Cost-Utility Analysis of Internet-Based Cognitive Behavioral Therapy for Major Depressive Disorder: Results Based on A Pragmatic Randomized Controlled Trial in China

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Abstract

Background: Major depressive disorder (MDD) is one of the leading causes of disability and death by suicide globally. Unguided Internet-based cognitive behavioral therapy (ICBT), with the promise to improve accessibility and affordability, has been proven to be effective for MDD. However, few studies have examined the cost-effectiveness of unguided ICBT for MDD in low-resource countries and under non-specialist routine care.

Objective: This study aimed to evaluate the short- and long-term cost-utility of unguided ICBT (named Morning Mood, a self-developed course on the WeChat Mini-program) compared to waiting-list control for persons suffering from MDD from the perspectives of society and healthcare system

Methods: This cost-utility analysis was implemented alongside an 8-week 2-arm pragmatic randomized controlled trial with a 12-month follow-up conducted in Shenzhen City, China (Trial Registration: ChiCTR2100046425). Outcome data including cost and health utility were collected at baseline or pre-treatment, post-treatment, 3, 6, and 12 months after the intervention. Both societal and healthcare system perspectives were adopted. Direct medical costs and indirect costs were prospectively collected through the hospital information system and the Sheehan Disability Scale. Health outcome was measured by the Chinese version of SF-6Dv2. The primary outcome was incremental cost-utility ratio (ICUR), expressed as the difference in costs between two therapies by the difference in quality-adjusted life years (QALYs). Seemingly unrelated regression and the bootstrap method were performed to estimate adjusted ICURs and the corresponding 95% confidence intervals. Cost-effectiveness planes and cost-effectiveness acceptability curves were used to demonstrate the uncertainty of the results. A series of scenario analyses were conducted to verify the robustness of base-case results.

Results: A total of 244 participants with MDD were randomly allocated to the ICBT (n=122) or the waiting-list (n=122) group. In the base-case analysis, the adjusted ICURs at post-treatment were respectively -194,720.38 and 49,700.33 Chinese Yuan (CNY) per QALY from societal and healthcare system perspectives, with the probability of unguided ICBT being cost-effective of 75.93% and 54.40% if the willingness-to-pay (WTP) was set at 1 time per capita gross domestic product. In scenario analyses, the probabilities respectively increased to 76.85% and 77.61%, indicating the potential of ICBT to be cost-effective over the long term from both the perspectives of society and healthcare system.

Conclusions: Unguided ICBT is a cost-effective treatment for MDD. This intervention not only helps patients with MDD to improve clinically but also generates societal savings. These findings provide the health economic evidence for a potential scalable MDD treatment method in developing countries. Clinical Trial: Chinese Clinical Trial Registry (ChiCTR2100046425); https://tinyurl.com/bdcrj4zv

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Title Page

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Short Title: Cost-Utility of Internet-Based Cognitive Behavioral Therapy for Depression

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performed to estimate adjusted ICURs and the corresponding 95% confidence intervals. Cost-effectiveness planes and cost-effectiveness acceptability curves were used to demonstrate the uncertainty of the results. A series of scenario analyses were conducted to verify the robustness of base-case results.

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Trial Registration: Chinese Clinical Trial Registry (ChiCTR2100046425); https://tinyurl.com/bdcrj4zv

Keywords: Cost-utility analysis (CUA); cost-effectiveness; economic evaluation; costs; quality of life; internet-based cognitive behavioral therapy (ICBT); digital psychiatry; major depressive disorder; depression; China.

Introduction

Major depressive disorder (MDD) is a highly prevalent mental disorder, estimated to affect 332 million people worldwide in 2021.[1]MDD is associated with significant impairment of health-related quality of life (HRQoL),[2]substantial healthcare utilization,[3]and huge societal impacts on employment and productivity.[4,5]Now, MDD is ranked among the second leading cause of global non-fatal disability,[1]and MDD-attributed lost productivity costs the global economy 1 trillion United States dollars annually.[6]Effective and cost-effective therapies are needed to reduce the disease burden caused by MDD.[7]

Individuals with MDD are faced with a series of barriers to treatment including social discrimination, stigma, healthcare costs, and a shortage of specialists.[8,9]Unguided Internet-based cognitive behavioral therapy (ICBT), a form of cognitive behavioral therapy (CBT) delivered through the Internet without therapeutic support, has the attraction of privacy, accessibility, flexibility, and ease of implementation with constrained healthcare resources and personnel and has been gradually applied to the treatment of MDD.[10]Existing research across low-, middle- and high-income countries has demonstrated the effectiveness of unguided ICBT for MDD in comparison with usual care.[8,11,12]In China, our team has also developed an unguided ICBT course for MDD and its efficacy has also been confirmed.[13]

In contrast with the well-established evidence of effectiveness, research on the cost-effectiveness of unguided ICBT for MDD remains relatively understudied.[14–20]Extant evaluations are mostly conducted alongside randomized controlled trials

(RCT) and adopt societal or healthcare system perspectives. These cost-effectiveness studies are mainly carried out in high-income countries and show mixed results. For example, an evaluation conducted in Spain found supporting evidence from the perspective of society that unguided ICBT exhibited cost-utility and cost-effectiveness compared with usual care over 12 months.[19]In addition, evidence from the Canadian healthcare system perspective showed that unguided ICBT for MDD had a higher probability of being cost-effective than the usual care at a 12-week follow-up period at the given willingness-to-pay (WTP) cut-off.[20]However, an economic evaluation based on a large pragmatic trial in the UK drew the opposite conclusion with unguided ICBT not appearing as more cost-effective than usual care from the healthcare provider's perspective.[16,18]This indicates the heterogeneity in study settings, perspectives, time horizons, and healthcare systems making it hard to arrive at a unanimous conclusion. To our knowledge, no study has reported the cost-effectiveness of unguided ICBT for MDD in China. It is necessary to extend the analysis to China and account for both societal and healthcare system perspectives to provide decision-making evidence for the optimization and allocation of the limited healthcare resources.

Therefore, this study aims to comprehensively assess the short- and long-term cost-utility of unguided ICBT among persons with MDD in China from the perspectives of society and healthcare system.

Methods

Study design

This economic evaluation was performed prospectively alongside an 8-week pragmatic, unblinded, 2-arm RCT with a follow-up period of 12 months. Participants were randomly allocated to the ICBT (ICBT plus usual care) or waiting-list control (usual care) groups with a ratio of 1:1. The detailed study design and procedures have been described in a published paper.[13]

The RCT was registered with the Chinese Clinical Trial Registry (ChiCTR2100046425) and obtained ethical approval from the Ethics Review Committee of Shenzhen Nanshan Center for Chronic Disease Control (ll20210012). Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were applied to conduct and guide the economic evaluation.[21]

Study participants

In this study, participants were recruited from the Department of Depressive Disorder, Shenzhen Kangning Hospital, and the Department of Psychiatry, Shenzhen Nanshan Center for Chronic Disease Control between August 2021 and December 2022. To be eligible for this study, participants must meet the inclusion criteria: (1) between the ages of 18-60 years, (2) a positive screening result of Patient Health Questionnaire-9 (PHQ-9≥5),[22] (3) had a diagnosis of MDD through the Mini International Neuropsychiatric Interview (M.I.N.I)[23] by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), (4) had access to internet-connected mobile devices, (5) did not receive any other psychotherapy or physical therapy currently, (6) had no changes in condition during last one month (e.g. patients with antidepressants use did not change the dosage), and (7) provided

informed consent. The exclusion criteria included (1) experienced neurological illness (e.g., traumatic brain injury or functional impairment), (2) a moderate to high risk of suicide, (3) had alcohol abuse or substance use disorder, (4) was pregnant or breastfeeding, and (5) diagnosed with severe physical disease, psychosis or bipolar disorder. Eligible participants were asked to complete the baseline assessment, including sociodemographic information (e.g., age, sex, nationality), clinical history (e.g., antidepressant use, history of psychopathology), lifestyle (e.g., smoking, drinking) and baseline clinical symptoms (measured by PHQ-9, Generalized Anxiety Disorder-7 (GAD-7), and Kessler 10-item Psychological Distress scale (K-10)).

Intervention

Participants of the ICBT group are provided with an ICBT course for 8 weeks in addition to usual care. The ICBT course is called *Morning Mood,* which is embedded in the WeChat Mini-program and can be accessed via smartphones, tablets, and computers. The course was grounded in CBT principles aiming at teaching emotional regulation skills and restructuring cognitive. In total, there are seven modules. Participants were required to complete one module per week. Technical support and reminder services by telephone call and SMS were provided by trained non-specialists (i.e., lay health workers, nurses, and social workers) throughout the intervention and follow-up period to promote engagement.

Participants in the waiting-list control group were on a waiting list for ICBT and did not receive any additional specific intervention. However, individuals' usual treatment was maintained during the 8-week control period. After 8 weeks, the

participants in the control arm completed the observation phase and began to receive ICBT treatment. To promote participant retention, financial incentives in the form of small amounts of electronic cash were distributed post-completion of assessments.

Health outcomes

The primary health outcome was quality-adjusted life year (QALY) based on health utility as measured by the second version of the Short-Form Six-Dimension (SF-6Dv2) questionnaire at baseline, post-treatment, and 3-, 6-, and 12-month follow-up timepoints. The SF-6Dv2 was one of the recommended generic self-reported measures of health state by the Chinese guidelines for economic evaluations[24]and the Chinese version was validated in the Chinese population.[25]It was reported that the SF-6Dv2 was suitable for Asian patients with mental disorders.[26]The health utility score was converted based on the Chinese value set for SF-6Dv2,[27] ranging from 0 to 1, with a score of 0 representing death and 1 representing full health. QALY was finally calculated by multiplying health utility by time duration using the Area-Under-the-Curve method.[28]

Cost analyses

Costs were respectively calculated from societal and healthcare system perspectives. Three main categories of costs were identified including intervention costs, healthcare costs, and societal costs attributed to lost or declined productivity. Intervention costs refer to the expenses associated with the intervention administered. For the ICBT group, the intervention costs comprised the costs of development and maintenance of *Morning Mood*, implementation support, and personnel training.

Based on the practical operation, we estimated the costs were 545 Chinese Yuan (CNY) per participant. For the waiting-list control group, the intervention costs were 0 CNY per participant. Healthcare costs, also called direct medical costs, consist of expenses produced by healthcare resource utilization including, but not limited to, diagnostic tests, examinations, medications, and other treatments. In this study, direct medical costs were retrieved from the Shenzhen Hospital Information System and calculated using the bottom-up method.[29]Societal costs, also known as indirect costs, are the quantified economic value of lost and declined productivity attributed to MDD. The Sheehan Disability Scale (SDS) was applied to measure days of lost and declined productivity over the last week at all assessment points. The human capital approach was adopted for the estimation.[30]Loss of productivity was calculated by days of lost productivity multiplied by the monthly average wage in Shenzhen city. [31]For declined productivity, a weighting coefficient of 42.98% was used for the adjustment.[32,33]All costs were collected alongside the RCT and were reported in CNY for the reference year 2022. The baseline cost was identified as costs incurred during the 3 months before the individuals' time of enrollment and was used to control for baseline differences.

Statistical analysis

Baseline characteristics and outcome measures were described by group and by phase with continuous variables using mean, standard deviation (SD), and frequency for categorical variables. Mann-Whitney *U* tests, 2-tailed *t*-tests, and Chi-square tests were used to investigate the differences in baseline characteristics and outcomes

between the two arms. Estimates of the difference between groups in health utility scores were derived at each time point with 95% confidence intervals (95% *CI*s) and *P*-values. Statistical significance was determined when the *P*-value was less than 0.05.

Missing data was imputed using the multiple imputation by chained equations (MICE) package in R language under the assumption of data being missing at random. A total of five imputed datasets were generated and used for analysis. Rubin's rules were performed to pool the results.[34]Health utility and costs at post-treatment and every follow-up timepoint were imputed based on age, gender, antidepressant use, baseline values (utility and cost), and values from the previous or next measurement moment.

Cost-utility analysis

Cost-utility analyses were conducted from the perspectives of the healthcare provider and society for 8 weeks, 3 months, 6 months, and 12 months, with no account of the discount rate for both cost and QALY. Both the complete cases (CC) and intention-to-treat (ITT) samples were adopted. Incremental cost-utility ratios (ICUR) were calculated by the incremental difference in costs divided by the incremental difference in QALYs between the 2 arms. Considering the correlation between costs and QALYs, adjusted costs (age, gender, antidepressant usage, treatment group, and baseline costs), adjusted QALYs (age, gender, antidepressant usage, treatment group, and baseline utility) and the corresponding ICURs were calculated by seemingly unrelated regression.[35]Nonparametric bootstrapping methods were performed to account for the uncertainty. The cost-effectiveness planes

and the cost-effectiveness acceptability curves (CEACs) were applied to demonstrate the uncertainty of the results. In this study, the willingness-to-pay (WTP) threshold was set at 1.5 times of per capita gross domestic product (GDP) per QALY with ranges from 1 to 3 times per capita GDP (80,976 to 242,928 CNY).[24]Standard decision rules were utilized to determine whether the ICBT was cost-effective compared to waiting-list control.[35]

Base-case cost-effectiveness analysis was performed by using data at post-treatment (i.e., 8 weeks). Sensitivity analyses were implemented by a series of scenario analyses using data at follow-ups. The foregoing analyses assessed whether the results remained consistent after adjusting for baseline differences and adopting different analysis datasets. Because participants in the waiting-list control group did not have follow-up assessments after 8 weeks, the follow-up data in the control arm was not available. To explore the long-term cost-utility, 3-, 6- and 12-month follow-up data for the control group were predicted based on the predicted model formulated by data in the ICBT group. Detailed operations and practical reasons have been clearly described in a published article.[36]All analyses were conducted using R language (4.2.2) and Stata (17.0 version).

Results

Between August 2021 and December 2022, a total of 291 persons with MDD were recruited. Among these participants, 33 either refused to participate or lost contact, 13 did not meet the inclusion criteria and 1 met the exclusion criteria. Finally, a total of 244 eligible participants with baseline information and informed consent

were enrolled, with 122 participants in each group. In the ICBT group, a downward trend was observed in completion rates, with the highest rate at 8 weeks (76.2%) and the lowest rate at 12-month follow-up (70.5%). For the waiting-list group, a high completion rate was reported, with 94.3% of participants completing the post-treatment assessment. A detailed account of the study population and participant flow is demonstrated in Figure 1.

Baseline characteristics

Table 1 presents the baseline characteristics of participants by treatment group. The mean age was 28.3 years old and the female-to-male ratio was 3:1. The majority of the sample was Han ethnic (93.3%). Most of the participants were well-educated with 82.2% having received education beyond the undergraduate level. There were 169 participants (69.8%) were employed. More than half of the participants were experiencing their first episode of MDD (60.3%) and were not receiving antidepressant treatment (52.0%). The mean scores of PHQ-9, GAD-7, SDS, and K-10 at baseline were 13.9 (SD=5.2), 10.5 (SD=4.7), 17.7 (SD=7.0), and 29.7 (SD=9.0), respectively. There was no significant difference in baseline characteristics between the ICBT and waiting-list control group, except for the SDS scale scores. The mean SDS scores in the ICBT group were significantly higher than that in the control group (*P*=0.022), indicating participants in the ICBT group had worse social functioning.

Table 1. Baseline characteristics of the participants

Variables [a]	Total n=244	ICBT n=122	Waiting-list n=122	*P*-value [c]
Age (years) [b], mean (SD)	28.3 (7.0)	28.6 (6.8)	28.0 (7.3)	0.501
Sex [b]				0.139
Female	183.0 (75.0)	86.0 (70.5)	97.0 (79.5)	

Male	61.0 (25.0)	36.0 (29.5)	25.0 (20.5)	
Nationality				0.823
Han	224.0 (93.3)	112.0 (94.1)	112.0 (92.6)	
Others	16.0 (6.7)	7.0 (5.9)	9.0 (7.4)	
Educational level				0.175
High school or below	43.0 (17.8)	27.0 (22.3)	16.0 (13.2)	
Undergraduate	168.0 (69.4)	80.0 (66.1)	88.0 (72.7)	
Master's degree or above	31.0 (12.8)	14.0 (11.6)	17.0 (14.0)	
Current employment status				0.114
Student	40.0 (16.5)	14.0 (11.6)	26.0 (21.5)	
Employed	169.0 (69.8)	90.0 (74.4)	79.0 (65.3)	
Unemployed	33.0 (13.6)	17.0 (14.0)	16.0 (13.2)	
Recurrent episodes				0.492
Yes	95.0 (39.7)	50.0 (42.4)	45.0 (37.2)	
No	144.0 (60.3)	68.0 (57.6)	76.0 (62.8)	
Current drinking status				0.161
Yes	204.0 (84.6)	106.0 (88.3)	98.0 (81.0)	
No	37.0 (15.4)	14.0 (11.7)	23.0 (19.0)	
Current smoking status				0.433
Yes	101.0 (42.1)	47.0 (39.2)	54.0 (45.0)	
No	139.0 (57.9)	73.0 (60.8)	66.0 (55.0)	
Antidepressant use [b]				0.442
Yes	117.0 (48.0)	55.0 (45.1)	62.0 (50.8)	
No	127.0 (52.0)	67.0 (54.9)	60.0 (49.2)	
PHQ-9 scores at baseline [b], mean (SD)	13.9 (5.2)	14.2 (5.5)	13.6 (4.9)	0.385
GAD-7 scores at baseline [b], mean (SD)	10.5 (4.7)	10.8 (4.8)	10.2 (4.6)	0.304
SDS scores at baseline [b], mean (SD)	17.7 (7.0)	18.8 (7.0)	16.7 (6.8)	0.022
K-10 scores at baseline [b], mean (SD)	29.7 (9.0)	29.3 (10.0)	30.1 (8.0)	0.473

[a] Unless otherwise indicated, data are expressed as No. (%) of participants.

[b] Variables with no missing data.

[c] Baseline characteristics were compared between two groups using two independent *t*-tests for continuous variables and Chi-square tests for categorical variables.

Abbreviations: ICBT, Internet-Based Cognitive Behavioral Therapy; Mean (SD), mean and standard deviation; PHQ-9, Patient Health Questionnaire-9 scale; GAD-7, Generalized Anxiety Disorder-7 Scale; SDS, Sheehan Disability Scale; K-10, Kessler 10-item Psychological Distress scale.

Health outcome

Table 2 provides the completion rates of SF-6Dv2 and the converted health utility scores. At baseline, the mean utility in the ICBT group was lower than that of the control group (0.5190 vs. 0.5625); however, the difference was not statistically significant (P=0.111). After an 8-week intervention, increases in the average utility

scores were observed in both groups (0.6002 vs. 0.6012; *P*=0.976) with completion rates of 72.95% and 94.26%, respectively. The ICBT group demonstrated continuous improvement in health utility scores over the 6-month follow-up period, with a slight decline at 12 months. The highest health utility score in the ICBT group (0.6240) was observed at the 6-month follow-up. Supplementary Table 1 depicts the health utility scores and subsequent QALY estimations in ITT samples. In the ICBT group, the mean QALYs were 0.1414 (Standard Error, SE=0.0021), 0.2952 (SE=0.0041), 0.4539 (SE=0.0059), and 0.7765 (SE=0.0096) at 8-week, 3-, 6-, and 12-month follow-up timepoints, respectively. In the control group, the average QALYs at the follow-up time points were 0.1463 (SE=0.0019), 0.3000 (SE=0.0038), 0.4598 (SE=0.0053), and 0.7839 (SE=0.0080), respectively. There was no significant difference in QALYs between groups at all time points. Both the CC and ITT analysis suggested sustained improvement in health utility for the ICBT group over 12 months and waiting-list control over 8 weeks.

Table 2. Mean and standard deviation for health utility measured by SF-6Dv2 by timepoint in the complete case analysis

Utility at different time points	ICBT (n=122)				Waiting-list (n=122)				Mean Dif. between two groups (*P*-value) [a]
	Timepoint (T_i)		Dif. timepoints, T_i-T_{i-1}		Timepoint (T_i)		Dif. timepoints, T_i-T_{i-1}		
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	
T_0	122 (100.00)	0.5190 (0.2286)			122 (100.00)	0.5625 (0.1949)			-0.0435 (0.111)
T_1	89	0.6002	89	0.0892	115	0.6012	115	0.0420	-0.0010

	(72.95)	(0.2285)	(72.95)	(0.1843)	(94.26)	(0.2149)	(94.26)	(0.1602)	(0.976)
T_2	87 (71.31)	0.6057 (0.2416)	83 (68.03)	0.0018 (0.1509)	/	/	/	/	
T_3	85 (69.67)	0.6240 (0.2198)	84 (68.85)	0.0172 (0.2074)	/	/	/	/	
T_4	82 (67.21)	0.6146 (0.2590)	81 (66.39)	-0.0088 (0.2012)	/	/	/	/	

[a] Utility at different timepoints were compared between the two groups using *t*-tests.

Abbreviations: SF-6Dv2, Short-Form Six-Dimension Version Two; ICBT, Internet-Based Cognitive Behavioral Therapy; n (%), the number of people who completed the measure at the specific timepoint or at two given timepoints; Mean (SD), mean and standard deviation; T_0, T_1, T_2, T_3, T_4 were respectively the timepoints of pre-treatment, post-treatment, 3-month follow-up, 6-month follow-up and 12-month follow-up.

Costs

Table 3 displays the cost in CC analysis by the trial arm and cost category. At all timepoints, the cost of antidepressants constituted the primary component of direct medical costs. At pre-treatment (i.e., baseline), the average direct medical costs in the ICBT and control group were 6,588.7 (SD=14,093.7) CNY and 5,861.7 (SD=10,198.6) CNY, respectively. Indirect costs approximately amounted to 22,225.9 (SD=16,225.3) CNY in the ICBT group and 18,853.1 (SD=16,197.5) CNY in the control group. After an 8-week intervention, both the direct medical costs and indirect costs decreased in both groups.

Supplementary Table 2 presents the result of cost analysis in ITT samples. Both groups revealed a decreasing trend in direct medical costs and indirect costs during post-treatment and follow-up periods. For patients in the ICBT group, the declining trend was sustained throughout the follow-up period.

Table 3. Average costs per participant (in CNY) by trial-arm for the complete case analysis at pre- and post-treatment

Timepoints	ICBT (n=122)		Waiting-list (n=122)		*P*-value
	Resource-user, n (%)	Mean (SD)	Resource-user, n (%)	Mean (SD)	
Pre-treatment					
Drug costs	64.0 (52.5)	5881.5 (13772.6)	65.0 (53.3)	4858.6 (9619.1)	0.676
Treatment costs	12.0 (9.8)	179.6 (674.4)	9.0 (7.4)	246.1 (1365.0)	0.503
Diagnostic and examination costs	64.0 (52.5)	527.6 (746.6)	70.0 (57.4)	757.0 (907.8)	0.084
Direct medical costs	79.0 (64.8)	6588.7 (14093.7)	82.0 (67.2)	5861.7 (10198.6)	0.411
Indirect costs	109.0 (92.6)	22225.9 (16225.3)	107.0 (87.7)	18853.1 (16197.5)	0.097
Post-treatment					
Drug costs	16.0 (13.1)	2281.8 (11545.3)	23.0 (18.9)	1336.8 (4567.0)	0.241
Treatment costs	2.0 (1.6)	92.9 (940.5)	2.0 (1.6)	21.5 (175.0)	0.997
Diagnostic and examination costs	10.0 (8.2)	46.6 (186.8)	14.0 (11.5)	58.4 (201.0)	0.404
Direct medical costs	18.0 (14.8)	2421.2 (12416.4)	24.0 (19.7)	1416.7 (4697.8)	0.309
Indirect costs	109.0 (92.6)	14817.3 (10816.9)	87.0 (77.0)	11115.6 (11147.5)	0.005

[a] Costs at different timepoints were compared between the two groups using Mann-Whitney *U* tests.

Abbreviations: CNY, Chinese Yuan; ICBT, Internet-Based Cognitive Behavioral Therapy; n (%), the number of people who completed the measure at the specific timepoint or at two given timepoints; Mean (SD), mean and standard deviation.

Cost-utility analysis

In this health economic evaluation, adjusted mean costs and QALYs (bootstrapped SE and 95% CIs) in base-case analysis and scenario analyses from the perspectives of society and healthcare system in CC and ITT samples were summarized (see Supplementary Table 3-4**)**. The corresponding results of incremental cost-effectiveness analysis are displayed in Table 4. In the base-case analysis, the adjusted incremental costs (-899.45 CNY) and QALYs (0.0046) resulted in an ICUR of -194,720.38 CNY per QALY, which was much lower than the setting WTP threshold. This dominant ICUR indicates ICBT is more cost-effective compared to the waiting-list group from societal perspective. The cost-effectiveness plane and CEAC, generated based on 5000 bootstrapping replications, further illustrated the robustness

of the point estimates. Specifically, 29.84% of replications fell within the north-east quadrant (more expensive, more effective) and 65.82% fell within the south-east quadrant (less expensive, more effective) (see Figure 2). The probability of ICBT being cost-effective at the setting WTP ranged from 75.93% to 86.24% and showed an upward trend with the increase of WTP (see Figure 3). Similarly, analysis from the perspective of the healthcare system indicated that ICBT was more cost-effective than waiting-list control with probabilities ranging from 54.40% to 71.03%. Notwithstanding the foregoing observation, no cost-saving effect for the healthcare system was observed.

Table 4. Summary of incremental cost-effectiveness (CE) results for baseline adjusted (BA) complete case, intention-to-treat and scenario analyses from societal and healthcare system perspectives

Analysis	Dif. Mean costs (bSE)	Dif. Mean QALYs (bSE)	ICUR	ICURs by CE plane quadrant (%)						Prob. CE (%)	
				SE	SW	NE	NW	S	E	≤1*GDP per capita	≥3*GDP per capita
Societal perspective											
Complete case-8 weeks											
BA Cost /BA QALY	-149.65 (1645.32)	0.0042 (0.0028)	-35456.18	50.70	3.58	42.25	3.47	54.28	92.95	62.28	74.63
Intention to treat-8 weeks											
BA Cost/ BA QALY	-899.45 (2064.49)	0.0046 (0.0028)	-194720.38	65.82	3.28	29.84	1.06	69.10	95.66	75.93	86.24
Intention to treat-3 months											
BA Cost/ BA QALY	-1278.93 (3378.79)	0.0126 (0.0079)	-101283.17	63.36	3.03	31.88	1.73	66.39	95.24	76.85	88.46
Intention to treat-6 months											
BA Cost/ BA QALY	-1761.24 (4952.93)	0.0179 (0.0116)	-98146.80	62.53	3.17	31.78	2.52	65.70	94.31	75.32	86.32

Intention to treat-12 months										
BA Cost/ BA QALY	-2698.94 (7396.60)	0.0278 (0.0211)	-97064.62	61.13	4.81	30.42	3.64	65.94	91.55	75.62	85.48
Healthcare system perspective										
Complete case-8 weeks										
BA Cost/ BA QALY	507.13 (161.95)	0.0043 (0.0028)	118884.70	0.11	0.00	93.05	6.84	0.11	93.16	28.60	76.90
Intention to treat-8 weeks										
BA Cost/ BA QALY	201.90 (1568.36)	0.0041 (0.0027)	49700.33	41.75	3.02	52.22	3.00	44.78	93.97	54.40	71.03
Intention to treat-3 months										
BA Cost/ BA QALY	136.60 (1963.81)	0.0110 (0.0073)	12400.87	44.10	3.42	49.60	2.88	47.52	93.70	66.97	86.28
Intention to treat-6 months										
BA Cost/ BA QALY	112.37 (2060.10)	0.0153 (0.0108)	7332.67	44.39	3.95	48.16	3.50	48.34	92.55	72.33	88.34
Intention to treat-12 months										
BA Cost/ BA QALY	68.40 (2210.68)	0.0228 (0.0189)	3001.31	43.43	6.10	45.56	4.91	49.53	88.99	77.61	87.58

The scenario analysis represents a scenario whereby the waiting-list control participants health-related quality of life and care costs after 8 weeks up to twelve months followed the same trend as was observed in the intervention group; therefore, the difference in costs and QALYs are based on the observed values for the intervention group at each time-point but predicted values using regression analysis for the waiting-list control, the regression model for which is described in the methods section.

Abbreviations: Dif. Mean, difference in mean values between trial arms; bSE, bootstrapped standard error; ICUR, incremental cost-utility ratio; Prob. CE, Probability of being cost-effective; QALY, Quality-adjusted life years; SE, south-east quadrant; SW, south-west quadrant; NE, north-east quadrant; NW, north-west quadrant; S, south quadrant; E, east quadrant; 1*GDP per capita, willingness-to-pay of 1 times per capita gross domestic product; 3*GDP per capita, willingness-to-pay of 3 times per capita gross domestic product.

Sensitivity analysis

Sensitivity analyses were conducted by varying follow-up time duration (3-, 6- and 12-month follow-up) through subsequent scenario analyses. Figure 2 and Figure 3

respectively display the cost-effectiveness planes and CEACs at different time points from the societal and healthcare system perspectives for comparison. From the societal perspective, the results similarly indicated lower costs but higher QALY for participants in the ICBT group, with an 88.46% probability of being cost-effective, suggesting the long-term health and economic value of ICBT. In addition, from the healthcare system perspective, no cost-saving effect was observed. Higher direct medical costs and QALY were observed in the ICBT group, with the probability of being cost-effective reaching 88.34%. When the baseline values were not adjusted, the ICBT and waiting-list control groups revealed no difference in terms of cost-utility in both base-case and scenario analyses (see Supplementary Figure 1 and Supplementary Figure 2).

Discussion

This study aimed to evaluate the short- and long-term cost-effectiveness of the unguided ICBT compared to waiting-list control for MDD in China. The base-case findings of this cost-utility analysis showed that ICBT intervention was more cost-effective for persons with MDD compared to the waiting-list control over 8 weeks from the perspectives of society and healthcare system. Sensitivity analyses further confirmed the results by changing data analysis sets (i.e., CC and ITT samples), study periods (i.e., 3-, 6- and 12-month follow-up), and whether to adjust for baseline conditions. To the best of our knowledge, this is the first cost-effectiveness study on the unguided ICBT for MDD in China, contributing to the research gap in low- and middle-income countries and providing economic evidence for policy-makers to

rationally allocate limited health resources.

According to the base-case analysis, ICBT resulted in dominant ICURs from societal and healthcare system perspectives (-194,720.38 CNY and 49,700.33 CNY, respectively), with the probability of ICBT being cost-effective ranging from 54.40% to 88.46% at the setting WTP thresholds. These findings were consistent with prior research conducted in high-income countries demonstrating the cost-utility of unguided ICBT for MDD from the perspective of society.[14,15,19]However, only one study has also suggested the clinical and cost-saving effect of the unguided ICBT, [19]with the other two studies reporting more effectiveness at higher costs. [14,15]This might be owing to the difference in recruited study participants. Individuals with more severe depressive symptoms are likely to benefit more from the ICBT treatment, with greater responsiveness and more substantial health improvements. As a result, their social functions are getting better and enable them to engage in daily activities and return to work, leading to decreased societal costs. [37]Moreover, similar economic results from healthcare system perspective in previous research have also been found in this analysis that the unguided ICBT was more cost-effective than usual care at the given WTP.[16,18]However, in previous research, ICBT appeared to dominate usual care (lower mean costs and higher QALYs), while in our study, ICBT exhibited greater health effects at the price of higher costs. A possible explanation could be the variations in mental health-seeking behaviors under different contexts. In China, individuals are less likely to approach mental health care due to stigma.[38]However, the ICBT course helps people with

MDD transform their inappropriate or negative thought patterns to promote healthcare utilization.[37]Hence, the costs of healthcare in the ICBT group appeared higher than that of the waiting-list group in our analysis. This in turn explains the results from societal perspective. It's plausible that increased patient investment in mental healthcare and service yields improved social functioning. Consequently, reduced days of lost or decreased productivity and indirect costs associated with cost-savings were observed.[39,40]

The robustness of the results in base-case analysis was verified by different sensitivity analyses. Scenario analyses over 3-, 6- and 12-month follow-ups all suggested higher likelihoods of ICBT being cost-effective, aligning with previous studies and confirming the long-term cost-effectiveness of ICBT.[19,36]It is important to note that adjustment for differences in baseline costs and QALYs leads to slightly different results compared to that without baseline correction. At lower levels of WTP, ICBT showed an even chance of being cost-effective in both baseline-adjusted and non-adjusted analyses. However, with the increase of WTP, it had come to the opposite conclusion in the choice between the two treatments in terms of cost-utility. One plausible explanation is that the effect of the intervention on utility was mild and the differences between the intervention and control group in costs and QALYs were relatively minor.[18]Moreover, it was assumed that the baseline utility and costs were strongly correlated with the subsequent estimates, potentially leading to different outcomes when adjusting for baseline variables.[14]It was argued that in economic evaluation controlling for baseline utility and costs should be necessary. [41]

Despite the outcomes of the economic evaluation, the results suggest that there is no statistically significant difference in HRQoL and cost estimates between the two groups at all time points, which is consistent with the findings in previous research. [14,18]It is reported that the between-group (ICBT vs. control) effect size of HRQoL is small and a longer time duration is required to capture meaningful observations. [11,12,42,43]Given the high variability of costs,[44] research with larger sample sizes may be needed to detect statistical differences.

There were several strengths in this study. First, this cost-utility analysis was carried out and reported following international economic evaluation guidelines. Moreover, the outcome data was collected alongside a pragmatic RCT. Therefore, the validity and reliability of the data was guaranteed. Second, in the recording of direct medical costs, the hospital information system was used to collect at an individual level. Hence, the recall bias was reduced to some extent compared with self-reported data. In addition, the self-developed ICBT courses were embedded in the WeChat Mini-program, one of the most popular platforms among the Chinese population, which led to a high retention rate. Under the support of non-specialists, the retention rate in the waiting-list group was also maintained at a high level. Thus, the changes in clinical effectiveness and quality of life might reflect the real effect of the interventions. Fourth, the implementation of our intervention was executed by non-professional personnel such as primary healthcare workers, which was in line with practical operations under routine care, indicating the results had good features of scalability in the current medical environment.

Notwithstanding, several methodological limitations may affect inferences and interpretations of our findings. The primary limitation was the short-term follow-up period in the control group due to ethical considerations. Consequently, given the time-dependent nature of QALY, the potential lag effect of ICBT, and results reported in previous studies, rigorous statistical extrapolations on costs and QALYs were made for the control group, with the assumption that the trends of costs and QALYs were the same in the intervention and control arm. Scenario analysis was conducted based on predicated data, suggesting the long-term cost-effectiveness results should be interpreted with caution. Moreover, although the sample size in this RCT had sufficient statistical power to detect clinically significant improvements in depression, it did not necessarily have the statistical power to detect differences in cost-utility due to the high variability of costs. Replications with large sample sizes were needed. Third, since direct non-medical costs data were unavailable, only direct medical and indirect costs were included in this analysis. The foregoing limitation might potentially underestimate the overall total economic burden. Finally, in this study, female participants account for around 75% of total participants and the majority are well-educated, which affects the extrapolation at the population level.

Conclusions

In comparison with the waiting-list control, unguided ICBT is more cost-effective for MDD both from the healthcare system and societal perspectives in China. This intervention not only helps patients with MDD to improve clinically but also generates societal savings. These findings suggest that the unguided ICBT has

broad application prospects in low-resource countries like China and can serve as scalable resource access to MDD care for developing countries.

Data sharing

The datasets used for analysis are not publicly available due to ethnical restrictions but are available from the corresponding author on reasonable request.

Code availability

The code used for analysis are available from the corresponding author on reasonable request.

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Author contributions

All authors conceptualized and designed the trial. WZ, YC, YL, YL, HZ, CG and JH

conducted the trial and follow-up. WZ, HW, ZH, YL, GS and WW collected and prepared the data. WZ and YC analyzed and interpreted the patient data and were major contributors in writing the manuscript. WW, GHL and RSM polished the manuscript and revised the paper. XH and LC offered administrative, technical and material support for the implementation of trial. XH and CL provided supervision for the whole trial. CL obtained the funding for the trial. All authors read and approved the final manuscript.

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Competing interests

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Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Neurawell, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular, NewBridge Pharmaceuticals, Viatris, Abbvie and Atai Life Sciences. Dr. S. Roger McIntyre is a CEO of Braxia Scientific Corp.

Abbreviations

MDD: major depressive disorder

ICBT: Internet-based Cognitive Behavioral Therapy

ICUR: incremental cost-utility ratio

QALY: Quality-Adjusted Life Years

CNY: Chinese Yuan

WTP: willingness-to-pay

HRQoL: health-related quality of life

CBT: Cognitive Behavioral Therapy

RCT: randomized controlled trial

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

PHQ-9: Patient Health Questionnaire-9

M.I.N.I: Mini International Neuropsychiatric Interview

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

GAD-7: Generalized Anxiety Disorder-7

K-10: Kessler 10-item Psychological Distress scale

SF-6Dv2: Short-Form Six-Dimension

SDS: Sheehan Disability Scale

SD: standard deviation

CI: confidence interval

MICE: multiple imputation by chained equations

CC: complete cases

ITT: intention-to-treat

CEAC: cost-effectiveness acceptability curve

GDP: gross domestic product

SE: standard error

Figure 1. Flow chart of participants

Figure 2. Cost-effectiveness planes showing difference in baseline adjusted (BA) incremental quality-adjusted life years (QALYs)(x-axis) and incremental costs(y-axis) of 5,000 bootstrapping samples between trial-arms across 8-weeks, 3, 6, and 12-months.

Abbreviations: WTP, willingness-to-pay; GDP, Gross Domestic Product.

(A). Adjusted incremental QALYs and costs at 8 weeks from societal perspective. (B). Adjusted incremental QALYs and costs at 8 weeks from healthcare system perspective. (C). Adjusted incremental QALYs and costs at 3 months from societal perspective. (D). Adjusted incremental QALYs and costs at 3 months from healthcare system perspective. (E). Adjusted incremental QALYs and costs at 6 months from societal perspective. (F). Adjusted incremental QALYs and costs at 6 months from healthcare system perspective. (G). Adjusted incremental QALYs and costs at 12 months from societal perspective. (H). Adjusted incremental QALYs and costs at 12 months from healthcare system perspective. Red dashed line presents WTP at 1 times per capita GDP; Green dashed line presents WTP at 1.5 times per capita GDP; Blue dashed line presents WTP at 3 times per capita GDP; Count represents the distribution of bootstrap sample, with light-colored dot indicating high density.

Figure 3. Cost-effectiveness acceptability curves (CEAC) presenting the probability of cost-effectiveness of ICBT relative to waiting-list control over 8-weeks, 3, 6, and 12-months.

Abbreviations: WTP, willingness-to-pay; GDP, Gross Domestic Product.

(A). CEACs for 8-week, 3-, 6-, and 12-month follow-up analyses from societal perspective. (B). CEACs for 8-week, 3-, 6-, and 12-month follow-up analyses from healthcare system perspective. Red dashed line presents WTP at 1.5 times per capita GDP.

Supplementary Files

Related publication(s) - for reviewers eyes onlies

Figure 2. Cost-effectiveness planes showing difference in baseline adjusted (BA) incremental quality-adjusted life years (QALYs)(x-axis) and incremental costs(y-axis) of 5,000 bootstrapping samples between trial-arms across 8-weeks, 3, 6, and 12-months.
URL: http://asset.jmir.pub/assets/d95d58fa1506bdedfe3472f39322046a.pdf

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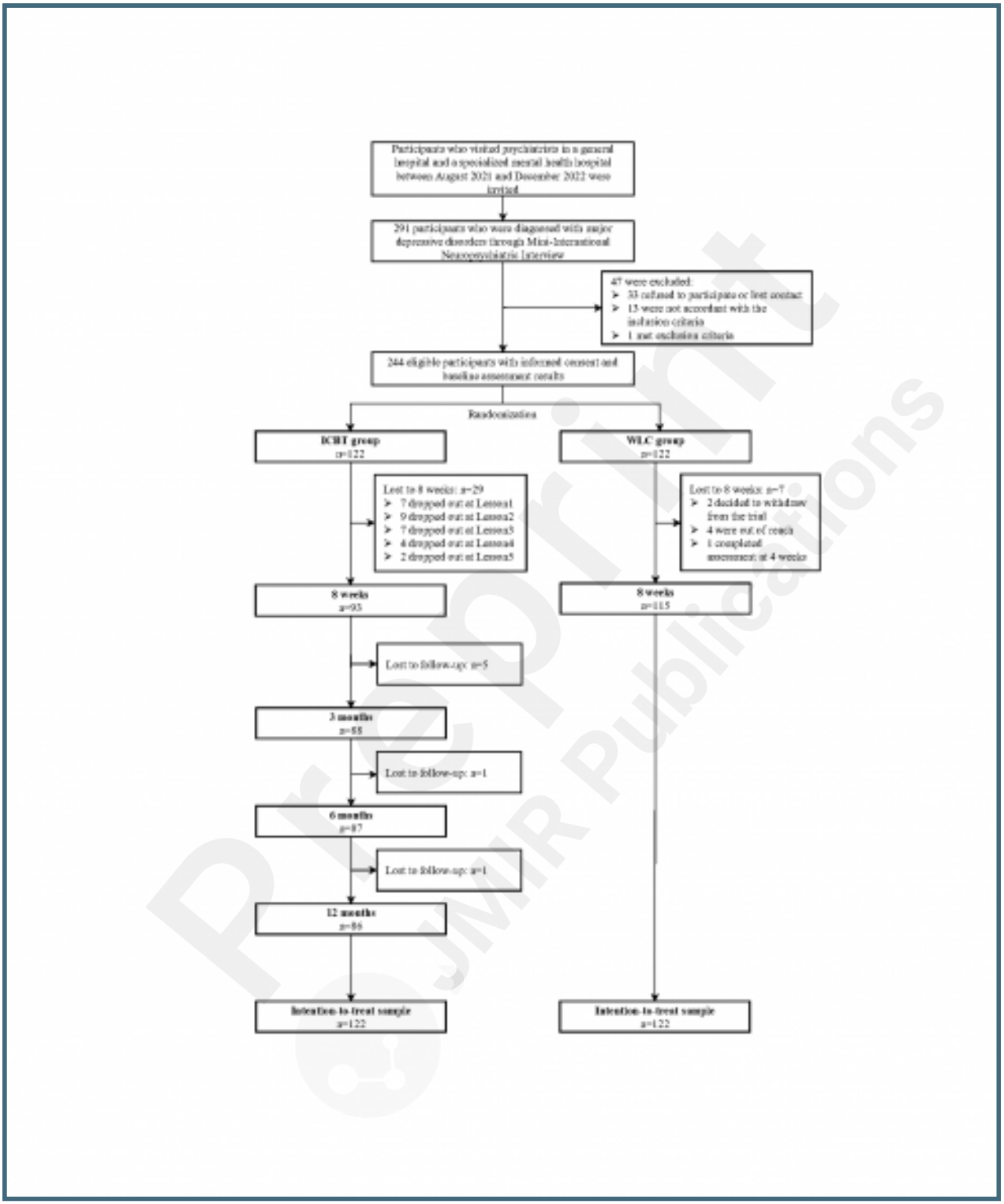

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Supplementary material.
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