Therapist-guided internet-based psychodynamic therapy versus cognitive behavioural therapy for adolescent depression in Sweden: a randomised, clinical, non-inferiority trial

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Summary

Background Adolescent major depressive disorder (MDD) is highly prevalent and associated with lifelong adversity. Evidence-based treatments exist, but accessible treatment alternatives are needed. We aimed to compare internet-based psychodynamic therapy (IPDT) with an established evidence-based treatment (internet-based cognitive behavioural therapy [ICBT]) for the treatment of adolescents with depression.

Methods In this randomised, clinical trial, we tested whether IPDT was non-inferior to ICBT in the treatment of adolescent MDD. Eligible participants were 15–19 years old, presenting with a primary diagnosis of MDD according to DSM-5. Participants were recruited nationwide in Sweden through advertisements on social media, as well as contacts with junior and senior high schools, youth associations, social workers, and health-care providers. Adolescents who scored 9 or higher on the Quick Inventory of Depressive Symptomatology for Adolescents (QIDS-A17-SR) in an initial online screening were contacted by telephone for a diagnostic assessment using the Mini International Neuropsychiatric Interview. Participants were randomly assigned to ICBT or IPDT. Both interventions comprised eight self-help modules delivered over 10 weeks on a secure online platform. The primary outcome was change in depression severity measured weekly by the QIDS-A17-SR. Primary analyses were based on an intention-to-treat sample including all participants randomly assigned. A non-inferiority margin of Cohen's d=0·30 was predefined. The study is registered at ISRCTN, ISRCTN12552584.

Findings Between Aug 19, 2019, and Oct 7, 2020, 996 young people completed screening; 516 (52%) were contacted for a diagnostic interview. 272 participants were eligible and randomly assigned to ICBT (n=136) or IPDT (n=136). In the ICBT group, 51 (38%) of 136 participants were classified as remitted, and 54 (40%) of 136 participants were classified as remitted in the IPDT group. Within-group effects were large (ICBT: within-group d=1·75, 95% CI 1·49 to 2·01; IPDT: within-group d=1·93, 1·67 to 2·20; both p<0·0001). No statistically significant treatment difference was found in the intention-to-treat analysis. Non-inferiority for IPDT was shown for the estimated change in depression during treatment (d=–0·18, 90% CI –0·49 to 0·13; p=0·34). All secondary outcomes showed non-significant between-group differences.

Interpretation IPDT was non-inferior to ICBT in terms of change in depression for the treatment of adolescents with MDD. This finding increases the range of accessible and effective treatment alternatives for adolescents with depression.

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Introduction

Depression is one of the leading causes of illness and disability among adolescents[1] and lifetime prevalence is suggested to be as high as 15–21%.[2] Adolescent depression is associated with a vast array of negative outcomes, such as recurrent depression, other mental health issues, lower educational attainment, drug abuse, and poor social functioning.[3]

For adult populations, there is strong evidence for the efficacy of internet-based cognitive behavioural therapy (ICBT) for various disorders, including depression.[4,5] Meta-analyses indicate that ICBT and computer-based CBT are effective in the treatment of adolescent depression, with moderate effects compared with passive control conditions.[6–8] Grist and colleagues[9] reported that CBT-based interventions were more effective than treatments based on other approaches, and that therapist-guided interventions showed larger effects than self-guided programmes for children and adolescents. ICBT augmented with chat sessions for adolescents with depression was tested in two randomised controlled trials, and showed moderate to large effects compared with waitlist controls, and 42–46% of participants were classified as having achieved clinically significant change.[10,11] Although the results were promising, a substantial proportion of participants

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Research in context

Evidence before this study

Major depressive disorder (MDD) in adolescents is a leading cause of illness and disability worldwide. Untreated MDD in adolescence is related to further illness and adversity during the lifespan but there is a paucity of accessible and cost-effective treatments. Internet-based cognitive behavioural therapy (ICBT) has shown efficacy but a large number of depressed adolescents do not respond to treatment and there is a need for treatment alternatives to meet the needs of this large patient group. One treatment alternative might be internet-based psychodynamic psychotherapy (IPDT). We searched PubMed between Jan 1, 1990, and Dec 31, 2020, for studies published in English, with the following search terms: Depression AND Adolescent OR adolescence OR adolescents AND internet-delivered OR internet-based OR computer-based OR technology delivered. The search identified four systematic reviews investigating internet-based interventions for MDD in children and adolescents showing effect sizes for ICBT between 0·60 and 0·76. ICBT interventions seem to have larger effects than other treatments and therapist-guided interventions seem to have larger effects than non-guided interventions. The search identified no trials investigating effects of IPDT except the pilot study by our research team.

Added value of this study

Our findings show that both 10 weeks of therapist-supported ICBT and IPDT are effective treatments for adolescent MDD with effects on depressive symptoms and anxiety, emotion regulation, and self-compassion. IPDT is not inferior to ICBT and there were no significant differences on any of the outcomes in the intention-to-treat analyses between the treatment groups. Both treatments were associated with a 48–49% response rate and a 38–40% remission rate.

Implications of all the available evidence

To our knowledge, this work is the only fully powered, non-inferiority study comparing IPDT with ICBT for the treatment of depression in adolescents. This study suggests that the IPDT programme developed by our research group is an effective treatment for adolescent depression, similar to ICBT in terms of effectiveness. Both IPDT and ICBT are effective on a range of outcomes with no differences between the treatments. Our results indicate that IPDT and ICBT should both be offered to adolescents with depression by health-care providers. Such an offering would increase the range of accessible and effective treatment alternatives for adolescents with depression. Future research should address potential factors that affect suitability for any of the treatments.

did not respond to ICBT, indicating a need for treatment alternatives.

Psychodynamic psychotherapy has been found to be as effective as CBT for adults and adolescents with depression.[12–14] Internet-based psychodynamic therapy (IPDT) has been evaluated for adolescent depression with promising results.[15] However, to our knowledge, IPDT has not been directly compared against ICBT in a sufficiently powered study with a strict criterion for achieving non-inferiority.

The aim of this study was to compare the efficacy of IPDT with an established evidence-based treatment (ICBT) for adolescent depression.

Methods

Study design and participants

In this randomised, controlled, non-inferiority trial, participants were recruited nationwide in Sweden through advertisements on social media, as well as contacts with junior and senior high schools, youth associations, social workers, and health-care providers. Potential participants were referred to a study website with information about the study and the treatment format (ie, guided self-help, duration, and intensity). Those interested in partaking could then start the application process via a link on the website. Adolescents who scored 9 or higher on the Quick Inventory of Depressive Symptomatology for Adolescents (QIDS-A17-SR[16]) in an initial online screening were contacted by telephone for a diagnostic assessment using the Mini International Neuropsychiatric Interview (MINI 7.0[17]). To accurately assess depression in adolescents, the item addressing the irritability criterion was added from the MINI for Children and Adolescents. MINI interviews were done by psychologists or Master's students in clinical psychology in their final year of education, who had been specifically trained in the MINI. Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS[18]). An independent clinical psychologist with extensive experience in psychiatric assessment of adolescents rated a random selection of 10% of the conducted interviews. Interrater reliability for current depressive episode was excellent (Cohen's κ=0·84, 95% CI 0·62–1·05).

Inclusion criteria included being 15–19 years old, presenting with a primary diagnosis of major depressive disorder (MDD) according to DSM-5,[19] having access to a computer, smartphone, or tablet with internet connection, and being able to read, write, and speak Swedish. Participants were excluded if they fulfilled any of the following exclusion criteria: substantial risk of suicide (ie, clear intent or plans) or earlier suicide attempts, ongoing participation in other psychological treatment(s), psychotropic medication not stable in the past month (or with planned adjustments within the coming 3 months), or deemed unable to comprehend what it meant to participate in the research (in line with Swedish law). Participants were also excluded if they fulfilled a primary diagnosis other than MDD, or any psychotic disorder,

bipolar disorder, antisocial personality disorder, alcohol or substance use disorder, or autism spectrum disorder. Withdrawal from the study was considered for participants who expressed increased suicidality; if deemed necessary they were referred to psychiatric services.

Written informed consent was provided by the participants online before screening. Next, they were given oral information at the beginning of the diagnostic telephone interview, encouraged to ask questions, and again asked to confirm their consent via phone. Furthermore, after a decision to include a participant, before random allocation, participants were asked to again confirm their consent to participate. According to Swedish law, if an adolescent is aged 15 years or older and able to understand what it means to partake in research, parental consent is not necessary. All participants were encouraged to tell their parents about partaking in the study, but parental consent was not mandatory. No material directed to parents was included in either of the two interventions.

The study was approved by the Swedish Ethical Review Authority on Aug 14, 2019 (reference number 2019-03023). A study protocol was published before recruitment completion.[20]

Randomisation and masking

Participants were randomly assigned to IPDT or ICBT using permuted block randomisation (1:1) in blocks of different sizes (mean 21, range 8–36) depending on the number of adolescents found eligible at each inclusion conference (meetings where assessments of potentially eligible participants were discussed to reach a conclusion regarding whether to include or exclude the participant based on inclusion or exclusion criteria). Two independent researchers with no involvement in the rest of the study performed the randomisation, using the computerised randomisation tool random.org. Randomisation was done after completion of all baseline measures and final enrolment. Further details about the randomisation procedure can be found in the appendix (p 1).

Procedures

Both interventions comprised eight self-help modules delivered over 10 weeks on a secure online platform. The modules contained text and videos, and exercises that the participants completed online. Therapists sent feedback on completed exercises within 24 h on weekdays. Furthermore, all participants were offered 30 min of weekly therapist support via synchronous text chat. A protocol (available upon request) was used to standardise the extent of contact between therapists and participants. The aim was to ensure that there were no systematic differences between treatments, beyond the therapy focus itself.

The IPDT programme has been evaluated in a previous randomised controlled trial for adolescent depression.[15] Through text, videos, and a series of experiential exercises, participants are encouraged to reflect on and experience underlying emotional conflicts that give rise to and perpetuate depressive symptoms. The treatment also focuses on noticing when anxiety is too high, anxiety regulation, and avoidance of emotions (defences). The aim of treatment is to achieve greater insights into the underlying emotional dynamics of the depression and decrease emotional avoidance. The final part of the programme contains material on how to talk about and share emotions in close relationships.

The ICBT programme has previously been evaluated for adolescents with depression.[10,11] The modules target behavioural and cognitive factors documented to reduce symptoms of depression and anxiety. The treatment programme contains psychoeducation, behavioural activation, cognitive restructuring, affect regulation, anxiety management, and relapse prevention. Two of the modules contain partly tailored material on anxiety and problems often associated with depression (such as procrastination or sleep problems), which is chosen by the participant and their therapist based on the participants unique needs.

Participants were not informed of what the two treatment alternatives were before random allocation. However, as CBT was mentioned in the ICBT treatment material, participants in the ICBT condition did not remain masked throughout treatment. Neither CBT nor PDT were mentioned in the IPDT treatment.

The study therapists were 38 Master's students in their final year of psychologist training. Therapists were specialised in the respective modality of treatment that they delivered. All therapists had previous experience through their clinical training in treating patients face-to-face with either CBT or PDT. Therapists had a one-day training in either IPDT or ICBT, held by the treatment developers, and received mandatory weekly group supervision of 120 min by experienced psychologists and psychotherapists in their respective treatment modality. Treatment adherence was not systematically monitored, but supervision was based on written transcripts from chat sessions or exercise feedback. Both treatments were manualised, providing guidance regarding content of messages and text chat. A total of 18 therapists conducted ICBT and 20 therapists conducted IPDT.

See Online for appendix

Outcomes

The predetermined primary outcome measure[20] was change in depression severity measured weekly by the QIDS-A17-SR.[16] QIDS-A17-SR is a brief self-report measure that covers all symptoms of adolescent depression (including the irritability criterion). The brevity of QIDS-A17-SR allows for repeated measurements and research suggests that this measure can be digitally delivered without loss of psychometric properties.[21] QIDS-A17-SR has also been found to be more sensitive to changes in adolescent depression compared with the Patient Health Questionnaire-9 Modified.[22] As the target of the treatment was MDD-diagnosed using the criteria from the Diagnostic and Statistical Manual of Mental

Disorders, fifth edition, it made sense to choose a reliable depression measure covering all the criteria of adolescent depression. The QIDS-A17-SR has been translated to numerous languages and is freely available, rendering it easy to compare results from the present trial with future implementations in clinical practice. The QIDS-SR16 has shown acceptable to excellent reliability in samples with adults (α=0·69–0·89) and convergent validity with the Hamilton Depression Rating Scale (r=0·76, 95% CI 0·69–0·81).[23] QIDS-A17-SR seems reliable in adolescent samples (α=0·86).[16] The QIDS-A17-SR is identical to the QIDS-16SR except for the addition of an item assessing the irritability criterion. In the present sample, QIDS-A17-SR had a mean α of 0·80 across all weeks in treatment.

Secondary outcome measures included anxiety symptoms, as measured by the Generalized Anxiety Disorder 7-item scale (GAD-7[24]), a brief self-report instrument with seven items scored from 0 to 3. The maximum score is 21 and higher scores indicate more severe anxiety. The GAD-7 showed good internal consistency (α=0·74) in the present sample.

Emotion regulation was measured by the Emotion Regulation Skills Questionnaire (ERSQ-27[25]), a 27-item self-report questionnaire that uses a five-point rating from 0 to 4 on each item. Higher scores imply a greater capacity for emotion regulation. ERSQ-27 measures nine facets of adaptive emotion regulation skills but also presents a global score assessing general emotion regulation. In the present study, we only used the total score of the questionnaire. ERSQ-27 showed good reliability in the present study sample (α=0·88).

Self-compassion was measured by the Self-compassion Scale Short Form,[26] which comprises 12 items scored from 1 to 5. The instrument covers four facets of self-compassion but also presents a total score. In the present study, only the total score was used and the instrument showed good reliability (α=0·72).

Adverse events were defined as any clinically significant unfavourable change in the participant's mental condition, regardless of its relationship to treatment. Serious adverse events were mortality, hospitalisation, suicide, or attempted suicide.

Statistical analysis

Power calculations and the non-inferiority margin were decided a priori.[20] To assess non-inferiority using a repeated-measures design, power calculations for two-level linear mixed models (LMMs) were made following Galbraith and Marschner[27] using the R-package powerlmm version 0.4. With an α at 0·05, a non-inferiority margin of 0·30, an estimated variance ratio of 0·75, an attrition rate of 20%, and intermittent missing data on weekly measures of 20%, a total sample size of 270 (135 in each group) was needed to reach 80% power. Power calculations were based on data from a previous randomised controlled trial.[15]

Primary analyses were based on an intention-to-treat sample including all participants randomly assigned. To fully explore trajectories of change, a multilevel growth curve level strategy was employed using weekly measurements, comparing the estimated rate of change in depressive symptom severity from baseline to the end of treatment between groups. The difference in effects between the conditions was investigated by modelling interaction effects of treatment and time. LMM analyses were done using STATA version 16. Assumptions for LMMs, including normality of residuals, were checked. Skewness was 0·19 and kurtosis was 3·58. Growth curve modelling starts by finding the shape of change that fits the data best.[28] Since data seemed to have a non-linear shape, we used fractional polynomials[29] to find the best-fitting model. Compared with conventional polynomial models (eg, quadratic models), fractional polynomials offer more flexible modelling of trajectory shapes. The best-fitting model was a second-order fractional polynomial model with powers (0·5, 0·5) selected based on deviance statistics. Time variables were centred at baseline to allow interpretation of the intercept. Longitudinal equality of residual variances (homoscedasticity) was checked by running a model with this assumption relaxed and comparing model fit to the model with residual variances constrained to equality across time. The constrained model had an Akaike information criterion (AIC) value of 12 898·84, whereas the unconstrained model had an AIC of 12 905·72, showing that the constrained model was a better compromise between model fit and parsimony.[30] Residual autocorrelation was checked by comparing the model used with a model including an AR(1) (first-order autoregressive structure with homogenous variances) residual structure term. The inclusion of the AR(1) term improved fit somewhat (the AIC for the AR(1) model was 12 840·27), thus it was retained. Treatment—coded as 0 for ICBT and 1 for IPDT—was entered both as a fixed main effect, to test for possible differences between groups at pretreatment assessment, and in interaction with the two time variables, to test for treatment differences in change rates and trajectories over time. All models were fitted with restricted maximum-likelihood estimation and an unstructured covariance structure for the random effects, providing unbiased estimates with a relatively unrestrictive assumption about missing data (ie, missing at random). Non-inferiority was predefined as fulfilled when the upper bound of the two-sided 90% CI of the between group difference was below Cohen's *d*=0·30 (ie, the non-inferiority margin).[20,31] Cohen's *d* was calculated following recommendations by Feingold,[32] using change over time from estimated fixed effects from the final model and the observed pretreatment sample SD. The primary analysis was done masked to treatment allocation. Hence, two non-inferiority tests were made but only the one testing non-inferiority of IPDT was retained after the masking was broken by the principal investigator. The other non-inferiority test where ICBT was tested against

IPDT was discarded as this was not part of our research plan. A secondary analysis was done post hoc, entering five covariates (age, gender, dysfunctional personality traits, self-compassion, and emotion regulation) associated with missing data into the model. Post-hoc sensitivity analyses were done and are described in the appendix (pp 2–3).

As secondary outcomes were measured before and after treatment, analyses were made using ANCOVA, controlling for baseline values on the respective measures. Assumptions including linearity, normality, homogeneity of residuals, and homogeneity of regression slopes were all met. Missing data were handled through multiple imputation using linear regression with fully conditional specification. 50 datasets were imputed. The multiple imputation model included baseline and endpoint data for all secondary measures, as well as QIDS-A-17-SR score and group. Analyses were done using SPSS version 26.

Per-protocol analyses were done on participants who completed at least five modules (defined as completing at least one exercise per module) and attended five or more chat sessions while having completed the post-treatment assessment. Mixed model analyses were done on the primary outcome measure following the same procedure as in the primary analyses. Analyses of secondary outcomes were done following the same procedures as for the intention-to-treat analyses of secondary outcomes.

Participants were classified as responders if they changed reliably on the QIDS-A17-SR during the course of treatment while also scoring 2 or more SDs below the pretreatment mean (ie, achieving gains of clinical significance according to Jacobson and Truax's criterion A[33]). Participants who changed reliably (a reduction of ≥5 points), while not reaching the cutoff of at least 2 SDs below the pretreatment mean, were considered partial responders. Participants who reliably worsened in terms of depressive symptoms during treatment were considered deteriorators. Cases where post-treatment assessment was missing were classified as showing no change. Remission from depression was assessed through a cutoff score of 6 or less on the QIDS-A17-SR[34] and remission from anxiety was defined as a score of 5 or less on GAD-7.[24]

A Data Monitoring Committee (DMC) comprising an independent researcher, an administrator, and a clinician not otherwise involved in the study monitored the progress of the study (eg, reviewed recruitment and retention rates) and participant safety. The DMC also made periodic checks of data completeness and accuracy.

The study is registered at ISRCTN, ISRCTN12552584.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 19, 2019, and Oct 7, 2020, 996 young people completed screening; 516 (52%) were contacted for a diagnostic interview (figure 1). 272 participants were eligible and randomly assigned to ICBT (n=136) or IPDT (n=136). Demographic and clinical characteristics of the sample are summarised in table 1. Missing data for the primary outcome measure was 22% on weekly measures and 4% on the post-treatment assessment. Further

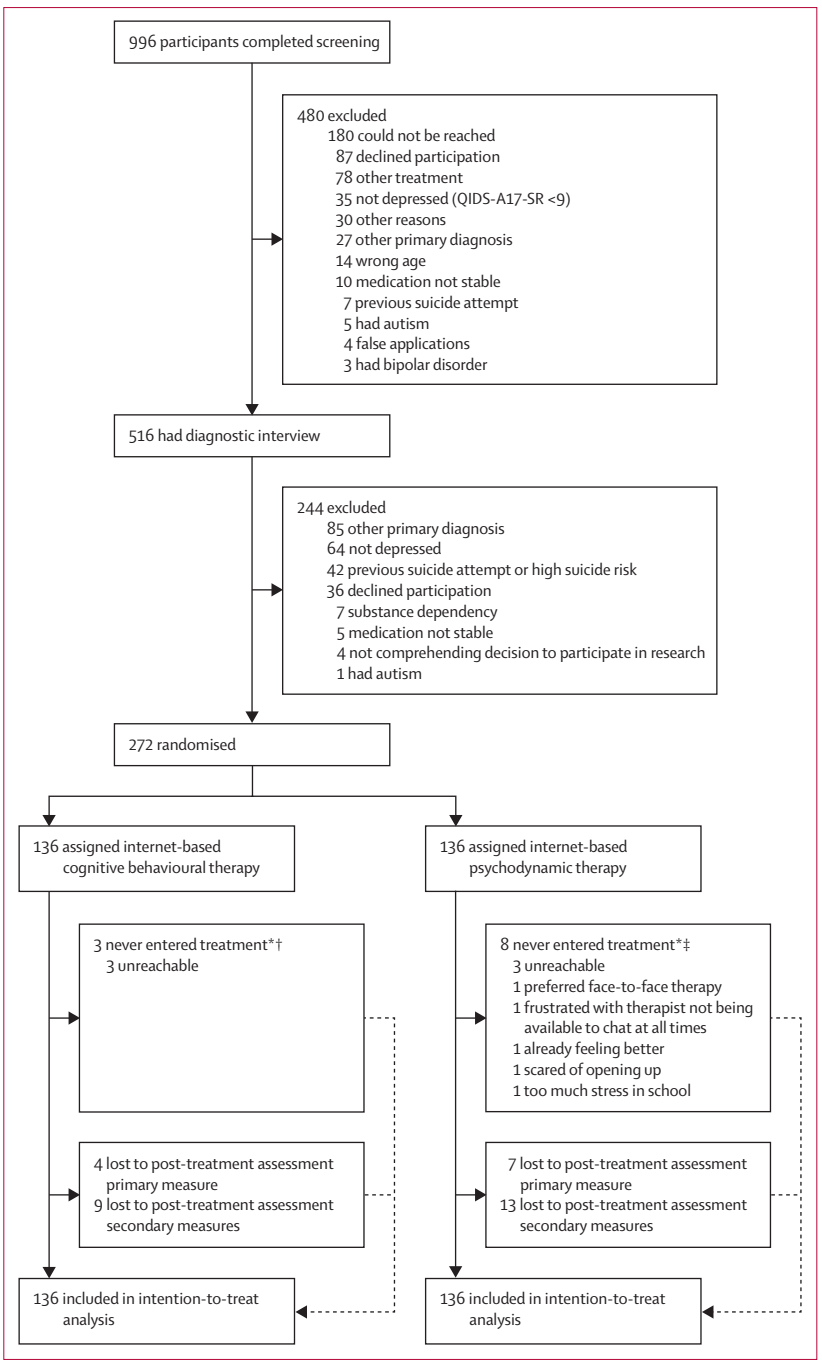

Figure 1: **Trial profile**
QIDS-A17-SR=Quick Inventory of Depressive Symptomatology for Adolescents. *Defined as not completing at least one chat or at least one exercise. †Two participants opened one module and one opened zero modules. ‡Five participants opened one module and three opened zero modules.

	ICBT (n=136)	IPDT (n=136)
Gender		
Female	115 (85%)	112 (82%)
Male	15 (11%)	21 (15%)
Uncertain or other	6 (4%)	3 (2%)
Age, years	17·29 (1·28)	17·35 (1·25)
Diagnosis		
Major depressive disorder	136 (100%)	136 (100%)
Major depressive disorder, recurrent	93 (68%)	101 (74%)
Persistent depressive disorder (≥1 year)	47 (35%)	58 (43%)
Panic disorder	21 (15%)	13 (10%)
Agoraphobia	18 (13%)	11 (8%)
Social anxiety disorder	48 (35%)	32 (24%)
Generalised anxiety disorder	35 (26%)	35 (26%)
Post-traumatic stress disorder	11 (8%)	16 (12%)
Obsessive-compulsive disorder	7 (5%)	6 (4%)
Bulimia nervosa	4 (3%)	6 (4%)
Binge eating disorder	2 (1%)	5 (4%)
Non-suicidal self-injury, current	18 (13%)	18 (13%)
Non-suicidal self-injury, past	33 (24%)	42 (31%)
Currently on psychotropic medication	10 (7%)	12* (9%)

Data are n (%) or mean (SD). ICBT=internet-based cognitive behavioural therapy. IPDT=internet-based psychodynamic therapy. *Two participants in the IPDT group had multiple medications (three each).

Table 1: **Demographic data at baseline**

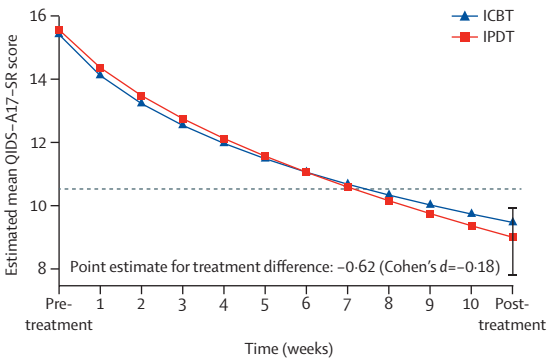

Figure 2: **Estimated trajectories of change with 90% CI of treatment difference**

The dashed horizontal line is the non-inferiority margin. ICBT=internet-based cognitive behavioural therapy. IPDT=internet-based psychodynamic therapy. QIDS–A17–SR=Quick Inventory of Depressive Symptomatology.

information regarding missing data is provided in the appendix (p 1). Participants opened a mean of 7·03 (SD 1·92) modules and attended 8·5 (2·81) chat sessions in the ICBT group, and opened 6·35 (2·44) modules and attended 7·85 (3·16) chat sessions in the IPDT group. The mean length of sessions was 32 min and 53 sec (SD 6 min 1 sec) in the ICBT group and 33 min and 46 sec (5 min 58 sec) in the IPDT group. The mean time spent by therapists on weekly feedback was 13 min and 12 sec (SD 3 min 50 sec) in the ICBT group and 13 min and 42 sec (3 min 26 sec) in the IPDT group.

22 participants reported being on any stable psychotropic medication at baseline (ten [7%] of 136 participants in the ICBT group and 12 [9%] of 136 participants in the IPDT group; appendix p 1).

Depressive symptom scores in both groups improved during treatment (ICBT: within-group d=1·75, 95% CI 1·49 to 2·01; IPDT: within-group d=1·93, 1·67 to 2·20; both p<0·0001). Expressed as raw scores, the ICBT group improved 5·93 points on the QIDS-A17-SR (95% CI 5·05 to 6·82) and the IPDT group improved 6·55 points (5·65 to 7·44). Estimated marginal means for self-reported depression scores over time for both groups are presented in figure 2. After treatment, the estimated difference in change between groups in depressive symptoms during treatment was –0·62 (90% CI –1·67 to 0·44) points on the QIDS-A17-SR, corresponding to an effect size (Cohen's d) of –0·18 (90% CI –0·49 to 0·13; p=0·34) in favour of IPDT. The 90% CI upper bound of d=0·13 is less than the prespecified non-inferiority margin of d=0·30, showing that IPDT was non-inferior to ICBT regarding change in depressive symptoms. Estimates from the multilevel analysis for QIDS-A17-SR are shown in table 2.

Adding five covariates associated with missing data to the model did not change our main findings. The estimated difference in change between groups corresponded to an effect size (Cohen's d) of –0·14 (90% CI –0·45 to 0·17; p=0·46) in favour of IPDT, thus still fulfilling non-inferiority for IPDT. Expressed in scores on QIDS-A17-SR, the estimated difference was –0·47 (90% CI –1·52 to 0·58).

At the end of treatment, 67 (49%) of 136 participants in the ICBT group and 65 (48%) of 136 participants in the IPDT group were classified as responders. Partial response was attained for 16 (12%) of 136 participants in the ICBT group and 18 (13%) of 136 participants in the IPDT group. In the ICBT group, 51 (38%) of 136 participants were classified as remitted, and 54 (40%) of 136 participants were classified as remitted in the IPDT group. None of the differences reached statistical significance (response p=0·808; partial response p=0·714; remission p=0·709). ANCOVAs revealed no significant differences for any of the secondary outcome measures; all between-group effect sizes were small and in favour of IPDT (table 3).

107 (79%) of 136 participants in the ICBT group and 96 (71%) of 136 participants in the IPDT group were classified as completers (p=0·125). In a per-protocol analysis, depressive symptom scores in both groups decreased over time (ICBT: within-group d=1·80; IPDT: within-group d=2·04; both p<0·0001). After treatment, the estimated difference between treatment conditions was 0·79 points on the QIDS-A17-SR, corresponding to a between-group effect size of d=–0·23 (90% CI –0·57 to 0·10; p=0·25). Thus, IPDT was non-inferior to ICBT in the per-protocol analysis. IPDT was superior to

	Estimate (95% CI)	p value
Fixed effects		
Intercept	15·41 (14·86 to 15·96)	<0·0001
Treatment	0·15 (–0·63 to 0·93)	0·71
Time_1	–10·03 (–12·60 to –7·46)	<0·0001
Time_2	2·03 (0·11 to 3·94)	0·038
Treatment × time_1	0·85 (–2·82 to 4·51)	0·65
Treatment × time_2	–1·38 (–4·11 to 1·36)	0·32
Variance components		
Residual variance	5·04 (4·60 to 5·53)	..
Intercept	6·10 (4·48 to 8·30)	..
Time_1	85·85 (51·75 to 142·42)	..
Time_2	39·85 (21·64 to 73·38)	..
Correlation time_1–time_2	–45·72 (–76·57 to –14·86)	..
Correlation intercept–time_1	3·81 (–2·83 to 10·45)	..
Correlation intercept–time_2	–3·08 (–7·85 to 1·69)	..
Between group effect size (Cohen's *d*)	–0·18 (–0·49 to 0·13)*	0·34

*90% CI of treatment difference (in Cohen's *d*).

Table 2: **Multilevel models estimating changes over time in the primary outcome measure**

	Observed mean score (SD)		Between-group Cohen's *d*	
	Pre-treatment	Post-treatment	Post-treatment (95% CI)	p value
Generalized Anxiety Disorder 7-item scale				
ICBT	11·57 (4·32)	7·93 (4·82)	–0·18 (–0·44 to 0·09)	0·20
IPDT	11·67 (4·09)	7·24 (5·07)	..	..
Emotion Regulation Skills Questionnaire				
ICBT	1·70 (0·51)	2·38 (0·74)	0·11 (–0·21 to 0·43)	0·51
IPDT	1·62 (0·55)	2·41 (0·80)	..	..
Self Compassion Scale - Short Form				
ICBT	24·90 (6·10)	33·99 (8·53)	0·03 (–0·29 to 0·36)	0·84
IPDT	24·63 (5·97)	34·11 (9·38)	..	..

In all cases, n=136. ICBT=internet-based cognitive behavioural therapy. IPDT=internet-based psychodynamic therapy.

Table 3: **Secondary outcome results**

ICBT in reducing anxiety, but the effect size was small (d=–0·29; p=0·047). Treatment differences on emotion regulation and self-compassion were non-significant (d=0·11; p=0·45 and d=–0·03; p=0·90, respectively).

Reliable deterioration was found for two (2%) of 136 participants in the ICBT group and three (2%) of 136 participants in the IPDT group. When responding to an open-ended question regarding negative effects, most participants did not report any in either of the conditions (130 [96%] of 136 participants in the ICBT group and 124 [91%] of 136 participants in the IPDT group). This difference was not statistically significant (χ^2=2·14; p=0·14). Most negative effects reported concerned anxiety caused by facing difficult feelings or stress (appendix p 2). Adverse events during treatment were mostly increased suicidal ideation, expressed through weekly ratings of depression or in contact with study therapists (ie, in chat sessions or text messages), where the principal investigator was contacted for further assessment (appendix p 2). No differences were observed between the treatment conditions regarding the proportion of adverse events reported during treatment (six [4%] of 136 participants in the ICBT group and seven [5%] of 136 participants in the IPDT group; χ^2=0·08; p=0·78). No serious adverse events occurred during the trial. According to the study protocol, participants expressing severe suicidality were to be withdrawn from the trial. However, no such events occurred.

Discussion

Our results suggest that IPDT is non-inferior to ICBT in the treatment of adolescents with major depression. Response and remission rates were highly similar, 67 (49%) of 136 participants in the ICBT group and 65 (48%) of 136 participants in the IPDT group classified as responders. Results on completers were similar and in the same direction as the results for the intention-to-treat sample, further strengthening the validity of the non-inferiority finding. Negative effects were of similar frequency in the two conditions and mostly mild, and adverse events were rare. This investigation adds to the emerging evidence of psychodynamic short-term therapies targeting depression in general, and for IPDT in the treatment of adolescents with depression in particular.

Both treatments were effective in treating comorbid anxiety, difficulties in emotion regulation, and self-compassion, with no significant differences in the intention-to-treat sample. In the per-protocol analyses, the only significant difference between treatments was a small effect in favour of IPDT in the treatment of comorbid anxiety. This finding could perhaps be due to the traditionally larger emphasis on transdiagnostic processes in PDT. However, the per-protocol analysis uses comparisons based on non-randomly assigned groups, using ratings from seemingly more motivated participants, which could introduce selection bias, and the effect size is small, indicating a lack of meaningful differences on secondary outcome measures.

Although we found promising results from two relatively short treatments, most participants in either treatment condition did not remit during treatment. As residual symptoms at the end of treatment seem to be predictive of relapse,[35] future studies should aim to improve the efficacy of the treatments, develop methods for identifying participants at risk of non-response or deterioration, and identify whether there are patient characteristics that predict better response to either of the treatment formats. Another way to address the question of what works for whom could be through a study with a crossover design, where non-responders in one treatment are crossed over to the other treatment.

As there was no predefined minimal clinically important difference for the QIDS-A17-SR, the non-inferiority margin was expressed in the terms of a standardised effect size instead of absolute scores. An effect size of Cohen's d=0·30 was chosen based on previous non-inferiority trials by Driessen and colleagues[13] and Connolly-Gibbons and colleagues[12] who used non-inferiority margins equivalent of d=0·30 and d=0·29, respectively. Other researchers have put forward a slightly lower threshold for clinically relevant effects with a standardised mean difference of 0·24.[36] However, it should be noted that adhering to this somewhat smaller margin would not have changed our main finding. There is also a debate regarding the appropriate significance level to be used in non-inferiority trials; in the present study we adhered to Wellek,[31] using a 90% CI in our primary analysis. Post-hoc analyses showed that IPDT would still be non-inferior to ICBT if the α level was halved to 2·5% and a 95% CI was used (appendix p 3).

The two-sided 90% CI for the difference between the treatment effects ranged from d=–0·49 to 0·13 or, expressed in raw scores, –1·67 to 0·44. This fact means that the true difference probably lies somewhere between these two numbers. The non-inferiority test is designed to establish that the upper bound does not exceed d=0·3 or 1·01 in raw scores. The results from the present study suggest that, with 95% probability, the largest effect in favour of ICBT is no more than d=0·13 (or 0·44 in raw scores) compared with IPDT. Since the non-inferiority test is one-sided, the lower bound of the CI (ie, the effect in favour of IPDT) is outside the scope of this analysis, but it suggests that the true difference between the treatments could be 1·67 points or d=0·49 in favour of IPDT, a difference which could be clinically meaningful. Trials with superiority or equivalence designs would be needed to investigate this.

It is important to note that the study design does not provide information about isolated effects of the treatment programmes, chat sessions, or written feedback on exercises. To investigate this properly, dismantling studies should be done. Such studies exist for ICBT in adolescents with anxiety, showing no added effect of synchronous chat sessions,[37] but it is unclear whether this is also the case for adolescents with depression. For IPDT, no such studies exist on adolescents, but earlier studies on adults with depression seem to suggest similar effect sizes in treatments without synchronous chat sessions;[38] whether this is true also for depressed adolescents treated with IPDT requires investigation.

This study has a number of strengths. Nationwide recruitment and no selection criteria with regard to previous treatment, course of depressive illness, preference for internet-based treatment, or suitability for psychological treatment could all contribute to the generalisability of the results. A research group comprising researchers with allegiances to both PDT and CBT was intended to reduce bias due to researcher allegiance effects. The study was sufficiently powered to detect small differences and, to our knowledge, this is the first non-inferiority study testing IPDT against ICBT. Weekly measurements of the primary outcome and the relatively low amount of missing data are additional strengths of the study.

A limitation of the study is the absence of a control group, meaning that no firm conclusions about the effectiveness of the interventions can be drawn. It should be noted that both treatments have been tried against inactive control or wait list conditions in previous trials with large between-group effects.[10,11,15] Furthermore, participants were self-referred, which might have led to a sample more positively inclined towards internet-based treatments. Still, the number of participants with comorbidities or depression ongoing for more than 1 year suggests that this was indeed a sample with complex psychiatric problems. No diagnostic interviews were done at the end of the trial because of insufficient resources, meaning that the proportion of participants fulfilling diagnostic criteria after treatment is unknown. Another limitation of the study is the lack of observer-rated outcome measures and masked assessments.

All of the study therapists were trainees and not licensed psychologists. More experienced therapists could have yielded different results. However, evidence on ICBT for adult populations suggests that therapist experience does not affect outcomes.[39] All therapists were supervised by experienced therapists within each modality and supervision was based on transcripts from the treatment. Although this strategy should lessen the risks of therapist drift, the integrity of the two treatments could have been furthered by using independent, masked treatment adherence checks. However, a substantial part of the treatment did consist of pre-written, completely standardised self-help material.

In trials with varying adherence, intention-to-treat analyses always come with a risk of biased treatment effects, since non-participators will influence the results. Thus, a non-inferiority result on an intention-to-treat analysis could simply be due to poor adherence to treatment. At the same time, it can be argued that per-protocol analyses constitute a risk of overestimating treatment effects, since there can be reasons within the treatment causing dropout and non-adherence, which are not taken into account. In the present trial, intention-to-treat and per-protocol analyses yielded similar results, strengthening robustness of our findings.

Although the present trial has a very low amount of missing data, there were some timepoints where missingness was higher. Missing data could lead to a risk of biased estimates. To address this, we did a number of post-hoc sensitivity analyses that supported our main findings.

In conclusion, non-inferiority of IPDT relative to ICBT was shown in the treatment of adolescents with major depression in a large sample. Almost half of participants responded to treatment and 38–40% reached remission within 10 weeks of either treatment. Our findings extend

the evidence base of both IPDT and ICBT for the treatment of adolescents with depression, thereby increasing access and availability of two treatments in this patient group.

Contributors

All authors conceived and designed the study. JM, KL, PC, NT, FF, PL, GA, RJ, NM, JE-C, H-SJD, RS, RU, and BP devised the methodology. All authors acquired the study funding. JM, KL, and BP curated the data. JM, KL, PC, NT, and BP collected the data. JM, KL, PC, NT, PL, GA, KLB, and BP provided study resources. JM and KL wrote the original draft of the manuscript. All authors reviewed and edited the manuscript. JM, KL, and FF analysed the data. JM, KL, PC, FF, and BP interpreted the data. JM, KL, and FF created the figures. JM, KL, NT, GA, PC, and BP were responsible for project administration. PC and BP supervised the study. JM, KL, PC, FF, and BP accessed and verified the data. JM, KL, PC, NT, and BP were the study investigators. BP was the principal investigator. All authors could access all data by request and approved the final submission. JM was responsible for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

In the written informed consent before entering the trial, participants were informed that data from the study, which could not be used to identify them as individuals, could be shared with other researchers. The datasets presented in this Article are not readily available because participants were mostly minors and the datasets contained sensitive data. Therefore, the datasets are available if the material requested does not contain information that is classified as secret in accordance with the Public Access to Information and Secrecy Act. The assessment of the information in the material requested must be done at the time of the request and only if the information is secret can the request be denied. The decision over whether data are secret in cases where other researchers request data sharing includes judgment over whether individual people could be harmed by the data sharing. Requests to access the datasets should be directed to the principal investigator BP (bjorn.philips@psychology.su.se).

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