Internet-delivered treatment was non-inferior to face-to-face treatment in reducing alcohol consumption among help-seeking patients with alcohol use disorder but failed to show non-inferiority on some secondary outcomes.

Keywords Alcohol, alcohol use disorder, cognitive behaviour therapy, internet intervention, non-inferiority, randomized controlled trial, treatment.

INTRODUCTION

Background

Alcohol use is a leading risk factor for premature death and disability-adjusted life-years. Among the population aged 15–49 years, alcohol use was the leading risk factor in 2016, accounting for nearly 10% of global deaths. A dose–response relationship exists between alcohol use and many major diseases [1]. Alcohol use disorder (AUD) is characterized by impaired control and continued heavy use, despite these known negative consequences [2]. The prevalence of AUD is estimated to be 4.9% world-wide and 6.1% in western Europe [3]. Effective treatment options are available, both psychological and
pharmacological, that can help an individual reduce their alcohol consumption [4,5]. However, of all mental disorders, alcohol and substance use disorders have the widest treatment gap between the number of individuals affected and the number in treatment, with only approximately 7% estimated to receive treatment [6]. Shame, stigma and poor access to attractive treatment options are common reasons why people with AUDs do not receive treatment [7].

Digital interventions for problematic alcohol use have been developed for access via computers and the internet during the last 30 years. Meta-analyses have shown that internet interventions yield significantly better effects in terms of reduced alcohol consumption compared to control groups [8,9]. The majority of studies on digital interventions for alcohol have been conducted on brief single-session interventions aimed at students or similar risk populations [10]. Extended digital interventions, aimed at people with AUDs, are intended to be used over a number of weeks and are often based on treatment principles such as cognitive–behavioural therapy (CBT) and/or motivational interviewing (MI) [11]. An individual patient meta-analysis has reported a significant effect of guided internet interventions for alcohol, with a reduction of 10 weekly standard units [95% confidence intervals (CI) = 5.4–14.6, P = 0.001] compared to controls [9].

Although several studies have shown that digital interventions are effective in reducing alcohol use, it is not clear how effective they are compared to face-to-face interventions. A recent Cochrane Review of internet interventions found no evidence of a difference in effect on alcohol consumption between internet and face-to-face intervention arms in five trials of brief interventions targeting college students’ alcohol use [8]. Research on other psychiatric and somatic disorders has suggested that internet interventions that are therapist-guided have effects comparable to those of face-to-face interventions [12]. Previous studies conducted in clinical settings have tested digital interventions for alcohol as an alternative to treatment as usual (TAU) [13–15] or as an addition to TAU [15–17]. A recent meta-analysis found that when digital CBT for alcohol was tested as an addition to TAU, compared with TAU only, the effect size from seven studies was positive and significant. It also found that the pooled effect size from two studies comparing digital CBT for alcohol use to TAU did not suggest superior efficacy [18].

In order to investigate whether a new treatment modality such as internet-delivered treatment is actually no less effective than an established treatment, a non-inferiority or equivalence design is needed. Such a design can also help to avoid ethical problems with using placebo or inactive control groups in the evaluation of a new treatment for a serious condition such as AUD, where there is already evidence of efficacy for an existing standard treatment. The use of a non-inferiority design can be problematic, however, if the new treatment does not offer other advantages compared to an already established treatment [19]. Possible advantages of internet-delivered treatment for alcohol use disorders include overcoming problems with cost, accessibility and stigma in traditional face-to-face treatment [20]. One previous non-inferiority study of an internet intervention for alcohol has been conducted in primary care, with the proportion of hazardous drinkers in each group as the primary outcome. The study failed to show non-inferiority for facilitated access to an internet self-help programme compared to a face-to-face brief intervention at 3- and 12-month follow-ups, when a biased outcome measure was removed from the analysis [21].

The purpose of this randomized controlled non-inferiority trial was to investigate the effects of internet-delivered CBT, compared to face-to-face CBT, among adult users with AUD at a specialized clinic for AUDs. The main hypothesis of the trial was that internet-delivered CBT for reducing alcohol use would not be less effective in reducing alcohol consumption, in terms of standard units consumed per week, compared to face-to-face CBT. The margin for the difference between treatments, within which internet-delivered therapy would be considered non-inferior, was set to five standard units of alcohol consumed per week.

METHODS

Study design

The present study was a two-armed randomized controlled non-inferiority trial, with a parallel design. Participants were randomly assigned in blocks of 20 at a ratio of 1:1 to internet-delivered CBT or to face-to-face CBT.

Recruitment

Participants were recruited through the open access website of Riddargatan 1, an outpatient clinic within the Stockholm Centre for Dependence Disorders, specializing in treating AUDs. Visitors to the website were informed about the study on the front page as well as on the page with contact information for the clinic. Website visitors were invited to participate in a study on both internet- and clinic-based services, where they would be randomized and the number of visits to the clinic would vary, depending on study group. By clicking on a link, they accessed more information about the study, provided their informed consent and completed screening with the Alcohol Use Disorders Identification Test (AUDIT) [22], self-reported alcohol dependence criteria [International Classification of Disease 10 (ICD-10)] [23] and demographic questions. After screening, registrants under the age of 18 years or those having a low risk for AUD (fewer than three ICD-10...
criteria or a score lower than 15 points on the AUDIT) were informed that they did not qualify for the study and were referred to the clinic’s ordinary services for further help. Eligible registrants were instructed to create a personal account, with a unique user-name and password, and then asked to complete baseline measures.

Participants who completed the baseline measures were contacted via telephone by a research nurse, who registered them as patients at the clinic, instructed them on how to provide a blood sample for biological markers and booked an appointment for assessment with a physician at the clinic. At that visit, the physician established whether the patient had an AUD, and furthermore did not meet any of the following exclusion criteria: risk for severe withdrawal symptoms, risk for suicide, requiring medication for AUD, having a mental illness requiring separate care, not residing in Stockholm County, not undergoing other treatment for AUD or lacking sufficient understanding of the Swedish language. Participants had no other contact with the researchers or clinic staff before being randomized.

Randomization and masking

After the visit, all participants who were not excluded were given one part of a sealed opaque double envelope, prepared and shuffled in bunches of 20 by the first author. The envelope included information on the plan for the assigned treatment. The other part of the envelope was opened by one of the therapists, who then contacted the participant to start treatment via internet or face-to-face. The participants did not receive information on which of the groups was of interest for the research and which was considered a control for study purposes. All research and clinical staff were blinded to allocation until after the participant was included and given their sealed envelope.

Interventions

Internet-delivered treatment

The Internet CBT (ICBT) was delivered on-line at the same website that was used for recruitment and assessment in the study, programmed in the open-source platform Drupal (drupal.org) by the first author. The CBT programme was based on self-help material previously used in studies on the internet and in specialist care [24–27]. The content and exercises in the programme were based on motivational interviewing, preventing relapse, three optional problem-solving modules (handling feelings, drink-refusal skills and handling craving) and 11 fact sheets (blood alcohol level, anxiety, depression, anger, stress, handling thoughts, relaxation, sleep, leisure activities and communication). The first module included brief feedback on the assessment. Users were also encouraged to register their alcohol consumption and craving estimates, with space to provide details on the situation where they drank or experienced craving. All the therapists were CBT-trained psychologists or psychotherapists. Participants were recommended to spend between 1 and 2 weeks on each module and between 10 and 12 weeks for the whole treatment. In the internet-based treatment the modules were released one-by-one by the therapist and all the communication between the therapist and the patient was conducted on-line asynchronously, without any visits at the clinic during the treatment. Automated e-mails were sent to the patient at the release of every new module and with every new message from the therapist. Patients who did not start the internet programme or stopped using it were sent reminders via text messages to use the intervention. Telephone numbers were provided on the website for technical assistance and to the clinic in case of emergency.

Face-to-face treatment

The same programme as in the ICBT was provided as a paper printout for face-to-face patients. Each of the main modules and the optional additional modules and content were discussed in five 30–45-minute pre-booked sessions at the clinic. If the patient missed a session, it was re-scheduled by telephone. The participants could not contact their therapist via telephone, but they could contact the clinic to re-book their session or in case of emergency. The same eight therapists who delivered the internet CBT provided the face-to-face CBT. The instructions to the therapist were to keep the delivery of the CBT modules as similar as possible in both interventions. Sessions were recorded on audio and all therapists received regular supervision from the first author.

Follow-up

At 3 and 6 months after randomization, participants were e-mailed a link to the follow-up questionnaires. If they spontaneously logged-on to the programme at 3 or 6 months after randomization, they were also redirected to the follow-up questionnaires. The same questionnaires as at baseline were used at follow-up, adjusted for the time since the last assessment (3 months). Participants who did not respond to this initial request received up to five automated e-mail reminders, followed by a manual e-mail reminder and a mobile text message from the first author.
Once a participant completed the follow-up measures, no further reminders were sent.

**Measures**

**Primary outcome**

The primary outcome was the difference between groups in alcohol consumption, measured by the total number of standard drinks consumed during the previous week at 6-month follow-up. The number of standard drinks consumed on each of the 7 days was self-reported using the time-line follow-back (TLFB) method [28]. According to the Swedish definition, one standard drink contains 12 g of pure alcohol. The TLFB has also been shown to be a valid and reliable procedure to document recent drinking when administered via the internet [29] and in a 7-day version [30].

**Secondary outcomes**

Secondary outcomes were alcohol consumption at 3-month follow-up, measured by the total number of standard drinks consumed during the previous week. Additional outcomes, calculated for the preceding week based on the TLFB score, included the number of non-drinking days, the number of binge-drinking days (defined as days with three or more drinks for women and four or drinks for men), the average number of drinks on drinking days and low-risk score, as well as the ‘zone’ categories described below, and use-categories. Consumption (according to Swedish guidelines) was no more than 14 drinks per week and no binge drinking for men or, for women, no more than nine drinks per week and no binge drinking. Problematic alcohol use was assessed with the AUDIT total score, as well as the ‘zone’ categories described below, and use-categories. AUDIT is a 10-item instrument that has been validated in Swedish and via computer [31,32]. For descriptive purposes at baseline, as well as for assessment of non-improved and deteriorated participants, the AUDIT total score was categorized into four risk-level zones as follows: (I) 0–8p, (II) 9–15p, (III) 16–19p and (IV) 20–40p. AUD was assessed by the self-reported number of AUD criteria fulfilled according to the Diagnostic and Statistical Manual version 5 (DSM-5) [2] during the past year. Health-related quality of life was assessed with the EuroQol-5 dimension (EQ-5D-5L). Index scores were calculated with Crosswalk value sets, using the United Kingdom as a reference [33,34]. Readiness to change was measured with two visual analogue scale (VAS) entries, where users responded on a scale of 0–10 to the statements: ‘I am not ready to reduce/quit my drinking’ (0) and ‘I am very much ready to reduce/quit my drinking’ [35]. Symptoms of depression were measured by the Montgomery Asberg Depression Rating Scale-Self Rated (MADRS-S) [36,37]. Symptoms of anxiety were measured by the Generalized Anxiety Disorder assessment-7 items (GAD-7) [38,39]. Use of other support for reducing or eliminating alcohol use was assessed by four questions covering with whom and in what context participants had spoken to someone about their alcohol problems, which medication they had used or which other internet resources they had used regarding alcohol.

The primary and secondary outcomes were assessed on-line at baseline and at 3 and 6 months post-randomization. At 3- and 6-month follow-ups the time-frame for AUDIT and DSM-5 was adjusted from 12 to 3 months.

**Additional measures**

All participants received e-mail invitations 3 and 6 weeks after beginning treatment to answer the Working Alliance Inventory (WAI) and Session Rating Scale (SRS) [40]. Questions concerning satisfaction with treatment and perceived knowledge-gains from treatment were completed at 6 months. Blood samples were collected at baseline and 6-month follow-up and were analysed for levels of carbohydrate-deficient transferrin (CDT), which rises following recent heavy alcohol use.

**Non-inferiority limit**

The non-inferiority limit should be based on the effect of the reference treatment [19]. It is important to note that the basis for the limit is not the overall effect of interventions aimed at reducing alcohol use or effects of previous internet interventions, which have often been self-help interventions studied in public health or prevention settings [8]. The margin was calculated with the fixed-margin method [41] and a preserved effect of 50% of the lower margin of the 95% CI, as suggested by guidelines [42]. The non-inferiority limit in the current study was based on the effect of CBT for substance use disorder compared to no intervention \[g = 0.85 (0.69–1.01)]\, shown in meta-analysis [4]. The non-inferiority limit was set to five standard drinks for primary outcome and \(d = 0.32\) for secondary outcomes.

**Sample size**

Based on preliminary data from a previous study, the power calculation included in the original protocol was performed with the G*Power program, showing that the required number of study participants needed in the statistical analysis was 176 per group. An updated power calculation for non-inferiority using sealedenvelope.com was performed in the autumn of 2017 based on a standard deviation (SD) of 13.5, observed at baseline for recruited participants to this study. With no difference between the face-to-face and internet-based CBT, 115 patients per group would be
required for 80% certainty that the lower limit of a 95% two-sided confidence interval would be above the non-inferiority limit of five drinks at 6-month follow-up.

Analytical plan and statistical procedure

The analysis of the primary outcome was performed using a linear model, with alcohol consumption at 6 months as the dependent variable and treatment group as the factor variable, adjusting for baseline consumption. The same statistical model was used for analyses of secondary outcomes, adjusting for the baseline value of each respective outcome. Outcomes that, according to visual inspection of data and residuals, were not normally distributed were analysed using generalized linear models with either a negative binomial or a Poisson family function, depending on the goodness-of-fit statistics. Between-group effect sizes (Cohen’s d) were calculated by dividing differences in estimated mean values (at 3- and 6-month follow-ups) by the pooled SD. Additional analyses used t-tests and \(^{2}\)-tests. All analyses used two-sided tests and a significance level of \(P < 0.05\). The primary outcome analysis was based on the intention-to-treat (ITT). Under the assumption that data were missing at random, missing data were handled with multiple imputation with 100 different imputed data sets that were combined using the pooled estimate. The imputations were performed using predictive mean matching and fully conditional specification (10 maximum iterations), with the constraint that baseline variables were predictors-only. The study featured no design aspects that risks introducing non-random missingness, including separating outcome reporting from treatment delivery. In addition, anecdotal experience from reaching participants who had initially not provided follow-up data suggested no bias in any direction. Multiple imputation was chosen for the primary analysis over baseline carried forward imputation, as the latter type of simple imputation has been shown to give biased estimates of treatment effects [43] and decreases power to detect between-group differences [44], which could unduly favour a hypothesis of non-inferiority. Two sensitivity analyses were performed: one according to per-protocol (PP), only including those who completed the 3- or 6-month follow-ups, respectively, and who accessed the allocated treatment but not any other treatment; and the second according to the assumption of missing not at random (MNAR), where missing values at the 3- or 6-month follow-ups were replaced by baseline values. Data imputation and all tests were carried out using SPSS version 25. Little’s overall test of randomness indicated that missing data on the primary outcome occurred completely at random \(\chi^2 = 1.163\), degrees of freedom (d.f.) = 7, \(P = 0.992\). Imputation was used for 38% of the data in the ITT and the MNAR analysis.

RESULTS

Participants

During the 2-year recruitment period, 735 individuals were screened for participation in the study. A total of 301 participants were randomly allocated to the two study arms (see flow-chart in Fig. 1). This was lower than the initially intended sample size, but in line with the updated sample calculation made after recruitment start. During the last year prior to treatment, six (2%) randomized participants had talked to someone in specialized care and 78 (26%) to any professional about their alcohol use. Full demographic and clinical variables at baseline are presented in Table 1.

Loss to follow-up

Attrition was 33\% (\(n = 98\)) at the 3-month follow-up and 43\% (\(n = 129\)) at the 6-month follow-up. There was no difference in attrition between the internet and the face-to-face group, neither at 3 months (\(\chi^2 = 2.062, P = 0.151\)) nor at 6 months (\(\chi^2 = 0.004, P = 0.947\)). The number of participants completely missing from both follow-ups was 25\% in both groups (\(n = 38\) versus \(n = 37\); \(\chi^2 = 0.004, P = 0.947\)). A difference in baseline GAD-7 scores occurred between participants who were lost and those who completed the 6-month follow-up (7.31 versus 6.14, \(t = 2.116, P = 0.035\)). No differences in any other baseline variables were found between those lost to follow-up at 3 or 6 months and those who completed both follow-ups. No significant interactions between group assignment and being lost at 3- or 6-month follow-ups were found on any baseline variables, indicating no overall confounding effects of missing data.

Treatment usage

The face-to-face group completed more modules than the internet-based group (4.19 versus 3.74, \(t = 2.49, P = 0.013\)). In the internet-based treatment, the mean number of comments per module sent by patients was 1.6 (SD = 1.1) and by therapists 4.1 (SD = 2.5). Treatment was never accessed by seven participants in the internet group and 12 in the face-to-face group. Other treatment than that according to protocol was given to 13 participants: in the internet group, three participants received additional treatment visits at the clinic and two received pharmacological treatment; in the face-to-face group, eight participants received pharmacological treatment. In a few cases the last treatment session was after the post-treatment follow-up, which was conducted 3 months after randomization for all participants.
Primary outcome analysis

Controlling for baseline consumption, the difference between internet and face-to-face treatment was non-inferior according to the pre-specified limit of five standard drinks of alcohol the previous week at 6-month follow-up. In the PP sensitivity analysis, only including those who completed 6-month follow-up, who received the allocated treatment but not any other treatment, and in the separate MNAR sensitivity analysis, where missing values were replaced by baseline alcohol consumption, the results also showed non-inferiority of internet compared to face-to-face treatment at 6-month follow-up (see Fig. 2 and Table 2 for detailed results).

Secondary outcome analyses

At 6 months, internet treatment was inferior to face-to-face treatment in all secondary outcomes, with the exception of the AUDIT score and the number of binge drinking days in the ITT analysis, as well as all outcomes in the MNAR analysis. In the PP analysis, the AUDIT score, the number of fulfilled AUD criteria and the biomarker of alcohol consumption CDT did not show non-inferiority for internet treatment. At 3 months, several of the outcomes did not show non-inferiority for internet treatment compared to face-to-face treatment (see Table 3 for estimated means, effect sizes and CI).

Clinical outcomes

Low-risk alcohol consumption according to Swedish guidelines was reported by 35 of 86 (41%) of follow-up participants in the internet group and 32 of 86 (37%) participants in the face-to-face group at 6 months, with no significant differences found between the groups ($\chi^2 = 0.22, P = 0.64$).

Deterioration and non-response

Among follow-up participants at 6 months, one participant in the internet group and two in the face-to-face group deteriorated to a more severe category of alcohol use according to AUDIT, while 14 participants (16%) in the internet group and seven in the face-to-face group (8%) had not changed and remained within the highest AUDIT category. The difference in deterioration and non-response between the groups was not statistically significant ($\chi^2 = 1.26, P = 0.26$).

Adverse events

There were no reported adverse events due to the intervention reported by participants. Two participants reported
Table 1  Demographic and baseline values.

| Sex                        | Face-to-face | Internet |
|----------------------------|--------------|----------|
|                            | n | %  | n | %  |
| Women                      | 60 | 39.7 | 55 | 36.7 |
| Men                        | 91 | 60.3 | 94 | 62.7 |
| Civil state                |   |      |   |      |
| Married                    | 63 | 41.7 | 66 | 44.0 |
| Cohabitating               | 38 | 25.2 | 40 | 26.7 |
| Single                     | 30 | 19.9 | 27 | 18.0 |
| Divorced                   | 16 | 10.6 | 11 | 7.3  |
| Widow                      | 4  | 2.6  | 5  | 3.3  |
| Country of birth           |   |      |   |      |
| Sweden                     | 143| 94.7 | 138| 92.0 |
| Other Nordic country       | 7  | 4.6  | 4  | 2.7  |
| North America              | 0  | 0.0  | 1  | 0.7  |
| Rest of Europe             | 1  | 0.7  | 6  | 4.0  |
| Education                  |   |      |   |      |
| University/college         | 104| 68.9 | 100| 66.7 |
| Upper secondary school, Training school or equivalent | 41 | 27.2 | 41 | 27.3 |
| Primary school/folk school | 6  | 4.0  | 7  | 4.7  |
| Source of income           |   |      |   |      |
| Employment                 | 124| 82.1 | 124| 82.7 |
| Pension                    | 13 | 8.6  | 13 | 8.7  |
| Study allowance            | 6  | 4.0  | 4  | 2.7  |
| Other                      | 8  | 5.4  | 7  | 4.7  |
| Residence                  |   |      |   |      |
| Condominium                | 71 | 47.0 | 64 | 42.7 |
| Rental apartment           | 43 | 28.5 | 37 | 24.7 |
| Villa or townhouse         | 31 | 20.5 | 44 | 29.3 |
| Other                      | 6  | 4.0  | 4  | 2.7  |
| Living arrangements        |   |      |   |      |
| With partner and children  | 60 | 39.7 | 51 | 34.0 |
| With partner only          | 43 | 28.5 | 50 | 33.3 |
| With children only         | 9  | 6.0  | 8  | 5.3  |
| Alone                      | 22 | 14.6 | 18 | 12.0 |
| Other/varied               | 17 | 11.2 | 22 | 14.7 |
| AUDIT risk-level           |   |      |   |      |
| Zone II (9–15)             | 9  | 6    | 9  | 6    |
| Zone III (16–19)           | 55 | 36   | 40 | 27   |
| Zone IV (20–40)            | 87 | 58   | 101| 67   |
| ICD alcohol dependence     | 24 | 84   | 24 | 84   |

|                             | n | Mean | SD | n | Mean | SD |
|-----------------------------|---|------|----|---|------|----|
| Readiness to reduce alcohol consumption (scale 0–10) | 151 | 8.9 | 1.7 | 150 | 9.1 | 1.7 |
| Drinks/last week            | 151| 22.9 | 13.3 | 150 | 24.9 | 13.7 |
| Sober days (last week)      | 151| 2.9  | 2.1 | 150 | 2.7  | 1.8 |
| Binge drinking days (last week) | 151| 3.3  | 2.1 | 150 | 3.5  | 1.8 |
| AUDIT-score (0–40)          | 151| 21.0 | 4.8 | 150 | 21.9 | 4.8 |
| DSM-5 AUD                   | 151| 6.3  | 2.1 | 150 | 6.6  | 2.1 |
| GAD-7                       | 151| 6.4  | 4.5 | 150 | 6.9  | 5.0 |
| MADRS-S                     | 151| 13.5 | 8.3 | 150 | 15.0 | 8.6 |
| EQ-5D-5L                    | 151| 0.831| 0.131| 150| 0.832| 0.148|
| CDT                         | 134| 2.0  | 1.6 | 128 | 2.0  | 1.2 |

AUDIT = Alcohol Use Disorders Identification Test; DSM = Diagnostic and Statistical Manual; GAD = Generalized Anxiety Disorder; CDT = carbohydrate-deficient transferrin; ICD = International Classification of Disease; MADRS-S = Montgomery Asberg Depression Rating Scale–Self Rated; EQ-5D-5L = EuroQol-5 dimension.

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negative consequences from being registered as patients at a clinic for AUD. One was refused additional life insurance and one was refused an in-vitro fertilization procedure.

Working alliance during treatment

Participants who completed the alliance rating during treatment gave a significantly higher rating of the working alliance in the face-to-face group compared to the internet group, according to both WAI and SRS (see Tables 3 and 4 for details).

Satisfaction with treatment

A higher proportion of participants in the internet group indicated that they missed other forms of contact, and a lower proportion viewed the received treatment as effective compared to the face-to-face group. The internet group also viewed the treatment as less personal (see Tables 3 and 4 for details).

DISCUSSION

Principal results

This randomized controlled non-inferiority trial investigated the effects of internet-delivered CBT compared to face-to-face CBT among participants with AUD who sought help in a specialized clinic. As hypothesized, the internet-delivered treatment was non-inferior to face-to-face treatment in the primary ITT analysis of alcohol consumption 6 months after recruitment, as well as in the two sensitivity analyses. At 6 months, non-inferiority was also shown in most secondary outcomes. Nonetheless, non-inferiority could not be shown at 6 months in the secondary outcomes measured by the total AUDIT score and the number of binge drinking days in the ITT analysis, or in the PP analysis, for the total AUDIT score, AUD criteria and CDT biomarker levels. At the 3-month follow-up, non-inferiority could not be shown in the PP analysis for number of days sober and EQ-5D-5L in any analysis, or in drinks per week and binge drinking days. Overall, there were small differences in outcomes between the treatment groups.

The fact that the findings from some of the secondary outcomes did not show non-inferiority, especially in the PP analysis of outcomes immediately after treatment, could indicate that there may have been some additional benefits from having met a therapist face-to-face. Treatment use was slightly higher among participants in the face-to-face group and they were more satisfied with the treatment compared to the internet group. Many internet patients said they missed other forms of therapist contact. Receiving treatment through internet interventions has both advantages and disadvantages, and might not be for everyone. The special method of communicating asynchronously can give both participants and therapists more time to think and reflect about what they want to express, but can make it harder to understand details [45]. Communicating asynchronously via the internet can negatively affect the working alliance between the patient and the therapist, and this might explain some of the differences between the groups observed in the current study.

Limitations

This study had several limitations. Similar to previous studies on the internet-based treatment [46], attrition at follow-up was relatively high, although lower than in previous studies on internet-based alcohol interventions. This
Table 3 Estimated means adjusted for baseline and between group effect sizes with 95% CI for secondary outcomes at three- and six-months follow-up.

| 6 months                      | Internet | Face-to-face | Diff | 95% CI |
|-------------------------------|----------|--------------|------|--------|
| **ITT**                       | Mean     | SD           | Mean | SD     | d       | 95% CI |
| AUDIT                         | 12.26    | 6.25         | 11.57| 5.70   | 0.11    | −0.11 0.34 |
| DSM-5 AUD<sup>a</sup>         | 3.83     | 2.80         | 3.59 | 2.76   | 0.09    | −0.14 0.31<sup>c</sup> |
| Binge days<sup>a</sup>        | 1.13     | 1.33         | 0.99 | 1.14   | 0.11    | −0.11 0.34 |
| Sober days                   | 3.87     | 1.98         | 3.93 | 2.01   | −0.03   | −0.26 0.20<sup>c</sup> |
| GAD-7<sup>a</sup>            | 3.75     | 4.07         | 3.59 | 4.07   | 0.04    | −0.19 0.27<sup>c</sup> |
| MADRS-S<sup>a</sup>          | 7.79     | 6.92         | 7.22 | 6.92   | 0.08    | −0.14 0.31<sup>c</sup> |
| EQ-5D-5L                     | 0.842    | 0.142        | 0.852| 0.137  | 0.07    | −0.29 0.16<sup>c</sup> |
| CDT                           | 2.01     | 1.72         | 1.85 | 1.72   | 0.09    | −0.13 0.32<sup>c</sup> |

| **PP**                        | Mean     | SD           | Mean | SD     | d       | 95% CI |
|-------------------------------|----------|--------------|------|--------|---------|--------|
| AUDIT                         | 12.22    | 6.65         | 10.75| 6.32   | 0.23    | 0.00   0.45 |
| DSM-5 AUD<sup>b</sup>         | 3.75     | 2.77         | 3.28 | 2.87   | 0.17    | −0.06 0.39 |
| Binge days<sup>a</sup>        | 1.20     | 1.56         | 1.05 | 1.56   | 0.10    | −0.13 0.32<sup>c</sup> |
| Sober days                   | 3.76     | 2.00         | 3.88 | 2.13   | −0.06   | −0.28 0.17<sup>c</sup> |
| GAD-7<sup>a</sup>            | 2.09     | 2.80         | 2.32 | 2.82   | −0.08   | −0.31 0.14<sup>c</sup> |
| MADRS-S<sup>a</sup>          | 5.26     | 7.57         | 4.66 | 6.11   | 0.09    | −0.14 0.31<sup>c</sup> |
| EQ-5D-5L                     | 0.870    | 0.110        | 0.880| 0.140  | −0.08   | −0.31 0.15<sup>c</sup> |
| CDT                           | 1.83     | 1.06         | 1.62 | 1.06   | 0.20    | −0.03 0.42 |

| **MNAR**                     | Mean     | SD           | Mean | SD     | d       | 95% CI |
|-------------------------------|----------|--------------|------|--------|---------|--------|
| AUDIT                         | 16.35    | 7.70         | 15.70| 7.55   | 0.08    | −0.14 0.31<sup>c</sup> |
| DSM-5 AUD<sup>b</sup>         | 4.72     | 2.90         | 4.59 | 2.90   | 0.04    | −0.18 0.27<sup>c</sup> |
| Binge days<sup>a</sup>        | 1.95     | 1.95         | 1.79 | 1.89   | 0.08    | −0.14 0.31<sup>c</sup> |
| Sober days                   | 3.39     | 1.92         | 3.39 | 2.06   | 0.00    | −0.23 0.23<sup>c</sup> |
| GAD-7<sup>a</sup>            | 4.62     | 5.05         | 4.39 | 4.85   | 0.05    | −0.18 0.27<sup>c</sup> |
| MADRS-S<sup>a</sup>          | 10.52    | 9.00         | 9.73 | 9.00   | 0.09    | −0.14 0.31<sup>c</sup> |
| EQ-5D-5L                     | 0.842    | 0.137        | 0.854| 0.137  | −0.08   | −0.31 0.14<sup>c</sup> |
| CDT                           | 2.01     | 1.42         | 1.91 | 1.42   | 0.07    | −0.16 0.30<sup>c</sup> |

3 months

| Drinks/week                   | Internet | Face-to-face | Diff | 95% CI |
|-------------------------------|----------|--------------|------|--------|
| **ITT**                       | Mean     | SD           | Mean | SD     | d       | 95% CI |
| AUDIT                         | 11.82    | 6.16         | 11.56| 6.16   | 0.04    | −0.18 0.27<sup>c</sup> |
| DSM-5 AUD<sup>b</sup>         | 4.47     | 2.86         | 4.30 | 2.85   | 0.06    | −0.17 0.29<sup>c</sup> |
| Binge days<sup>a</sup>        | 1.01     | 1.43         | 0.91 | 1.40   | 0.07    | −0.16 0.30<sup>c</sup> |
| Sober days                   | 4.16     | 1.89         | 4.57 | 1.96   | −0.21   | −0.44 0.01 |
| GAD-7<sup>a</sup>            | 3.12     | 3.76         | 2.80 | 3.16   | 0.09    | −0.13 0.32<sup>c</sup> |
| MADRS-S<sup>a</sup>          | 7.61     | 7.17         | 6.87 | 6.14   | 0.11    | −0.12 0.34 |
| EQ-5D-5L                     | 0.856    | 0.145        | 0.876| 0.117  | −0.15   | −0.37 0.08 |
| CDT                           | 2.01     | 1.42         | 1.91 | 1.42   | 0.07    | −0.16 0.30<sup>c</sup> |

| **PP**                        | Mean     | SD           | Mean | SD     | d       | 95% CI |
|-------------------------------|----------|--------------|------|--------|---------|--------|
| AUDIT                         | 11.74    | 6.32         | 11.29| 6.32   | 0.07    | −0.16 0.30<sup>c</sup> |
| DSM-5 AUD<sup>b</sup>         | 4.28     | 2.87         | 4.23 | 2.87   | 0.02    | −0.21 0.24<sup>c</sup> |
| Binge days<sup>a</sup>        | 1.10     | 1.55         | 0.86 | 1.56   | 0.15    | −0.07 0.38 |
| Sober days                   | 3.98     | 3.96         | 4.45 | 2.13   | −0.15   | −0.37 0.08 |
| GAD-7<sup>a</sup>            | 3.31     | 3.79         | 2.77 | 2.82   | 0.16    | −0.07 0.39 |
| MADRS-S<sup>a</sup>          | 7.43     | 7.57         | 6.81 | 6.11   | 0.09    | −0.14 0.32<sup>c</sup> |

(Continues)
might be a consequence of allowing users a fast and accessible way of signing up for participation. The current trial only measured outcomes at three time points. More measuring time points during the intervention could allow more flexibility in the modelling approach and also in examination of moderators and mediators [47]. The non-inferiority limit of five standard drinks might be considered too lenient; for example, if the limit is compared to the effects of brief internet-based or face-to-face interventions aimed at reducing alcohol use in community and primary care settings [8,48]. An additional limitation is that the non-inferiority limit, and consequently the results of this study, mainly have relevance in CBT treatment of AUDs in specialized clinical settings. The participants in the current study were mainly well-educated, employed full time and had stable living arrangements. All participants had also shown an interest in internet-based services, as they were recruited from the web and informed that parts of the study were conducted via the internet. The results cannot be generalized to all people with AUD, and especially not to patients with more severe or complex problems. Finally, as always, causal interpretations of PP analyses should be made with caution, as the reasons for attrition are largely unknown.

Table 3. (Continued)

| Drinks/week | Internet | Race-to-face | Diff | 95% CI | 0.01 |
|-------------|----------|--------------|------|--------|------|
| EQ-5D-5L    | 0.850    | 0.140        | 0.880| 0.140  | 0.21 | -0.44 |
| MNAR Mean   | 14.67    | 7.66         | 15.20| 7.77   | 0.07 | -0.29 |
| AUDIT       | 2.84     | 2.84         | 2.84 | 2.84   | 0.04 | -0.06 |
| Binge days  | 2.10     | 2.10         | 1.53 | 2.07   | 0.04 | -0.18 |
| Sober days  | 3.62     | 3.62         | 3.94 | 2.22   | 0.15 | -0.38 |
| GAD-7       | 4.15     | 4.15         | 3.81 | 3.81   | 0.07 | -0.16 |
| MADRS-S     | 9.34     | 9.34         | 8.20 | 8.20   | 0.04 | -0.19 |
| Diff 95% CI | 0.140    | 0.140        | 0.140| 0.140  | 0.01 |

Table 4. Working alliance and satisfaction with treatment in each group.

|                  | Internet | Race-to-face | t    | P    |
|------------------|----------|--------------|------|------|
| WAI total score  | 79       | 5.23         | 1.11 | 63   | 5.71 |
| WAI_bond         | 79       | 5.17         | 1.41 | 63   | 5.57 |
| WAI_goal         | 79       | 5.56         | 0.97 | 63   | 6.02 |
| WAI_task         | 79       | 4.95         | 1.23 | 63   | 5.54 |
| SRS total score  | 79       | 30.21        | 8.69 | 63   | 34.87 |
| SRS relationship | 79       | 8.32         | 2.22 | 63   | 8.92 |
| SRS goals and topics | 79   | 7.97         | 2.17 | 63   | 8.96 |
| SRS approach or method | 79   | 7.31         | 2.92 | 63   | 8.62 |
| SRS overall      | 79       | 6.62         | 2.83 | 63   | 8.37 |
| Experienced the treatment received as | | | | | |
| Pleasant (0–5)   | 73       | 4.03         | 1.04 | 70   | 4.24 |
| Personal (0–5)   | 73       | 2.37         | 1.56 | 70   | 3.84 |
| Safe (0–5)       | 73       | 3.90         | 1.45 | 70   | 4.14 |
| Missed other form of contact with their therapist | 44 | 60 | 2.32 | 8 | 11 | 38.16 > 0.001 |
| Would recommend the programme to others | 57 | 78 | 87 | 2.67 | 0.26 |
| Considered the programme an effective method for changing their drinking | 39 | 53 | 50 | 7.49 | 0.02 |
Strengths

This is the first study, to our knowledge, showing that internet-based treatment is non-inferior to face-to-face treatment for AUD in reducing alcohol consumption as well as symptoms of AUD, anxiety and depression. A major strength was that it was conducted in a dependency clinic with regular patients, lending the study high ecological validity. Treatments were well established in both modes of delivery, with several previous studies conducted in the current setting. Another strength was that the same therapists and the same treatment material was used in both groups. A majority of the participants reduced their drinking and many lowered their drinking to a low-risk level of use at follow-ups.

Comparison with prior work

The findings are in line with results found in other forms of internet-based psychological treatment, such as depression and anxiety [49], and are also in line with previous studies comparing face-to-face and internet alcohol interventions [8]. The level of dependence was similar to a recent Swedish clinical trial in specialized and primary care for AUD, but lower than in regular specialized care for AUD [26]. Participants had lower AUD severity than those who usually receive treatment, but they are representative of the majority of individuals with AUD [50], a population that can be reached via internet interventions.

Future research

There is a need for more studies that compare internet interventions with other treatments for AUD, including studies with long-term follow-up. The difficulties, risks and advantages of delivering alcohol treatment via the internet should be studied more carefully. Internet interventions seem to be effective in changing alcohol consumption, but more studies are needed to understand how they can be used and combined with other interventions to improve treatment for people with AUD. In sparsely populated areas, where people often need to travel a long distance to visit a clinic in person, internet interventions might be the only available alternative for receiving treatment for AUD.

CONCLUSION

In this study we found that internet-delivered treatment was not inferior to face-to-face treatment in reducing alcohol consumption among help-seeking patients with alcohol use disorder. Differences in secondary outcomes indicate that internet-delivered treatment might be inferior to face-to-face treatment on some alcohol-related outcomes.

Clinical trial registration details

The original study protocol including the non-inferiority margins was registered with and approved by the Stockholm Regional Ethical Review Board (ref 2014/1758–31/2, 5 November 2014). The trial was also registered at www.ClinicalTrials.gov (NCT02671019).

Declaration of interests

M.J. configured the internet platform and co-authored the programme used in the study. The programme is licensed under creative commons and the internet platform Drupal is open-source. A.H.B is co-owner of a company, TeleCoach AB, aiming to disseminate digital interventions; the company is not currently active. M.J., S.A. and U.H. are employed at the clinic Riddargatan 1, M.J., P.L. and M.G. are employed at the Addiction eClinic, both part of the Stockholm Center of Dependency disorders that offers face-to-face and internet-based treatments for alcohol use disorders. All other authors declare no competing interests.

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Author Contributions

Magnus Johansson: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization. Kristina Sinadinovic: Conceptualization; funding acquisition; methodology; project administration; supervision. Mikael Gajecki: Investigation; methodology; resources. Philip Lindner: Formal analysis; investigation; visualization. Anne H. Berman: Conceptualization; funding acquisition; methodology; software; supervision. Ulric Hermansson: Conceptualization; funding acquisition; methodology; project administration; resources; supervision. Sven Andreasson: Conceptualization; funding acquisition; methodology; project administration; resources; supervision.
A randomized controlled non-inferiority trial

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