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# A Precision Treatment Model for Internet-Delivered Cognitive Behavioral Therapy for Anxiety and Depression Among University Students
## A Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Guided internet-delivered cognitive behavioral therapy (i-CBT) is a low-cost way to address high unmet need for anxiety and depression treatment. Scalability could be increased if some patients were helped as much by self-guided i-CBT as guided i-CBT.

**OBJECTIVE** To develop an individualized treatment rule using machine learning methods for guided i-CBT vs self-guided i-CBT based on a rich set of baseline predictors.

**DESIGN, SETTING, AND PARTICIPANTS** This prespecified secondary analysis of an assessor-blinded, multisite randomized clinical trial of guided i-CBT, self-guided i-CBT, and treatment as usual included students in Colombia and Mexico who were seeking treatment for anxiety (defined as a 7-item Generalized Anxiety Disorder [GAD-7] score of ≥10) and/or depression (defined as a 9-item Patient Health Questionnaire [PHQ-9] score of ≥10). Study recruitment was from March 1 to October 26, 2021. Initial data analysis was conducted from May 23 to October 26, 2022.

**INTERVENTIONS** Participants were randomized to a culturally adapted transdiagnostic i-CBT that was guided (n = 445), self-guided (n = 439), or treatment as usual (n = 435).

**MAIN OUTCOMES AND MEASURES** Remission of anxiety (GAD-7 scores of ≤4) and depression (PHQ-9 scores of ≤4) 3 months after baseline.

**RESULTS** The study included 1319 participants (mean [SD] age, 21.4 [3.2] years; 1038 women [78.7%]; 725 participants [55.0%] came from Mexico). A total of 1210 participants (91.7%) had significantly higher mean (SE) probabilities of joint remission of anxiety and depression with guided i-CBT (51.8% [3.0%]) than with self-guided i-CBT (37.8% [3.0%]; $P = .003$) or treatment as usual (40.0% [2.7%]; $P = .001$). The remaining 109 participants (8.3%) had low mean (SE) probabilities of joint remission of anxiety and depression across all groups (guided i-CBT: 24.5% [9.1%]; $P = .007$; self-guided i-CBT: 25.4% [8.8%]; $P = .004$; treatment as usual: 31.0% [9.4%]; $P = .001$). All participants with baseline anxiety had nonsignificantly higher mean (SE) probabilities of anxiety remission with guided i-CBT (62.7% [5.9%]) than the other 2 groups (self-guided i-CBT: 50.2% [6.2%]; $P = .14$; treatment as usual: 53.0% [6.0%]; $P = .25$). A total of 841 of 1177 participants (71.5%) with baseline depression had significantly higher mean (SE) probabilities of depression remission with guided i-CBT (61.5% [3.6%]) than the other 2 groups (self-guided i-CBT: 44.3% [3.7%]; $P = .001$; treatment as usual: 41.8% [3.2%]; $P < .001$). The other 336 participants (28.5%) with baseline depression had nonsignificantly higher mean (SE) probabilities of depression remission with self-guided i-CBT (54.4% [6.0%]) than guided i-CBT (39.8% [5.4%]; $P = .07$).

**CONCLUSIONS AND RELEVANCE** Guided i-CBT yielded the highest probabilities of remission of anxiety and depression for most participants; however, these differences were nonsignificant for anxiety. Some participants had the highest probabilities of remission of depression with self-guided i-CBT. Information about this variation could be used to optimize allocation of guided and self-guided i-CBT in resource-constrained settings.

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Supplemental content

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Although clinically significant anxiety and depression are common among university students, few receive treatment.[1] Guided internet-delivered cognitive behavioral therapy (i-CBT) is a potentially attractive way to address this problem because it can be delivered at low cost, reduces common barriers to treatment, and has significantly better outcomes than self-guided i-CBT or treatment as usual.[2]

An earlier report on a 3-group pragmatic trial to reduce clinically significant anxiety and depression among Colombian and Mexican undergraduates reported that a significantly higher proportion of participants treated with guided i-CBT (50.3%) underwent remission than those treated with either self-guided i-CBT (37.1%) or treatment as usual (39.0%) (C. Benjet, PhD, et al, written communication, 2023). However, given the high prevalence of these disorders[3] and the constrained intervention resources in these universities, it would be desirable if some students could be treated as effectively with self-guided i-CBT as with guided i-CBT. For this to be true, though, significant heterogeneity of treatment effects (HTE) would have to exist.

To our knowledge, only limited previous research has investigated HTE of guided vs self-guided i-CBT.[4,5] These prior studies were all based either on small samples with low power to detect HTE or on individual-level meta-analyses with the limited predictors assessed in all pooled trials. We addressed these limitations by conducting a comparatively large trial, using a rich baseline assessment of hypothesized prescriptive predictors, and carrying out a preplanned secondary analysis presented here to estimate an individualized treatment rule (ITR) using a state-of-the-art machine learning method.[6]

### Key Points

**Question** Can an individualized treatment rule identify patients who benefit as much or more from self-guided internet-delivered cognitive behavioral therapy (i-CBT) as from guided i-CBT?

**Findings** In this secondary analysis of a randomized clinical trial of 1319 university students with anxiety and/or depression, guided i-CBT optimized the probability of (1) joint remission of anxiety and depression for 91.7% of participants, (2) remission of anxiety for 100% of participants, and (3) remission of depression for 71.5% of participants. Self-guided i-CBT, in comparison, optimized the probability of remission of depression for the remaining 28.5% of participants.

**Meaning** Self-guided i-CBT is sometimes equally or more effective than guided i-CBT for depression but not anxiety.

## Methods

### Participants and Procedures

Participants were undergraduates at 7 universities in Colombia and Mexico, aged 18 years or older, with clinically significant anxiety (7-item Generalized Anxiety Disorder [GAD-7] scores of ≥10)[7] and/or depression (9-item Patient Health Questionnaire [PHQ-9] scores of ≥10).[8] Exclusion criteria were positive screens for lifetime bipolar disorder or nonaffective psychosis or recent suicidal ideation with intent. Each university had a clinical liaison who carried out evaluation of recruited students who reported suicidal ideation with intent. Other ineligible students were referred to treatment as usual, which consisted of whatever mental health service each university normally provided. Participants provided written informed consent to be in a randomized clinical trial. The protocol, which focused centrally on developing an ITR, was approved by the institutional review board of Harvard Medical School and the research ethics committee of the National Institute of Psychiatry Ramon de la Fuente Muñiz (Comité de Ética en Investigación del Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz). We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline[9] and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline[10] in reporting results (see the trial protocol in Supplement 1 for more details).

Participants at 6 universities were recruited by emails sent to a weekly random sample of approximately 1000 students in conjunction with social media postings. At the seventh university, only students from the mental health clinic waiting list were invited to participate. In 1 of the other 2 universities with student clinics, recruitment was allowed from both the general student body and the clinic waiting list.

Enrollment occurred from March 1 to October 26, 2021. After obtaining informed consent, each participant completed a 30- to 45-minute baseline online self-administered questionnaire (SAQ) before randomization (see the trial protocol and statistical analysis plan in Supplement 1). A follow-up online SAQ was administered 3 months after randomization. Initial follow-up SAQ nonrespondents were sent email reminders, WhatsApp or Telegram messages, and telephone calls to minimize loss to follow-up (eMethods in Supplement 2). More details on the study design are reported elsewhere.[11] Initial data analysis for the present report was conducted from May 23 to October 26, 2022. Additional analysis addressing reviewer comments was conducted from January 4 to 12, 2023.

### Randomization

In this multisite, assessor-blinded randomized clinical trial, 1319 eligible baseline participants were block randomized, with stratification and equal allocation across the 3 intervention groups (eFigure 1 in Supplement 2).

### Interventions

The i-CBT intervention was a culturally adapted version of SilverCloud Health's Space from Anxiety and Depression, a transdiagnostic i-CBT program implemented with or without guidance that has demonstrated effectiveness in treating anxiety and depression (see eAppendix in Supplement 2 for details on the cultural adaptation process).[12] In the guided group, guides (with undergraduate psychology degrees) sent online weekly messages to users designed to create personalized experiences and provide feedback. Self-guided users, in comparison, received no personalized messages. As detailed in the eMethods in Supplement 2, the program has 7 core modules and several additional optional modules designed to be completed in 8 weeks.

In the 3 universities that had formal mental health clinics, treatment as usual consisted of referrals to the clinic. In the other universities, treatment as usual consisted of whatever informal counseling services faculty provided to students, with referrals to community treatment clinicians. Because of the COVID-19 pandemic lockdown at the time of randomization, most university services were provided only online via videoconferencing platforms during the study. The decision to use treatment as usual as the control rather than the more typical waiting list or active control condition was made to evaluate how much the interventions improved on usual practice.

## Assessments

### Anxiety and Depression

Anxiety was assessed with the GAD-7[7] and depression with the PHQ-9.[8] The primary outcome was 3-month joint remission in the total sample; that is, remission on both scales. The ranges used to define remission were 0 to 4 for both the GAD-7 and PHQ-9.[7,8] We also examined anxiety and depression remission (scores of 0-4 on each scale separately, ignoring scores on the other scale) among participants with clinically significant baseline scores on those separate scales.

### Predictors

The diverse constructs that have been hypothesized as prescriptive predictors of differential anxiety[13-16] or depression[17-21] treatment response can be organized conceptually into 11 domains: sociodemographic characteristics; university-related factors; stressors related to COVID-19; other recent and lifetime stressors; anxiety and depression characteristics; comorbid mental disorders; mental health treatment; physical health; social networks and supports; personality or temperament and psychological resilience; and internet literacy and preferences. As detailed in the eMethods and eTable 1 in Supplement 2, we included measures to assess all these constructs in a baseline SAQ, making it much more extensive (requiring 30-45 minutes to complete) than baseline assessments in previous CBT HTE trials (eTable 1 in Supplement 2).

## Statistical Analysis

All analyses were carried out using R, version 3.6.3 (R Group for Statistical Computing).[22] Data management was implemented with SAS, version 9.4 (SAS Institute Inc).[23] All *P* values were from 2-sided tests, and results were deemed statistically significant at $P < .05$.

### Estimating the ITRs

The HTE analysis, conducted from an intent-to-treat perspective, began by estimating predicted probabilities of remission within intervention groups, adjusting for loss to follow-up[24] using a machine learning method that combined results across multiple algorithms using the Super Learner R program (R Group for Statistical Computing) (eMethods, eTable 5, and eTable 6 in Supplement 2).[25,26] A within-group model discrimination was evaluated by calculating the 5-fold cross-validated (5F-CV) area under the receiver operating characteristic curve (AUC-ROC), positive predictive value (PPV), and negative predictive value. Within-group model calibration was evaluated by using a nonparametric locally weighted scatterplot smoother with 0.75 bandwidth[27] to generate calibration curves and calculate the Integrated Calibration Index (ICI).[28]

The 3 within-group 5F-CV predicted probabilities of remission were then imputed to all participants regardless of the intervention assigned. Each participant's optimal treatment within the set considered was defined as the intervention with the highest predicted probability of remission. The ITR was defined as the rule that assigned all of the participants to their optimal treatment using the sg package in R (eMethods in Supplement 2).[6] The ITR performance was then evaluated by replicating the experimental comparisons in 3 subgroups of participants defined by the ITR as the intervention group with the highest predicted probability of remission. All analyses were repeated 3 times: once for joint remission of anxiety and depression in the total sample and 2 other times for remission of anxiety or depression in subgroups of respondents with clinically significant baseline scores (ie, scores of ≥10) on the GAD-7 or PHQ-9.

### Predictor Importance

Predictor importance in defining the ITRs was examined using the kernel Shapley Additive Explanations (SHAP) method[29] implemented in the fastshap package in R (eMethods in Supplement 2).[30] The SHAP method is a general-purpose approach to examine predictor importance in any machine learning prediction model, not only in models used to develop ITRs.

# Results

## Sample Distribution

The study included 1319 participants (mean [SD] age, 21.4 [3.2] years; 555 women [42.1%] came from Mexico; 483 women [36.6%] came from Colombia; 170 men [12.9%] came from Mexico; 111 men [8.4%] came from Colombia; 738 [55.9%] were first-generation university students). A total of 928 participants (70.3%) met baseline criteria for clinically significant (ie, severe or moderate) anxiety, 1190 (90.2%) met baseline criteria for clinically significant depression, and 799 (60.6%) met baseline criteria for both (eTable 2 in Supplement 2).

## Loss to Follow-up

Three-month follow-up SAQs were completed by 65.4% of baseline participants (291 of 445) in the guided i-CBT group, 62.2% (273 of 439) in the self-guided i-CBT group, and 77.0% (335 of 435) in the treatment as usual group. Significant baseline predictors of 3-month SAQ completion were intervention group (higher in the treatment as usual group than others) and country (higher for Mexico than Colombia) (eTable 3 in Supplement 2). Three-month SAQ completion was also higher at universities with than without mental health clinics. None of these associations varied significantly across intervention groups. In addition, data obtained on engagement at the end of the intervention showed that 3-month SAQ completion was higher among participants who spent 3 or more hours than those who spent less than 3 hours using SilverCloud, both in

the guided i-CBT group (86.3% [107 of 124] vs 62.1% [169 of 272]) and in the self-guided i-CBT group (87.2% [41 of 47] vs 63.6% [211 of 332]).

### i-CBT Treatment Uptake

Call logs showed that 88.9% of participants (396 of 445) were randomly assigned to guided i-CBT and 86.3% (379 of 439) were randomly assigned to self-guided i-CBT initiated treatment, with median (IQR) numbers of logins of 5 (2-14) for guided i-CBT and 2 (1-5) for self-guided i-CBT. The median time using SilverCloud was 1.4 hours (IQR, 0.3-3.9 hours) for guided i-CBT and 0.5 hours (IQR, 0.1-1.4 hours) for self-guided i-CBT.

### Other Treatments

Among participants recruited from clinic waiting lists, very similar proportions across groups (66.4% [48 of 72] to 68.7% [55 of 80]) reported in the 3-month SAQ that they received some other anxiety and/or depression treatment since baseline, including 38.9% (33 of 85) to 43.3% (35 of 80) who received medication and 42.8% (31 of 72) to 51.7% (41 of 80) who received psychotherapy. Among respondents recruited from the general student body, in comparison, a significantly higher proportion of participants in the treatment as usual group (41.7% [104 of 250]) than in the i-CBT groups (guided i-CBT, 23.5% [50 of 211]; $\chi^2_1 = 18.0$; $P < .001$; self-guided i-CBT, 24.4%; $\chi^2_1 = 15.8$; $P < .001$) received some other treatment, with psychotherapy more common than medication both in the treatment as usual group (38.0% [95 of 250] vs 12.0% [30 of 250]; $\chi^2_1 = 6.7$; $P = .01$) and in the i-CBT group (guided i-CBT, 22.0% [46 of 211] and self-guided i-CBT, 22.3% [45 of 201] vs guided i-CBT, 5.1% [11 of 211] and self-guided i-CBT, 5.2% [10 of 201]; $\chi^2_1 = 5.2$; $P = .02$). Within each group, the probability of receiving other treatments was significantly higher among participants recruited from clinic waiting lists than the general student body (guided i-CBT, $\chi^2_1 = 53.2$; self-guided i-CBT, $\chi^2_1 = 47.5$; treatment as usual, $\chi^2_1 = 18.0$; $P < .001$).

### Predicting Within-Group Variation in Probabilities of Remission

The mean (SE) within-group 5F-CV AUC-ROC was 0.65 (0.08) to 0.72 (0.08) in the total sample, 0.60 (0.09) to 0.66 (0.10) among respondents with a baseline GAD-7 score of 10 or more, and 0.64 (0.09) to 0.72 (0.08) among respondents with a baseline PHQ-9 score of 10 or more (eTable 4 in Supplement 2). The mean (SE) PPV among predictive positive value (ie, 5F-CV predicted probability of remission >0.5) was consistently higher for the guided i-CBT group (53.3% [4.2%] to 66.5% [3.9%]) than the other groups (37.8% [4.3%] to 59.7% [5.4%]) and for the full sample (51.9% [6.2%] to 66.5% [3.9%]) than the anxiety (37.8% [4.3%] to 53.3% [4.2%]) or depression (46.8% [5.2%] to 60.1% [4.0%]) subgroups. The mean (SD) negative predictive value among predictive negative values was somewhat lower for self-guided i-CBT (67.5% [3.3%] to 76.3% [4.5%]) than the other groups (67.9% [4.6%] to 74.1% [3.2%]) and for the full sample (67.5% [3.3%] to 68.1% [3.0%]) than the anxiety (67.9% [4.6%] to 76.3% [4.5%]) or depression (69.9% [4.5%] to 74.1% [3.2%]) subgroups. The within-group models were well calibrated (typically defined as ICI <0.1) both in the total sample (ICI = 0.01-0.09) and in the anxiety (ICI = 0.04-0.09) and depression (ICI = 0.04-0.06) subgroups. Miscalibration was generally due to overestimation at low PPV and underestimation at high PPV (eFigures 2-10 in Supplement 2).

### Predicting HTE in Joint Remission

The initial ITR for joint remission predicted that guided i-CBT would be optimal for 1067 participants (80.9%), self-guided i-CBT for another 109 (8.3%), and treatment as usual for the remaining 143 (10.8%) (**Table 1**). However, 5F-CV experimental subgroup comparisons showed that the ITR failed because the aggregate remission rate under the ITR (mean [SE], 46.9% [4.6%]) was lower than when all participants were treated with guided i-CBT (mean [SE], 49.9% [5.0%]). This failure occurred because remission was highest with guided i-CBT not only among participants estimated by the ITR to be optimized by guided i-CBT (mean [SE], 51.6% [3.2%] vs self-guided i-CBT: mean [SE], 38.7% [3.2%]; $\chi^2_1 = 8.2$; $P = .004$; treatment as usual: mean [SE], 41.5% [2.9%]; $\chi^2_1 = 5.6$; $P = .02$) but also among participants estimated to be optimized by treatment as usual (mean [SE], 56.2% [9.6%] for guided i-CBT vs mean [SE], 27.9% [7.8%] for treatment as usual; $\chi^2_1 = 5.2$; $P = .02$). The remission rates among participants estimated to be optimized by self-guided i-CBT, in comparison, were consistently low across groups (guided i-CBT: mean [SE], 24.5% [9.1%]; $\chi^2_2 = 7.3$; $P = .007$; self-guided i-CBT, mean [SE], 25.4% [8.8%]; $\chi^2_2 = 8.3$; $P = .004$; treatment as usual: mean [SE], 31.0% [9.4%]; $\chi^2_2 = 10.9$ $P = .001$), suggesting that these participants represent a treatment-resistant segment of the population. A revised ITR based on these observations assigned guided i-CBT to all participants other than the small (8.3%) number who were treatment resistant and found that the aggregate remission rate was identical to the rate when treating 100% of participants with guided i-CBT (Table 1).

### Predicting HTE in Anxiety and Depression Remission

The ITR for remission of anxiety among respondents with a baseline GAD-7 score of 10 or more predicted that guided i-CBT would be optimal for 69.0% of participants (640 of 928), self-guided i-CBT for another 9.9% (92 of 928), and treatment as usual for the remaining 21.1% (196 of 928) (**Table 2**). This ITR failed, though, because the mean (SE) aggregate remission rate was lower under the ITR (56.6% [6.3%]) than when all participants were treated with guided i-CBT (62.7% [5.9%]). The remission rate for guided i-CBT was highest not only among the 640 participants estimated in the training sample to be optimized by guided i-CBT but also among the 92 estimated to be optimized by self-guided i-CBT and the 196 estimated to be optimized by treatment as usual. These advantages of guided i-CBT were consistently (ie, across all 3 subgroups) large in absolute terms (mean [SE], 11.0% [5.8%] to 25.4% [15.4%] compared with self-guided i-CBT; 6.8% [5.5%] to 17.2% [11.9%] compared with treatment as usual). However, none of these differences was statistically significant (guided vs self-guided i-CBT: optimal guided i-CBT, $\chi^2_1 = 3.6$; $P = .006$; optimal self-guided i-CBT, $\chi^2_1 = 2.7$; $P = .10$; optimal treatment as usual, $\chi^2_1 = 1.1$; $P = .29$; and guided i-CBT vs treatment as usual: optimal guided i-CBT, $\chi^2_1 = 1.5$; $P = .21$; optimal self-guided i-CBT, $\chi^2_1 = 1.0$; $P = .32$; optimal treatment as usual, $\chi^2_1 = 2.1$; $P = .15$).

Table 1. Estimated Joint Anxiety and Depression Remission Rates in the Total Sample Under Alternative ITRs

| ITR | Distribution, No. (%) | Evaluation of ITR effects, % (SE) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment-specific remission rates[a] | | | Differences for pairs of remission rates | | |
| | | G | SG | TAU | G vs SG | SG vs TAU | G vs TAU |
| Initial ITR | | | | | | | |
| G predicted to be best | 1067 (80.9) | 51.6 (3.2) | 38.7 (3.2) | 41.5 (2.9) | 12.9 (4.5)[b] | −2.7 (4.3) | 10.2 (4.3)[b] |
| SG predicted to be best | 109 (8.3) | 24.5 (9.1) | 25.4 (8.8) | 31.0 (9.4) | −0.9 (12.7) | −5.6 (12.9) | −6.4 (13.0) |
| TAU predicted to be best | 143 (10.8) | 56.2 (9.6) | 40.4 (11.3) | 27.9 (7.8) | 15.7 (14.9) | 12.5 (13.6) | 28.2 (12.4)[b] |
| Total[a] | 1319 | 49.9 (5.0) | 37.8 (5.4) | 39.1 (4.6) | NA | NA | NA |
| Revised ITR | | | | | | | |
| G or TAU predicted to be best | 1210 (91.7) | 51.8 (3.0) | 37.8 (3.0) | 40.0 (2.7) | 14.0 (4.2)[b] | −2.2 (4.0) | 11.8 (4.0)[b] |
| SG predicted to be best | 109 (8.3) | 24.5 (9.1) | 25.4 (8.8) | 31.0 (9.4) | −0.9 (12.7) | −5.6 (12.9) | −6.4 (13.0) |
| Total[a] | 1319 | 49.6 (3.9) | 36.8 (3.9) | 39.2 (3.7) | NA | NA | NA |

Abbreviations: G, guided i-CBT; i-CBT, internet-delivered cognitive behavioral therapy; ITR, individualized treatment rule; NA, not applicable; SG, self-guided i-CBT; TAU, treatment as usual.

[a] The treatment-specific remission rates represent the rates if all participants were assigned to the intervention in the column. The total estimates for guided i-CBT differ somewhat between the initial ITR (49.9%) and revised ITR (49.6%) and both differ from the estimate in a previous report on aggregate treatment effects (50.3% [C. Benjet, PhD, et al, written communication, 2023]) because of minor differences across models in adjustments for loss to follow-up. The mean (SE) estimated remission rate in the total sample if all participants in the subgroups defined by rows were assigned to those preferred treatments is 46.9% (4.6%) in the initial ITR and 50.1% (4.0%) in the revised ITR. The fact that the overall estimated remission rate in the initial ITR is lower than if all participants were assigned to guided i-CBT means that the initial ITR failed. Inspection of the subgroup remission rates in the initial ITR shows that this failure was due to participants estimated to be optimized by TAU having a significantly higher remission rate with guided i-CBT than with TAU. The revised ITR shows that the remission rate could be increased to equal the rate if all participants were assigned to guided i-CBT by assigning the 8.3% of participants estimated to be optimized by self-guided i-CBT to self-guided i-CBT and assigning all other participants to guided i-CBT. Treatment-specific remission rates estimated the aggregate remission rate with the treatment in the column estimated in a comparative effectiveness framework among participants in the subgroup defined by the row adjusted for imperfect randomization and informative loss to follow-up. The accuracy of these estimates was then evaluated by making experimental comparisons within each of the subgroups defined by the ITR.

[b] Significant at the .05 level, 2-sided test.

Table 2. Estimated Anxiety Remission Rates Among Respondents With Clinically Significant Baseline Anxiety Under Alternative ITRs

| ITR | Distribution, No. (%) | Evaluation of ITR effects, % (SE) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment-specific remission rates[a] | | | Differences for pairs of remission rates | | |
| | | G | SG | TAU | G vs SG | SG vs TAU | G vs TAU |
| Initial ITR | | | | | | | |
| G predicted to be best | 640 (69.0) | 62.4 (4.0) | 51.4 (4.2) | 55.6 (3.8) | 11.0 (5.8) | −4.1 (5.6) | 6.8 (5.5) |
| SG predicted to be best | 92 (9.9) | 61.1 (8.9) | 35.7 (12.4) | 46.7 (11.4) | 25.4 (15.4) | −11.0 (16.9) | 14.4 (14.3) |
| TAU predicted to be best | 196 (21.1) | 64.6 (8.7) | 53.0 (7.2) | 47.4 (8.0) | 11.6 (11.0) | 5.6 (10.5) | 17.2 (11.9) |
| Total[a] | 928 | 62.7 (5.9) | 50.2 (6.2) | 53.0 (6.0) | NA | NA | NA |
| Revised ITR | | | | | | | |
| G predicted to be best | 640 (69.0) | 62.5 (4.0) | NA | 55.4 (3.8) | NA | NA | 7.1 (5.5) |
| All others | 288 (31.0) | 63.7 (5.9) | NA | 47.3 (6.2) | NA | NA | 16.3 (8.5) |
| Total[a] | 928 | 62.9 (4.7) | NA | 52.9 (4.7) | NA | NA | NA |

Abbreviations: G, guided i-CBT; i-CBT, internet-delivered cognitive behavioral therapy; ITR, individualized treatment rule; NA, not applicable; SG, self-guided i-CBT; TAU, treatment as usual.

[a] The treatment-specific remission rates represent the rates if all participants were assigned to the intervention in the column. The total estimates for guided i-CBT differ somewhat between the initial ITR (62.7%) and revised ITR (62.9%) because of minor differences across models in adjustments for loss to follow-up. The mean (SE) estimated remission rate in the total sample if all participants in the subgroups defined by rows were assigned to those preferred treatments is 56.6% (6.3%) in the initial ITR and 57.1% (4.6%) in the revised ITR. The fact that the overall estimated remission rate in the initial ITE and revised ITR are lower than if all participants were assigned to guided i-CBT means that the initial SG-based ITR failed. Inspection of the subgroup remission rates in the initial ITR shows that this failure was due to all participants being optimized by guided i-CBT regardless of the treatment estimated to be optimal by the ITR. Treatment-specific remission rates estimated aggregate remission rate with the treatment in the column estimated in a comparative effectiveness framework among participants in the subgroup defined by the row adjusted for imperfect randomization and informative loss to follow-up. The accuracy of these estimates was then evaluated by making experimental comparisons within each of the subgroups defined by the ITR.

Table 3. Estimated Depression Remission Rates Among Respondents With Clinically Significant Baseline Depression Under Alternative ITRs

| ITR | Distribution, No. (%) | Evaluation of ITR effects, % (SE) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Treatment-specific remission rates[a] | | | Differences for pairs of remission rates | | |
| | | G | SG | TAU | G vs SG | SG vs TAU | G vs TAU |
| Initial ITR | | | | | | | |
| G predicted to be best | 841 (71.5) | 61.5 (3.6) | 44.3 (3.7) | 41.8 (3.2) | 17.2 (5.1) | 2.5 (4.8) | 19.7 (4.3)[b] |
| SG predicted to be best | 104 (8.8) | 42.4 (6.3) | 56.4 (7.8) | 46.8 (7.2) | −14.1 (9.9) | 9.6 (10.5) | −4.4 (13.0) |
| TAU predicted to be best | 232 (19.7) | 41.1 (10.8) | 49.5 (10.5) | 42.0 (9.7) | −8.4 (15.1) | 7.6 (14.2) | −0.8 (12.4) |
| Total[a] | 1177 | 55.8 (6.0) | 46.4 (6.1) | 42.3 (5.5) | NA | NA | NA |
| Revised ITR | | | | | | | |
| G predicted to be best | 841 (71.5) | 61.5 (3.6) | 44.3 (3.7) | NA | 17.2 (5.1)[b] | NA | NA |
| All others | 336 (28.5) | 39.8 (5.4) | 54.4 (6.0) | NA | −14.6 (8.0) | NA | NA |
| Total[a] | 1177 | 55.3 (4.2) | 47.2 (4.5) | NA | NA | NA | NA |

Abbreviations: G, guided i-CBT; i-CBT, internet-delivered cognitive behavioral therapy; ITR, individualized treatment rule; NA, not applicable; SG, self-guided i-CBT; TAU, treatment as usual.

[a] The treatment-specific remission rates represent the rates if all participants were assigned to the intervention in the column. The mean (SE) estimated remission rate in the total sample if all participants in the subgroups defined by rows were assigned to those preferred treatments is 57.2% (5.7%) in the initial ITR and 57.5% (4.3%) in the revised ITE. The fact that the overall estimated remission rate in the initial ITR is higher than if all participants were assigned to guided i-CBT is due to the estimated remission rate among participants estimated to be optimized by self-guided i-CBT being substantially higher among participants randomized to self-guided i-CBT than the other groups. Self-guided i-CBT was also best among participants estimated by the ITR to be optimized by TAU. The revised ITR shows that the remission rate in the total sample could be increased, although not significantly, if all participants estimated by the initial ITR to be optimized by guided i-CBT received guided i-CBT but all others received self-guided i-CBT. Treatment-specific remission rates estimated the aggregate remission rate with the treatment in the column estimated in a comparative effectiveness framework among participants in the subgroup defined by the row adjusted for imperfect randomization and informative loss to follow-up. The accuracy of these estimates was then evaluated by making experimental comparisons within each of the subgroups defined by the ITR.

[b] Significant at the .05 level, 2-sided test.

The ITR for remission of depression among respondents with baseline PHQ-9 scores of 10 or more predicted that guided i-CBT would be optimal for 71.5% of participants (841 of 1177), self-guided i-CBT for another 8.8% (104 of 1177), and treatment as usual for the remaining 19.7% (232 of 1177) (**Table 3**). The mean (SE) aggregate remission rate under this ITR (57.2% [5.7%]) was higher than when all participants were treated with guided i-CBT (55.8% [6.0%]) due to the remission rate for self-guided i-CBT being higher than for the other interventions among both the 104 participants estimated to be optimized by self-guided i-CBT and the 232 estimated to be optimized by treatment as usual. These advantages of self-guided i-CBT were large compared with guided i-CBT (mean [SE], 8.4% [15.1%] vs 14.1% [9.9%]) as well as with treatment as usual (mean [SE], 9.6% [10.5%] vs 7.6% [14.2%]) and were not statistically significant in either comparison (among optimized into self-guided: self-guided vs guided i-CBT, $\chi^2_1 = 2.0$; $P = .16$; self-guided i-CBT vs treatment as usual, $\chi^2_1 = 0.8$; $P = .36$; among optimized into treatment as usual: self-guided vs guided, i-CBT, $\chi^2_1 = 0.3$; $P = .58$; self-guided i-CBT vs treatment as usual, $\chi^2_1 = 0.3$; $P = .60$). A revised ITR that distinguished only between participants estimated by the initial ITR to be optimized by guided i-CBT vs others (who were assumed to be assigned to self-guided i-CBT) found that the mean (SE) aggregate remission rate was nonsignificantly higher under the revised ITR (57.5% [4.3%]) than when all participants were treated with guided i-CBT (55.3%[4.2%]) (Table 3).

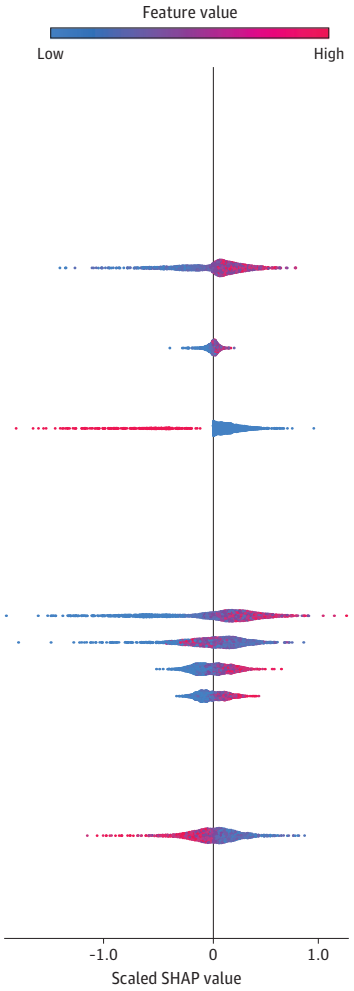
## Prescriptive Predictors of Differential Treatment Response

A total of 284 predictors were used to define the ITRs (eTable 1 in Supplement 2). We evaluated predictor importance by estimating separate machine learning models with these predictors for combined remission and depression remission, distinguishing participants estimated by the final ITR to be optimized by guided i-CBT vs others. In the total sample, proportional values of SHAP ($SHAP_P$) were highest for predictors in the physical health (58.7%), comorbid mental disorders (46.6%), and exposure to recent and lifetime stressors (26.4%) domains, indicating that exclusion of these predictors from the model would have the largest effects on overall outcome predicted values (**Figure 1**). The most important physical health predictors were indicators of role impairment, all associated with increased probabilities of being optimized by guided i-CBT. Key comorbid mental disorder predictors were comorbid 12-month posttraumatic stress disorder (PTSD), 30-day impairment in social activities due to mental health problems, and summary symptom scores on baseline measures of GAD-7, PHQ-9, and the PTSD Checklist, all associated with reduced probabilities of being optimized by guided i-CBT. Other key predictors (ie, $SHAP_P \geq 10.0\%$) of optimization by guided i-CBT were low 30-day health-related chronic stress, mild 2-week Patient Health Questionnaire Anxiety and Depression Scale severity, and low conscientiousness.

In the depression subgroup, $SHAP_P$ values were again highest for predictors in the physical health (93.4%), comorbid mental disorders (14.1%), and exposure to recent and lifetime stressors (11.6%) domains (**Figure 2**). Key physical health predictors were indicators of role impairment, associated with increased probability of being optimized by guided i-CBT. Key stressor domain predictors were reports of bullying, with complex interactions emerging such that frequency of any bullying correlated with increased probability of optimization by guided i-CBT,

Figure 1. Predictors of Being Optimized by Guided Internet-Delivered Cognitive Behavioral Therapy (i-CBT) or Treatment as Usual vs Self-Guided i-CBT in the Total Sample

| Source | Dominant direction of association[a] | Proportional mean absolute SHAP value[b] |
|---|---|---|
| Sociodemographic characteristics | | |
| Total | | 7.0 |
| University-related factors | | |
| Total | | 10.8 |
| Stressors related to COVID-19 | | |
| Total | | 0 |
| Recent and lifetime stressors | | |
| 30-d Chronic stressor-health | - | 23.8 |
| Total | | 26.4 |
| Anxiety and depression characteristics | | |
| 2-wk PHQ-ADS severity | - | 12.0 |
| Total | | 18.3 |
| Comorbid mental disorders | | |
| 12-mo PTSD diagnosis | - | 25.3 |
| 30-d Social activities impairment | - | 12.4 |
| Sum (PHQ-9, GAD-7, PTSD Checklist)[c] | - | 12.1 |
| Total | | 46.6 |
| Mental health treatment history | | |
| Total | | 3.7 |
| Physical health | | |
| 30-d Role impairment overall[d] | + | 36.9 |
| 30-d Role impairment on average[e] | + | 23.6 |
| 30-d Role impairment at school or work | + | 14.1 |
| 30-d Role impairment in relationships | + | 11.0 |
| Total | | 58.7 |
| Social networks and supports | | |
| Total | | 8.7 |
| Personality or temperament and psychological resilience | | |
| Low conscientious | - | 18.7 |
| Total | | 22.2 |
| Internet literacy and preferences | | |
| Total | | 1.9 |




PHQ-ADS indicates Patient Health Questionnaire Anxiety and Depression Scale.

[a] Shapley Additive Explanations (SHAP) values for a specific predictor can differ for participants having the same score on the predictor due to interactions with other predictors, leading to variation in the sign of the association between the predictor and the outcome. The dominant direction of association recorded was based on visual inspection of the beeswarm plot shown to the right of the figure.

[b] Key predictors are defined as the up to top 5 predictors in each domain with the highest mean absolute SHAP values of 0.010 or more.

[c] Sum of 2-week 9-item Patient Health Questionnaire (PHQ-9) score, 2-week 7-item Generalized Anxiety Disorder (GAD-7) score, and 30-day Posttraumatic Stress Disorder (PTSD) Checklist (scale, 0-72).

[d] Role impairment overall refers to how much physical health problems interfered with their life overall (scale, 0-10).

[e] Role impairment, on average, refers to how much physical health problems led to functional impairment at school or work, in social life or interpersonal relationships, with home management, and life overall (sum of 4 items for a 0-40 scale).

but relational and verbal bullying correlated with reduced probabilities of optimization by guided i-CBT. Similarly, complex interactions occurred in the comorbid mental disorders domain due to the social anxiety disorder sum score being correlated with increased probability of optimization by guided i-CBT, but the performance- and situation-related social phobia subscale scores were associated with reduced probability of optimization by guided i-CBT. No effort was made to elucidate these interactions, given that our focus was on subtyping rather than tracing out the pathways underlying predictor importance.

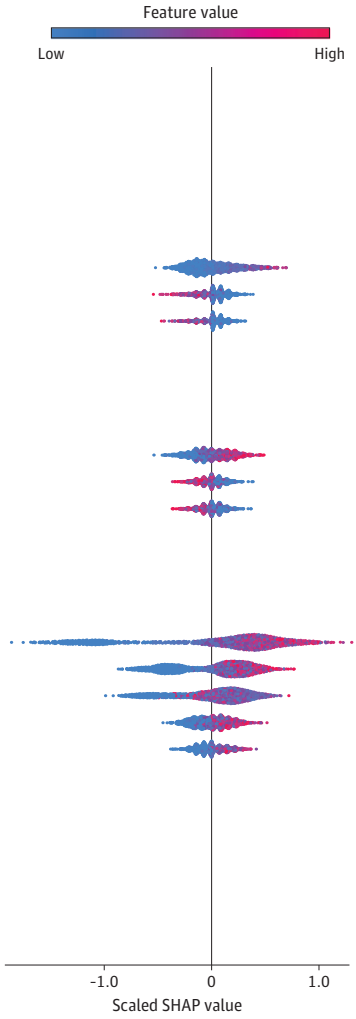
## Discussion

This preplanned secondary analysis of a randomized clinical trial found that guided i-CBT had the highest probability of joint remission of anxiety and depression for 91.7% of participants, the highest probability of anxiety remission for 100% of participants, and the highest probability of depression remission for 71.5% of participants. The small number of participants not optimized by guided i-CBT for joint remission had low probabilities of remission across all groups, while the 28.5% of participants not optimized by guided i-CBT for depression remission were optimized by self-guided i-CBT. These specifications provide a principled basis for restricting access to guided i-CBT in settings with constrained resources, although replication in larger samples is needed to confirm specifications.

The finding that physical disorders were associated with optimality of guided i-CBT is consistent with the suggestion in previous i-CBT trials that a human coach is useful in addressing interference related to psychosomatic distress.[31-33] The associations of psychiatric comorbidities with HTE expand on prior studies finding mixed evidence for psychiatric comorbidities predicting i-CBT response.[34-36] The important associations of bullying with HTE highlight the importance of institutionally embedded antibullying policies and the value of guided i-CBT in facilitating stress management efforts related to this salient student stressor.[37] The fact that baseline anxiety and depression severity were not important predictors of HTE adds caution to evidence from prior studies that anxiety and depression symptom severity predict reduced likelihood of being optimized by guided i-CBT[38,39]; however, our failure to find

Figure 2. Predictors of Being Optimized by Guided Internet-Delivered Cognitive Behavioral Therapy (i-CBT) vs All Others Among Participants With Clinically Significant Baseline Depression

| Source | Dominant direction of association[a] | Proportional mean absolute SHAP value[b] |
|---|---|---|
| Sociodemographic characteristics | | |
| Total | | 0.4 |
| University-related factors | | |
| Total | | 4.2 |
| Stressors related to COVID-19 | | |
| Total | | 1.2 |
| Recent and lifetime stressors | | |
| 12-mo Frequency of any bullying | + | 14.0 |
| 12-mo Frequency of relational bullying | - | |
| 12-mo Frequency of verbal bullying | - | |
| Total | | 11.6 |
| Anxiety and depression characteristics | | |
| Total | | 0.5 |
| Comorbid mental disorders | | |
| 30-d Sum of SAD (situational, performance)[c] | + | 11.6 |
| 30-d SAD performance[d] | - | 7.1 |
| 30-d SAD situational[e] | - | 7.0 |
| Total | | 14.1 |
| Mental health treatment history | | |
| Total | | 0 |
| Physical health | | |
| 30-d Role impairment overall[f] | + | 45.7 |
| 30-d Role impairment in relationships | + | 24.9 |
| 30-d Role impairment on average[g] | + | 22.0 |
| 30-d Role impairment at school or work | + | 11.0 |
| 30-d Role impairment at home | + | 8.8 |
| Total | | 93.4 |
| Social networks and supports | | |
| Total | | 3.2 |
| Personality or temperament and psychological resilience | | |
| Total | | 2.1 |
| Internet literacy and preferences | | |
| Total | | 4.0 |




SAD indicates social anxiety disorder.

[a] Shapley Additive Explanations (SHAP) values for a specific predictor can differ for participants having the same score on the predictor due to interactions with other predictors, leading to variation in the sign of the association between the predictor and the outcome. The dominant direction of association recorded was based on visual inspection of the beeswarm plot shown to the right of the figure.

[b] Key predictors are defined as the up to top 5 predictors in each domain with the highest mean absolute SHAP values of 0.010 or more.

[c] Social and performance-related anxiety scale (sum of social situation and performance-related anxiety scales).

[d] Performance-related anxiety scale (intensity of anxiety or fear × frequency of avoidance of situations).

[e] Social situation-related anxiety scale (intensity of anxiety or fear × frequency of anxiety).

[f] Role impairment overall refers to how much physical health problems interfered with their life overall (scale, 0-10).

[g] Role impairment, on average, refers to how much physical health problems led to functional impairment at school or work, in social life or interpersonal relationships, with home management, and life overall (sum of 4 items for a 0-40 scale).

these variables to be important occurred among a sample in which students with serious suicidality were excluded.

Turning to results about ITR strength, it is relatively clear that most participants were optimized by guided i-CBT. It is less clear, though, what the best alternative would be when guided i-CBT is not optimal. For joint remission of anxiety and depression, the small proportion of participants not optimized by i-CBT had a low probability of remission across groups, suggesting that they are treatment resistant and need more aggressive intervention than considered here. In the case of participants with baseline depression, in comparison, the evidence is suggestive that self-guided i-CBT might be best for a meaningful minority of patients, although statistical power was too low to determine whether this seeming benefit is genuine. We plan to address this limitation in the next stage of the trial when we can pool the current first-stage sample with a second-stage sample of equal size in which participants are randomized between 2 groups (ie, 50% assigned based on the final ITRs reported here and the other 50% randomized with the same proportional allocation across the 3 interventions).

## Strengths and Limitations

Our trial had strengths in addressing all 3 issues that have hindered prior attempts to document HTE for i-CBT treatment of anxiety and depression: limited predictors, low statistical power, and use of an inappropriate statistical algorithm. Our baseline assessment was more comprehensive than in prior CBT HTE studies. Our sample was larger than in previous trials, even though sample size limitations still existed for characterizing the small number of participants with depression who were optimized by self-guided i-CBT. We used a state-of-the-art machine learning method.

Three limitations are also noteworthy. First, use of a treatment as usual control group introduced ambiguity into the interpretation of nonsignificant subgroup differences between i-CBT and controls, as some controls in the treatment as usual group received treatment but others did not, and those who received treatment differed in the nature and intensity of that treatment. Second, the ITRs were developed from an intent-to-treat perspective, which means that we did not investigate mediating effects of differential intervention engagement. This

is important, given that prior research found low i-CBT engagement.[5] Methods exist to tease out mediating effects through engagement,[40] but the use of these methods requires a larger sample than in this first stage of the trial. Third, ITR evaluation was based on internal cross-validation rather than use of independent training and validation samples. This was necessary given the sample size in this first stage of the trial, but we will use separate training and test samples once we pool results across later stages of the trial.

## Conclusions

To our knowledge, this is the first study to develop a practical ITR in a 3-group randomized pragmatic trial of empirically supported i-CBT for anxiety and depression. Results suggest that such an ITR can distinguish between participants benefitting differentially from guided i-CBT and, in the case of depression, self-guided i-CBT. If confirmed in later stages of the trial, these ITRs could be used to optimize intervention assignment and provide a cost-effective approach to increase use of i-CBT in resource-constrained settings.[41] In addition, in cases in which the ITRs suggest that none of the interventions considered here will be effective, these estimates could be used to prevent counterproductive use of these interventions, allowing more intensive interventions to be provided with less delay than otherwise. Additional research should also be carried out to consider approaches such as inexpensive chatbot or peer support interventions that might increase the proportion of participants helped in cost-effective and scalable ways.[42] Finally, SMART (Sequential Multiple Assignment Randomized Trial) designs are needed to provide principled decision support rules for second-stage intervention assignment when a first scalable intervention does not result in remission.[43]


### ARTICLE INFORMATION

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