Refractory depression – mechanisms and efficacy of radically open dialectical behaviour therapy (RefraMED): findings of a randomised trial on benefits and harms

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Refractory depression - Mechanisms & Efficacy of Radically Open Dialectical Behaviour Therapy (RefraMED): findings of randomised trial on benefits and harms

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[Manuscript comprises 4211 words]

Abstract

Background

Depressed individuals often do not respond to medication or psychotherapy. Radically Open Dialectical Behaviour Therapy (RO DBT) is a new treatment targeting overcontrolled personality, common in refractory depression.

Aim

To compare RO DBT plus treatment as usual (TAU) for refractory depression with TAU alone.

Methods

RO DBT comprised 29 therapy sessions and 27 skills classes over six months. Our completed randomised trial evaluated RO DBT for refractory depression over 18 months in 3 British secondary care centres. Of 250 adult participants, we randomised 162 (65%) to RO DBT. The primary outcome was the Hamilton Rating Scale for Depression (HRSD), assessed blind and analysed by treatment allocated.

Results

After seven months, immediately following therapy, RO DBT had reduced depressive symptoms by 5.40 HRSD points relative to TAU [95% confidence interval (CI) +0.94 to +9.85]. After 12 months (primary end point), the difference of 2.15 HRSD points in favour of RO DBT was not significant (95% CI –2.28 to +6.59); nor was that of 1.69 HRSD points at 18 months (95% CI –2.84 to +6.22). Throughout RO DBT participants reported significantly better psychological flexibility and emotional coping than controls. However they reported eight possible Serious Adverse Reactions (SARs) compared with none by controls.

Conclusions

RO DBT participants reported significantly lower HRSD scores than controls after 7 months, but not thereafter. The imbalance in SARs was probably due to controls' limited opportunities to report these.

Declaration of interest

Six of the 16 authors have received royalties or fees for RO DBT.

[Abstract comprises 249 words cf limit of 250]

Introduction

Major depressive disorder is a recurrent, disabling condition causing substantial impairment in psychosocial functioning and quality of life.[1] Only one third of individuals respond fully to antidepressant medication (ADM) and only half to psychological treatment.[2] Recently treatments developed for refractory depression have achieved small to moderate effect sizes.[3] Treatments are seldom effective owing to co-morbidity, especially personality disorders (PD).[4] About half of unipolar depressed patients meet criteria for comorbid PD, with higher rates among those with chronic or treatment-resistant depression.[4,5] The commonest PDs among depressed individuals show excessive inhibitory control or overcontrol, including Cluster A (paranoid PD) and Cluster C (obsessive-compulsive and avoidant PD) — those that respond poorly to PD treatments.[6,7] The core characteristics of overcontrolled personality disorders are: cognitive and behavioural rigidity; strong desire to control one's environment; restrained emotional expression; limited social interaction; and problems with close relationships due to aloofness, distancing, mistrust and fear of rejection or criticism.[8] Radically Open Dialectical Behaviour Therapy (RO DBT), a novel trans-diagnostic psychotherapy, aims to address this rigid coping style.[9] Earlier versions of RO DBT showed promise in two pilot randomised trials of patients with refractory depression and comorbid PD.[10,11] This trial aimed to assess the efficacy of RO DBT for refractory depression,[12] and whether RO DBT causes identifiable harms.[13]

Methods

Design

RefraMED was a three-centre parallel-group randomised trial which compared RO DBT plus treatment as usual (TAU) with TAU alone. After an internal pilot in one centre, shortage of therapists reduced recruitment below the target rate. So we extended our recruitment period from 24 months to 32; and followed the last 27 participants for 12 months (the primary endpoint) rather than 18.

Participants

Patients were eligible for the RefraMED trial if they: were 18 years or older; had an IQ more than 70; spoke English well enough to participate; had a current diagnosis of major depressive disorder in SCID-I;[14] were suffering from refractory depression, defined as chronic depression lasting at least two years or recurrent depression with at least two previous episodes; had a Hamilton Rating Scale for Depression (HRSD)[15] score of at least 15; and had not responded to an adequate dose of ADM for at least six weeks in their current episode. Since we had developed RO DBT specifically for overcontrol, we excluded patients who: met criteria for bipolar disorder, psychosis, or dramatic-erratic PD in SCID-II;[16] had a primary diagnosis of substance dependence; or were currently receiving or waiting for standard DBT. We recruited these patients in three NHS secondary care centres already delivering standard DBT for dramatic-erratic PD – Dorset and Hampshire in England, and North Wales.[13]

Interventions

Treatment as usual (TAU)

As all three centres seek to deliver best practice, that was the natural control treatment. All participants received TAU, including prescribed ADM or psychotherapy. [13] Control participants could also access any treatment from NHS or privately, except standard DBT. At each follow-up assessors asked participants to report their ADM and adherence to it, and psychotherapy accessed since their previous assessment or in the six months before their baseline assessment.

Radically Open Dialectical Behaviour Therapy (RO DBT)

RO DBT is a trans-diagnostic therapy designed to address a spectrum of disorders that are difficult to treat, notably chronic depression.[9] It differs from other psychotherapies, notably by encouraging social bonding through emotional expression. At the time of the trial RO DBT comprised 29 weekly individual therapy sessions each lasting an hour and 27 skills training classes each lasting 2.5 hours. [9,12] The RO DBT lesson plan (Table S1) included new RO DBT lessons[9] and standard DBT lessons.[17] RO DBT began soon after participants learned their treatment allocation. Though they continued to receive

ADM as prescribed, we strongly discouraged them from seeking additional psychotherapy during RO DBT.

The RO DBT developer (TRL) did not contribute to treatment delivery. He led the ten-day programme to train the 23 recruited therapists – eight in Dorset, ten in Hampshire and five in North Wales; and supervised them thereafter. Two were male, and ages ranged from 32 to 61 years. All therapists were standard-DBT therapists with a minimum of 3 years clinical experience. To be recruited, therapists had to submit three treatment tapes rated as adherent on the standard DBT Adherence Coding Scale – the recognised measure of adherence in standard DBT,[18] relevant also to RO DBT. All therapists attended weekly team meetings, to enhance treatment adherence and reduce therapist burnout. We maintained treatment fidelity across the trial by applying the standard DBT scale[18] to randomly sampled sessions; and feeding scores back to therapists and their site leaders.

Outcome measures[13]

Primary outcome

The primary outcome was the severity of depressive symptoms 12 months after randomisation, that is five months after the end of treatment. Trained assessors measured this by the 17-item Hamilton Rating Scale for Depression (HRSD).[15] Participants completed the HRSD at four points – baseline, and seven (immediately after treatment), 12 and 18 months after randomisation. We chose seven months rather than six, when most clients were still attending treatment sessions, to make RefraMED more comparable with other trials that assess response to treatment immediately after that treatment. We judged it most useful to evaluate RO DBT after a full year, when remission is most important, even though psychotherapies are usually evaluated immediately after the end of therapy.

Secondary outcomes

We assessed remission from HRSD scores and psychosocial functioning measured by the Longitudinal Interval Follow-up Evaluation – Range of Impaired Functioning Tool (LIFE-RIFT):[19] We defined full remission as HRSD score below 8 and LIFE-RIFT score below 13; and partial remission as HRSD score below 15 and LIFE-RIFT score below 13 points.

We measured suicidal ideation using the assessor-rated Modified Scale for Suicidal Ideation (MSSI);[20] total scores less than 9 show low ideation.

After three months, and the other four points, we collected data on potential mediating variables:

Acceptance & Action Questionnaire-II (AAQ-II)[21] measuring psychological inflexibility.

Emotional Approach Coping (EAC) scale[22] measuring Emotional Processing and Emotional Expression.

Patient Health Questionnaire-9 (PHQ-9)[23] measuring depression severity.

The 3-item Social Support Questionnaire (SSQ-3)[24] measuring responders' satisfaction with support.

At baseline we also recorded potential moderating variables, notably age, sex and marital status.

Sample size

Two pilot studies of an earlier but similar version of RO DBT for refractory depression showed effect sizes at end of treatment of 0.85[11] and 0.71.[10] We aimed to recruit enough analysable participants to yield 80% power to detect as statistically significant at the 5% level a standardised difference of 0.4 between RO DBT and TAU. We judged that clinicians and the UK National Institute of Health and Care Excellence (NICE) would consider this, equivalent to a mean difference of two points on the HRSD, to be 'clinically important'.

If there were no correlation between patients with the same therapist, a sample of 200 analysable participants would detect such a difference. As we aimed to collect analysable data from at least 83% of participants, we increased our target to 240. To focus on the mechanisms of RO DBT we randomised in the ratio 3:2 by allocating 144 'unclustered' patients to RO DBT and 96 to TAU. However RO DBT participants cluster by therapist. To allow for an intra-therapist correlation coefficient of 0.025 between HRSD scores, and an average cluster size of 11 participants for each of the expected 16 therapists, we increased the RO DBT sample size to 180, yielding the same statistical power as 144 unclustered participants. Thus we aimed to randomise 276 patients – 180 to RO DBT and 96 to TAU. We planned no interim analysis or stopping rule apart from that imposed by funding.

Randomisation and masking

Once we had confirmed eligibility and received informed consent through the form approved by Hampshire Research Ethics Committee, we randomised participants between treatments. We used three stratifying variables to ensure balance between groups – early or late onset of depression, HRSD score above or below 25, and presence or absence of PD. Within the RO DBT group, we randomised participants between available therapists so as to use as many as feasible of the treatment slots at each centre. To minimise risk of subversion, the Swansea Trials Unit used dynamic randomisation to make these allocations stochastically rather than deterministically.[25] They emailed the resulting allocations to the Trial Manager for dissemination to participants and study therapists, but not assessors.

To keep assessors blind to treatment allocations they: conducted assessments away from treatment centres; asked participants not to reveal their allocations during assessments; and avoided clinical notes after initial assessment. If an allocation were revealed, we reblinded by using another assessor for later assessments. If the allocation were revealed during assessment, we used the unblinded ratings; this happened 17 times at month seven, 12 times at month 12, but not at all at month 18.

Assessor Reliability[13]

A clinical psychologist experienced in administering SCID and HSRD in clinical trials (HO'M) trained assessors to administer all these outcome measures. The minimum requirement for RefraMED assessors was a degree in Psychology or closely related field. In reality all assessors had postgraduate qualifications, mainly MSc, DClinPsy or PhD. We discussed queries at weekly consensus meetings. We assessed inter-rater reliability for the HRSD at 9-month intervals across nine assessors. We analysed the reliability of individual items, more rigorous than analysing total scores. Across all measurements Krippendorff's alpha was 0.89 (95% CI from 0.86 to 0.92), implying "very good" to "near perfect" inter-rater reliability.[26]

Statistical methods

To create a dataset for analysis, we linked study datasets by randomisation codes. We validated this database by comparing information across sources, and by entering data twice. We scored all measures according to their published rules for imputing missing data.

We used the lmerTest package for the statistical language R to fit linear mixed effects models to primary and secondary outcomes over the 18 months from baseline.[27] Covariates included treatment allocated, treatment centre, baseline HRSD score, early or late onset of depression, and presence or absence of PD at baseline. We used a 3-level mixed-effects model to account for clustering of data by patient and therapist, avoiding the assumption that all therapists are equally effective. These mixed models are efficient and unbiased when data are missing at random. Without suitable auxiliary data we did not impute missing responses, for example by multiple imputation. However, when fewer than 10% of items were missing in a given scale, we imputed them by linear regression using the other scale items as covariates. For each outcome we estimated the main effects of treatment allocation and time, and the interaction between them; and compared groups at months 7, 12 and 18 by treatment allocated.

In assessing remission from depression, we used Button's criterion of 17.5% change in HRSD scores from baseline.[28] We refitted our mixed models using the Bayesian software Stan, and the associated R package 'brms'.[29] We assessed heterogeneity in therapist performance by intra-therapist correlation coefficients (ICCs), and simulated prognoses for future patients on RO DBT. Analyses post

hoc estimated posterior odds ratios[30] for hypotheses of interest. We derived remission rates from predictions based on continuous outcomes, so did not need to test for differences in these rates directly.

Serious adverse events

Our report to NIHR describes how we monitored Serious Adverse Events (SAEs).[13] The Chief Investigator reviewed these immediately, and reported them to the Data Monitoring & Ethics Committee (DMEC) every year, or immediately if there was Suspicion of an Unexpected Serious Adverse Reaction (SUSAR).

Ethical approval and conduct

Before recruiting patients we gained approval from the Hampshire Research Ethics Committee (National Research Ethics Service [NRES] reference 11/SC/0146) and the Research Governance Department of the University of Southampton, the Sponsor of this trial. We asked trial participants for consent on three occasions: before telephone screening; before baseline assessment; and before randomisation.

Patient and public inclusion

The NIHR Mental Health Research Network and 'Involve', the national advisory group on public engagement, helped us recruit service users – two to the Trial Steering Committee (TSC) and two to the Trial Management Group (TMG). These users contributed to patient information leaflets, managing the trial, and disseminating findings.

Data availability

All non-confidential data and syntax for analyses reported here are available in the online data supplement with doi: 10.5281/zenodo.1442883.

Role of the funding source

The Efficacy & Mechanism Evaluation (EME) Programme, funded by the MRC and administered by the National Institute for Health Research (NIHR), funded this trial by grant 09/150/12. NIHR monitored the trial and appointed the independent members of the TSC and DMEC. The grant holders were responsible for: study design; collecting, analysing, and interpreting data; writing this paper; and submitting for publication.

Results

→ *Insert Figure 1 here*

Recruitment

Figure 1 shows the flow of participants through the RefraMED trial: we randomised 250 eligible patients, 162 (65%) to RO DBT and 88 to control. Recruitment started in Dorset in March 2012 with an internal pilot; started in Hampshire and North Wales in September 2012; and continued until April 2015. Of the 250 randomised participants, 170 (68%) came from secondary care, 55 (22%) from primary care database searches, 19 (8%) from self-referral and six (2%) from other sources, notably private practitioners.[13]

Of 162 participants allocated to RO DBT plus TAU, 34 (21%) withdrew, including ten who attended no sessions, four who attended only one or two sessions; and ten prevented from continuing by work or family commitments. If participants did not attend a follow-up appointment after 7 or 12 months, we asked them to attend the next scheduled follow-up. For example, six of the fourteen RO DBT participants who did not attend their appointment after 7 months did attend their appointment after 12 months. This explains why we analysed more participants after 12 months (130) than after 7 (124).

Of 88 control participants, 22 (25%) withdrew, including nine because they resented allocation to TAU. Only one of those withdrawing from treatment agreed to stay in the study for follow-up interviews. So the proportion of participants analysed at month 12 did not differ significantly between groups (Chi squared = 0.71 with one degree of freedom; $p = 0.40$).

Baseline data – demographic and clinical

Of the full sample of 250, 164 (64%) were female; 138 (55%) were aged between 35 and 55; 232 (97% of 238 responders) were 'white'; 106 (42%) reported being in a stable relationship; and 82 (34% of 241 responders) had a University qualification. Ninety-two participants (37%) reported a first depressive episode before the age of 16; 179 (84% of 213 responders) were chronically rather than recurrently depressed; and 191 (82% of 234 responders) had previously received psychotherapy. Our sample also showed high comorbidity: 217 (87%) with at least one axis-I disorder, and 197 (79%) with at least one axis-II disorder; only nine (4%) had no psychiatric comorbidity.[13] Our report also confirms that our adaptive randomisation procedure was effective in balancing the characteristics of participants across groups; treatment centres were also generally comparable in participants' characteristics.[13]

Delivery of therapy

Of 23 therapists we trained, one did not provide therapy within RefraMED. The number of participants seen by the other therapists ranged from one to 17, with a mean of 6.9 and median of 7. The mean number of individual sessions attended by participants was 22.9 (SD 6.9; 79% of the 29 planned); while the mean number of group sessions attended was 19.9 (SD 7.6; 74% of the 27 planned).

Treatment fidelity

We rated 273 (9%) tapes; and adjudged 221 (81%) of these adherent with a score of 4.0 or more.

Primary outcome: depressive symptoms measured by HRSD

Table 1 and Figure 2 compare HRSD and the five secondary continuous outcome variables between groups across all follow-ups.

→ *INSERT Table 1 and Figure 2*

Depressive symptoms in both groups improved continuously from baseline to 18 months. By the end of therapy at seven months, RO DBT had substantially reduced depressive symptoms relative to TAU by 5.40 HRSD points (95% CI 0.94 to 9.85; effect size = 1.03; p = 0.02). RO DBT participants maintained their improvement in depressive symptoms at 12 and 18 months, but control participants improved more after 7 months, reducing the difference between-groups. The difference of 2.15 HRSD points at 12 months exceeded our prior target of 2 points but was not statistically significant (95% CI -2.28 to 6.58; effect size = 0.41; p = 0.29). At 18 months the difference fell to 1.69 HRSD points (95% CI -2.84 to 6.22; effect size = 0.32; p = 0.42). Thus our planned contrasts revealed a statistically significant difference between RO DBT and TAU after seven months, but not after 12 or 18 months. In contrast Bayesian analysis post hoc provided evidence that RO DBT was superior to TAU across all follow-ups: the posterior odds ratio was: 46 at 7 months – suggesting "strong" evidence;[30] and 5.5 and 4.7 at 12 and 18 months respectively – suggesting "positive" evidence.[30] Figure 3 displays the posterior probability that RO DBT achieved the range of effects on the x-axis. The likely causes of the trial's reduced power was the combination of under-recruitment and unexpectedly large therapist heterogeneity, yielding an ICC of 0.14, much larger than the ICC of 0.025 postulated in our power analysis. The most and least effective therapists, judged by clinical outcomes of their participants, differed by 2.6 HRSD points, equivalent to a standardised effect size of 0.43.

→ *INSERT Figure 3*

Remission rates

Using primary criteria, full remission rates were low in both groups: 1%, 8% and 7% for RO DBT and 0%, 0% and 1% in controls, at 7, 12 and 18 months respectively; and partial remission rates were higher for RO DBT – 23%, 26% and 33% at successive assessments – than in controls – 6%, 22% and 24% at successive assessments. Using the criterion of 'worthwhile' change, namely 17.5% reduction in symptoms from baseline,[28] remission rates were: 59%, 69% and 59% for RO DBT at 7, 12 and 18 months; and 27%, 48% and 41% in controls.

To help patients and clinicians interpret our findings, we simulated likely outcomes for new patients, estimating that, for every 100 new patients, 32 would achieve 17.5% improvement in symptom scores after 12 months by choosing RO DBT rather than TAU, while ten would deteriorate by the same criterion, and 58 would remain essentially unchanged.

Secondary continuous outcomes

RO DBT participants achieved significant gains in psychological flexibility and emotional coping relative to controls throughout the trial (Table 1 and Figure 2). Mean AAQ scores, measuring psychological *inflexibility* decreased over time, especially after RO DBT; the effect size increased from 0.49 (medium) after seven months to 0.72 (large) after 12, and 0.79 after 18. EAC scores, measuring emotional coping, increased after RO DBT, but not after TAU; the effect size increased from 0.32 (small) after seven months to 0.76 (large) after 12 months and 0.64 (also large) after 18.

However Table 1 shows no significant advantage for RO DBT in suicidal ideation or perceived social support. Mean MSSI suicidal ideation scores remained low throughout the trial for both groups; and although mean SSQ (perceived social support) scores increased after RO DBT, the difference between groups was never significant.

Serious adverse events

We received reports of 32 serious adverse events (SAEs) – four from the 88 participants allocated to TAU and 28 from the 162 participants allocated to RO DBT;[13] none of these led to withdrawal from the trial. In the RO DBT group, 21 participants experienced a single event; two experienced two events each; and one participant experienced three events. Thus 24 RO DBT participants experienced SAEs. We judged that all four events in the TAU group and 13 in the RO DBT group were "definitely not related" to the study intervention, for example a leg fracture and one death due to natural causes. We judged that another eight were "unlikely to be related", for example recurrent non-suicidal self-injury starting before the trial. Of the remaining eight SAEs, all from the intervention group, we judged that

five were “possibly related” to RO DBT, including two overdoses, and three were “probably related”, including a prevented suicide attempt. Nevertheless we classed none of those eight serious adverse reactions (SARs) as “suspected unexpected” requiring immediate reporting to the Research Ethics Committee.

Thus all eight serious adverse reactions judged as potentially related to RO DBT occurred in the intervention group (Fisher’s Exact Test; one-tailed $p = 0.004$). However trial assessors saw control participants only at the three follow-up interviews, so that SAE reporting relied on their volunteering relevant information. In contrast trial therapists saw RO DBT participants twice a week, and they completed diary cards reporting on suicidal ideation and self-harm. We tried to ameliorate reporting bias by asking participants’ GPs to report any SAEs they encountered. However no one outside the RefraMED team reported an SAE: control participants reported all four SAEs either during assessment or to the trial office. In the RO DBT group therapists reported 23 (82%) SAEs, and participants reported only five. We believe the imbalance was due to these gross differences in reporting opportunities and encouragement from therapists to use those opportunities.

As in both previous trials of RO DBT,[10,11] there were no suicides in this trial. For all these reasons the Data Monitoring Committee saw “no reason to suspect RO DBT had adverse effects on patients”.

Discussion

Principal findings

In participants with refractory depression, Radically Open Dialectical Behaviour Therapy (RO DBT) was not statistically superior to treatment as usual (TAU) on the Hamilton Rating Scale for Depression (HRSD) at our primary endpoint of 12 months after randomisation, despite achieving the target moderate effect size of 0.40. However it was substantially better than TAU immediately after treatment, with an effect size of 1.03, much larger than reported by previous trials of psychotherapy for refractory depression.[4] The later fall in effect size stems from rapid improvement during RO DBT, and initially-slow but accelerating improvement during TAU. Bayesian analysis post hoc generated “positive” evidence of the superiority of RO DBT over 18 months; and suggests that 22% (viz 32% less 10%) more patients would experience “worthwhile change” at 12 months by choosing RO DBT over TAU.

Psychological outcomes

RO DBT aims to help individuals with rigid psychological and interpersonal styles learn flexibility. Reassuringly RO DBT participants reported significantly better psychological flexibility than the controls throughout the 18 months of follow up. RO DBT also aims to encourage appropriate

expression of emotion to avoid isolation. Again RO DBT participants reported significantly better emotional processing throughout these 18 months. Both findings suggest that participants continue to use and improve their RO DBT skills. However there was no significant advantage for RO DBT in suicidal ideation or perceived social support. Throughout the trial suicidal ideation was low in both groups; though this decreased further over time in both groups, the difference was never significant. This finding was probably due to both groups continuing to receive treatment and support either from the trial or from the National Health Service. Though social support scores increased after RO DBT and decreased after TAU, the difference between groups was never significant.

Strengths

RO DBT is the first treatment known to us to target deficits in social signalling as the main problem underlying overcontrolled emotional loneliness. We designed RefraMED as a hybrid between a Phase 2 efficacy trial and a Phase 3 effectiveness trial. The former yielded strengths in: the consistency of both intervention and assessment; allocating therapists to patients at random rather than allocating difficult patients to the most skilled therapists.[13] The latter yielded strengths in: minimising exclusion criteria thus including a wide range of patients with depression and maximising generalisability; enabling the treatment developer to train therapists rather than provide therapy; and facilitating cost-effectiveness analysis. [13]

Limitations

Despite our best efforts to recruit 276 participants, and analyse 229 (83%) of them, we recruited only 250 and analysed only 190 (76%); we also encountered unexpectedly large therapist heterogeneity. Despite achieving our target effect size at 12 months, the resulting loss of power meant our pre-planned analyses did not achieve statistical significance beyond month 7.

Interpretation

RefraMED was the first multi-centre trial of RO DBT. Though RO DBT greatly improved depressive symptoms by the end of treatment, our planned analyses were not statistically significant thereafter. Bayesian analysis post hoc suggests that RO DBT was superior to TAU throughout, but this effect was not clinically significant after month 7.

RO DBT does not label depression as the primary problem. Instead it targets emotional overcontrol – a maladaptive personality style known to predict the development of chronic internalising disorders like refractory depression. Overcontrolled PDs, including obsessive-compulsive PD, are more common than undercontrolled PDs; and patients' innate capacity to tolerate distress, delay gratification, and avoid public displays of emotion make their problems less noticeable, and them less likely to seek mental health treatment. Hence it is reassuring that RO DBT improved psychological flexibility and

emotional processing over 18 months in a highly symptomatic population, most of whom suffer several mental health problems.

Implications for future research

Given the recurring nature of depression, and RO DBT's aim of changing maladaptive personality, future studies should investigate long-term differences between RO DBT and other treatments. The high proportion of comorbid disorders in RefraMED (96%), and the evidence that patients with complex mental disorders do not benefit much from short-term psychotherapy,[31] support this proposal. RO DBT's trans-diagnostic approach justifies testing RO DBT across a range of conditions, including overcontrolled personality disorders (Clusters A and C), anxiety disorders, and eating disorders.[32]

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Authors' contributions

All authors contributed to writing and reviewing this paper.

- Sarah Byford (Professor of Health Economics) contributed to the design of the study and managed the economic evaluation.
- Rampaul Chamba (Patient and Public Representative) contributed to managing the study and to patient and public engagement.
- Paul Clarke (Professor of Social Statistics) was responsible for the design and analysis of the instrumental variable analysis.
- Susan Clarke (Visiting Professor, Consultant Clinical Psychologist; Principal Investigator and Clinical Lead for Dorset until 2014) contributed to the design of the study and clinical methods, supervised therapists and research assistants, and delivered therapy.

- Roelie Hempel (Senior Research Fellow) contributed to the design of the study and acted as Trial Manager throughout the study.
- David Kingdon (Professor of Mental Health Care Delivery; Site Principal Investigator) contributed to the design of the study, and supervised research assistants.
- Thomas Lynch (Emeritus Professor of Clinical Psychology; Chief Investigator) developed Radically Open Dialectical Behaviour Therapy and contributed to all aspects of the design and management of the study.
- Heather O'Mahen (Senior Lecturer in Clinical Psychology; Assessment Lead) trained clinical assessors, provided clinical supervision to research assistants, supported follow-up assessments, managed the study, and conducted reliability analyses.
- Bob Remington (Emeritus Professor in Psychology) contributed to writing the grant proposal and managing the study.
- Sophie Rushbrook (Consultant Clinical Psychologist, Clinical Lead for Dorset site) supervised therapists and delivered therapy.
- Ian Russell (Professor of Clinical Trials) was trial methodologist and contributed to the design and management of the study.
- James Shearer (Lecturer in Health Economics) undertook economic analyses.
- Maggie Stanton (Consultant Clinical Psychologist; Clinical Lead for Hampshire site) supervised therapists and delivered therapy.
- Michaela Swales (Consultant Clinical Psychologist; Reader in Clinical Psychology; Site Principal Investigator for North Wales site) supervised therapists and research assistants, and delivered therapy.
- Alan Watkins (Associate Professor of e-Trials Research) designed and managed the randomisation service, drafted the statistical analysis plan and reviewed its implementation, and contributed to validating data.
- Ben Whalley (Lecturer in Psychology) contributed to the design of the study and writing the grant proposal, and undertook data analyses.

Authors' competing interests

- Roelie Hempel is co-owner and director of Radically Open Ltd, the RO DBT training and dissemination company.
- David Kingdon reports grants outside the submitted work from NIHR.
- Thomas Lynch receives royalties from New Harbinger Publishing for sales of RO DBT treatment manuals, speaking fees from Radically Open Ltd, and a grant outside the submitted work from the Medical Research Council. He was co-director of Radically Open Ltd between

November 2014 and May 2015 and is married to Erica Smith-Lynch, the principal shareholder and one of two current directors of Radically Open Ltd.

- Heather O'Mahen reports personal fees from the Charlie Waller Institute and Improving Access to Psychological Therapy.
- Sophie Rushbrook provides RO DBT supervision through S C Rushbrook Ltd.
- Ian Russell reports grants outside the submitted work from NIHR and Health & Care Research Wales.
- Maggie Stanton reports personal fees from British Isles DBT Training, Stanton Psychological Services Ltd, and Taylor & Francis Ltd.
- Michaela Swales reports personal fees from British Isles DBT Training, Guilford Press, Oxford University Press, and Taylor & Francis Ltd.
- Ben Whalley was co-director of Radically Open Ltd between November 2014 and February 2015.

The remaining six authors declare no competing interests: Sarah Byford, Rampaul Chamba, Paul Clarke, Susan Clarke, Bob Remington, James Shearer and Alan Watkins

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	P1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	P2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P3
	2b	Specific objectives or hypotheses	P3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pp4 & 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	P4
Participants	4a	Eligibility criteria for participants	P4
	4b	Settings and locations where the data were collected	P4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pp4 & 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pp5 & 6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	P6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	P6

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P6
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	P7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P9, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	P9, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P9
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Description p9 – table can be added as supplemental

			material if requested
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig 1 & p2 & p7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pp10-11, Table 1, Figures 2 & 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	P11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Pp11 & 12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pp12 & 13
Other information			
Registration	23	Registration number and name of trial registry	P1
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 11
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Refractory depression - Mechanisms & Efficacy of Radically Open Dialectical Behaviour Therapy (RefraMED): findings of randomised trial on benefits and harms

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Keywords: Refractory depression, Treatment resistant depression, Chronic depression; Personality disorder; Radically Open Dialectical Behaviour Therapy (RO DBT), Randomised controlled trial; Hamilton Depression Rating Scale; Serious Adverse Events.

Trial registration: International Standard Randomised Controlled Trial Number (ISRCTN) 85784627.

[Manuscript comprises 4211 words]

Abstract

Background

Depressed individuals often do not respond to medication or psychotherapy. Radically Open Dialectical Behaviour Therapy (RO DBT) is a new treatment targeting overcontrolled personality, common in refractory depression.

Aim

To compare RO DBT plus treatment as usual (TAU) for refractory depression with TAU alone.

Methods

RO DBT comprised 29 therapy sessions and 27 skills classes over six months. Our completed randomised trial evaluated RO DBT for refractory depression over 18 months in 3 British secondary care centres. Of 250 adult participants, we randomised 162 (65%) to RO DBT. The primary outcome was the Hamilton Rating Scale for Depression (HRSD), assessed blind and analysed by treatment allocated.

Results

After seven months, immediately following therapy, RO DBT had reduced depressive symptoms by 5.40 HRSD points relative to TAU [95% confidence interval (CI) +0.94 to +9.85]. After 12 months (primary end point), the difference of 2.15 HRSD points in favour of RO DBT was not significant (95% CI –2.28 to +6.59); nor was that of 1.69 HRSD points at 18 months (95% CI –2.84 to +6.22). Throughout RO DBT participants reported significantly better psychological flexibility and emotional coping than controls. However they reported eight possible Serious Adverse Reactions (SARs) compared with none by controls.

Conclusions

RO DBT participants reported significantly lower HRSD scores than controls after 7 months, but not thereafter. The imbalance in SARs was probably due to controls' limited opportunities to report these.

Declaration of interest

Six of the 16 authors have received royalties or fees for RO DBT.

[Abstract comprises 249 words cf limit of 250]

Introduction

Major depressive disorder is a recurrent, disabling condition causing substantial impairment in psychosocial functioning and quality of life.[1] Only one third of individuals respond fully to antidepressant medication (ADM) and only half to psychological treatment.[2] Recently treatments developed for refractory depression have achieved small to moderate effect sizes.[3] Treatments are seldom effective owing to co-morbidity, especially personality disorders (PD).[4] About half of unipolar depressed patients meet criteria for comorbid PD, with higher rates among those with chronic or treatment-resistant depression.[4,5] The commonest PDs among depressed individuals show excessive inhibitory control or overcontrol, including Cluster A (paranoid PD) and Cluster C (obsessive-compulsive and avoidant PD) — those that respond poorly to PD treatments.[6,7] The core characteristics of overcontrolled personality disorders are: cognitive and behavioural rigidity; strong desire to control one's environment; restrained emotional expression; limited social interaction; and problems with close relationships due to aloofness, distancing, mistrust and fear of rejection or criticism.[8] Radically Open Dialectical Behaviour Therapy (RO DBT), a novel trans-diagnostic psychotherapy, aims to address this rigid coping style.[9] Earlier versions of RO DBT showed promise in two pilot randomised trials of patients with refractory depression and comorbid PD.[10,11] This trial aimed to assess the efficacy of RO DBT for refractory depression,[12] and whether RO DBT causes identifiable harms.[13]

Methods

Design

RefraMED was a three-centre parallel-group randomised trial which compared RO DBT plus treatment as usual (TAU) with TAU alone. After an internal pilot in one centre, shortage of therapists reduced recruitment below the target rate. So we extended our recruitment period from 24 months to 32; and followed the last 27 participants for 12 months (the primary endpoint) rather than 18.

Participants

Patients were eligible for the RefraMED trial if they: were 18 years or older; had an IQ more than 70; spoke English well enough to participate; had a current diagnosis of major depressive disorder in SCID-I;[14] were suffering from refractory depression, defined as chronic depression lasting at least two years or recurrent depression with at least two previous episodes; had a Hamilton Rating Scale for Depression (HRSD)[15] score of at least 15; and had not responded to an adequate dose of ADM for at least six weeks in their current episode. Since we had developed RO DBT specifically for overcontrol, we excluded patients who: met criteria for bipolar disorder, psychosis, or dramatic-erratic PD in SCID-II;[16] had a primary diagnosis of substance dependence; or were currently receiving or waiting for standard DBT. We recruited these patients in three NHS secondary care centres already delivering standard DBT for dramatic-erratic PD – Dorset and Hampshire in England, and North Wales.[13]

Interventions

Treatment as usual (TAU)

As all three centres seek to deliver best practice, that was the natural control treatment. All participants received TAU, including prescribed ADM or psychotherapy. [13] Control participants could also access any treatment from NHS or privately, except standard DBT. At each follow-up assessors asked participants to report their ADM and adherence to it, and psychotherapy accessed since their previous assessment or in the six months before their baseline assessment.

Radically Open Dialectical Behaviour Therapy (RO DBT)

RO DBT is a trans-diagnostic therapy designed to address a spectrum of disorders that are difficult to treat, notably chronic depression.[9] It differs from other psychotherapies, notably by encouraging social bonding through emotional expression. At the time of the trial RO DBT comprised 29 weekly individual therapy sessions each lasting an hour and 27 skills training classes each lasting 2.5 hours. [9,12] The RO DBT lesson plan (Table S1) included new RO DBT lessons[9] and standard DBT lessons.[17] RO DBT began soon after participants learned their treatment allocation. Though they continued to receive

ADM as prescribed, we strongly discouraged them from seeking additional psychotherapy during RO DBT.

The RO DBT developer (TRL) did not contribute to treatment delivery. He led the ten-day programme to train the 23 recruited therapists – eight in Dorset, ten in Hampshire and five in North Wales; and supervised them thereafter. Two were male, and ages ranged from 32 to 61 years. All therapists were standard-DBT therapists with a minimum of 3 years clinical experience. To be recruited, therapists had to submit three treatment tapes rated as adherent on the standard DBT Adherence Coding Scale – the recognised measure of adherence in standard DBT,[18] relevant also to RO DBT. All therapists attended weekly team meetings, to enhance treatment adherence and reduce therapist burnout. We maintained treatment fidelity across the trial by applying the standard DBT scale[18] to randomly sampled sessions; and feeding scores back to therapists and their site leaders.

Outcome measures[13]

Primary outcome

The primary outcome was the severity of depressive symptoms 12 months after randomisation, that is five months after the end of treatment. Trained assessors measured this by the 17-item Hamilton Rating Scale for Depression (HRSD).[15] Though Participants completed the HRSD at four points – baseline, and seven (immediately after treatment), 12 and 18 months after randomisation. We chose seven months rather than six, when most clients were still attending treatment sessions, to make RefraMED more comparable with other trials that assess response to treatment immediately after that treatment. We judged it most useful to evaluate RO DBT after a full year, when remission is most important, even though psychotherapies are usually evaluated immediately after the end of therapy.

Secondary outcomes

We assessed remission from HRSD scores and psychosocial functioning measured by the Longitudinal Interval Follow-up Evaluation – Range of Impaired Functioning Tool (LIFE-RIFT):[19] We defined full remission as HRSD score below 8 and LIFE-RIFT score below 13; and partial remission as HRSD score below 15 and LIFE-RIFT score below 13 points.

We measured suicidal ideation using the assessor-rated Modified Scale for Suicidal Ideation (MSSI);[20] total scores less than 9 show low ideation.

After three months, and the other four points, we collected data on potential mediating variables:

Acceptance & Action Questionnaire-II (AAQ-II)[21] measuring psychological inflexibility.

Emotional Approach Coping (EAC) scale[22] measuring Emotional Processing and Emotional Expression.

Patient Health Questionnaire-9 (PHQ-9)[23] measuring depression severity.

The 3-item Social Support Questionnaire (SSQ-3)[24] measuring responders' satisfaction with support.

At baseline we also recorded potential moderating variables, notably age, sex and marital status.

Sample size

Two pilot studies of an earlier but similar version of RO DBT for refractory depression showed effect sizes at end of treatment of 0.85[11] and 0.71.[10] We aimed to recruit enough analysable participants to yield 80% power to detect as statistically significant at the 5% level a standardised difference of 0.4 between RO DBT and TAU. We judged that clinicians and the UK National Institute of Health and Care Excellence (NICE) would consider this, equivalent to a mean difference of two points on the HRSD, to be 'clinically important'.

If there were no correlation between patients with the same therapist, a sample of 200 analysable participants would detect such a difference. As we aimed to collect analysable data from at least 83% of participants, we increased our target to 240. To focus on the mechanisms of RO DBT we randomised in the ratio 3:2 by allocating 144 'unclustered' patients to RO DBT and 96 to TAU. However RO DBT participants cluster by therapist. To allow for an intra-therapist correlation coefficient of 0.025 between HRSD scores, and an average cluster size of 11 participants for each of the expected 16 therapists, we increased the RO DBT sample size to 180, yielding the same statistical power as 144 unclustered participants. Thus we aimed to randomise 276 patients – 180 to RO DBT and 96 to TAU. We planned no interim analysis or stopping rule apart from that imposed by funding.

Randomisation and masking

Once we had confirmed eligibility and received informed consent through the form approved by Hampshire Research Ethics Committee, we randomised participants between treatments. We used three stratifying variables to ensure balance between groups – early or late onset of depression, HRSD score above or below 25, and presence or absence of PD. Within the RO DBT group, we randomised participants between available therapists so as to use as many as feasible of the treatment slots at each centre. To minimise risk of subversion, the Swansea Trials Unit used dynamic randomisation to make these allocations stochastically rather than deterministically.[25] They emailed the resulting allocations to the Trial Manager for dissemination to participants and study therapists, but not assessors.

To keep assessors blind to treatment allocations they: conducted assessments away from treatment centres; asked participants not to reveal their allocations during assessments; and avoided clinical notes after initial assessment. If an allocation were revealed, we reblinded by using another assessor for later assessments. If the allocation were revealed during assessment, we used the unblinded ratings; this happened 17 times at month seven, 12 times at month 12, but not at all at month 18.

Assessor Reliability[13]

A clinical psychologist experienced in administering SCID and HSRD in clinical trials (HO'M) trained assessors to administer all these outcome measures. The minimum requirement for RefraMED assessors was a degree in Psychology or closely related field. In reality all assessors had postgraduate qualifications, mainly MSc, DClinPsy or PhD. We discussed queries at weekly consensus meetings. We assessed inter-rater reliability for the HRSD at 9-month intervals across nine assessors. We analysed the reliability of individual items, more rigorous than analysing total scores. Across all measurements Krippendorff's alpha was 0.89 (95% CI from 0.86 to 0.92), implying "very good" to "near perfect" inter-rater reliability.[26]

Statistical methods

To create a dataset for analysis, we linked study datasets by randomisation codes. We validated this database by comparing information across sources, and by entering data twice. We scored all measures according to their published rules for imputing missing data.

We used the lmerTest package for the statistical language R to fit linear mixed effects models to primary and secondary outcomes over the 18 months from baseline.[27] Covariates included treatment allocated, treatment centre, baseline HRSD score, early or late onset of depression, and presence or absence of PD at baseline. We used a 3-level mixed-effects model to account for clustering of data by patient and therapist, avoiding the assumption that all therapists are equally effective. These mixed models are efficient and unbiased when data are missing at random. Without suitable auxiliary data we did not impute missing responses, for example by multiple imputation. However, when fewer than 10% of items were missing in a given scale, we imputed them by linear regression using the other scale items as covariates. For each outcome we estimated the main effects of treatment allocation and time, and the interaction between them; and compared groups at months 7, 12 and 18 by treatment allocated.

In assessing remission from depression, we used Button's criterion of a 17.5% change in HRSD scores from baseline.[28] We refitted our mixed models using the Bayesian software Stan, and the associated R package 'brms'.[29] We assessed heterogeneity in therapist performance by intra-therapist correlation coefficients (ICCs), and simulated prognoses for future patients on RO DBT. Analyses post

hoc estimated posterior odds ratios[30] for hypotheses of interest. We derived remission rates from predictions based on continuous outcomes, so did not need to test for differences in these rates directly.

Serious adverse events

Our report to NIHR describes how we monitored Serious Adverse Events (SAEs).[13] The Chief Investigator reviewed these immediately, and reported them to the Data Monitoring & Ethics Committee (DMEC) every year, or immediately if there was Suspicion of an Unexpected Serious Adverse Reaction (SUSAR).

Ethical approval and conduct

Before recruiting patients we gained approval from the Hampshire Research Ethics Committee (National Research Ethics Service [NRES] reference 11/SC/0146) and the Research Governance Department of the University of Southampton, the Sponsor of this trial. We asked trial participants for consent on three occasions: before telephone screening; before baseline assessment; and before randomisation.

Patient and public inclusion

The NIHR Mental Health Research Network and 'Involve', the national advisory group on public engagement, helped us recruit service users – two to the Trial Steering Committee (TSC) and two to the Trial Management Group (TMG). These users contributed to patient information leaflets, managing the trial, and disseminating findings.

Data availability

All non-confidential data and syntax for analyses reported here are available in the online data supplement with doi: 10.5281/zenodo.1442883.

Role of the funding source

The Efficacy & Mechanism Evaluation (EME) Programme, funded by the MRC and administered by the National Institute for Health Research (NIHR), funded this trial by grant 09/150/12. NIHR monitored the trial and appointed the independent members of the TSC and DMEC. The grant holders were responsible for: study design; collecting, analysing, and interpreting data; writing this paper; and submitting for publication.

Results

→ *Insert Figure 1 here*

Recruitment

Figure 1 shows the flow of participants through the RefraMED trial: we randomised 250 eligible patients, 162 (65%) to RO DBT and 88 to control. Recruitment started in Dorset in March 2012 with an internal pilot; started in Hampshire and North Wales in September 2012; and continued until April 2015. Of the 250 randomised participants, 170 (68%) came from secondary care, 55 (22%) from primary care database searches, 19 (8%) from self-referral and six (2%) from other sources, notably private practitioners.[13]

Of 162 participants allocated to RO DBT plus TAU, 34 (21%) withdrew, including ten who attended no sessions, four who attended only one or two sessions; and ten prevented from continuing by work or family commitments. If participants did not attend a follow-up appointment after 7 or 12 months, we asked them to attend the next scheduled follow-up. For example, six of the fourteen RO DBT participants who did not attend their appointment after 7 months did attend their appointment after 12 months. This explains why we analysed more participants after 12 months (130) than after 7 (124).

Of 88 control participants, 22 (25%) withdrew, including nine because they resented allocation to TAU. Only one of those withdrawing from treatment agreed to stay in the study for follow-up interviews. So the proportion of participants analysed at month 12 did not differ significantly between groups (Chi squared = 0.71 with one degree of freedom; $p = 0.40$).

Baseline data – demographic and clinical

Of the full sample of 250, 164 (64%) were female; 138 (55%) were aged between 35 and 55; 232 (97% of 238 responders) were 'white'; 106 (42%) reported being in a stable relationship; and 82 (34% of 241 responders) had a University qualification. Ninety-two participants (37%) reported a first depressive episode before the age of 16; 179 (84% of 213 responders) were chronically rather than recurrently depressed; and 191 (82% of 234 responders) had previously received psychotherapy. Our sample also showed high comorbidity: 217 (87%) with at least one axis-I disorder, and 197 (79%) with at least one axis-II disorder; only nine (4%) had no psychiatric comorbidity.[13] Our report also confirms that our adaptive randomisation procedure was effective in balancing the characteristics of participants across groups; treatment centres were also generally comparable in participants' characteristics.[13]

Delivery of therapy

Of 23 therapists we trained, one did not provide therapy within RefraMED. The number of participants seen by the other therapists ranged from one to 17, with a mean of 6.9 and median of 7. The mean number of individual sessions attended by participants was 22.9 (SD 6.9; 79% of the 29 planned); while the mean number of group sessions attended was 19.9 (SD 7.6; 74% of the 27 planned).

Treatment fidelity

We rated 273 (9%) tapes; and adjudged 221 (81%) of these adherent with a score of 4.0 or more. Krippendorff's alpha was 0.89 (95% CI from 0.86 to 0.92), suggesting "very good" consistency between those rating fidelity.

Primary outcome: depressive symptoms measured by HRSD

Table 1 and Figure 2 compare HRSD and the five secondary continuous outcome variables between groups across all follow-ups.

→ *INSERT Table 1 and Figure 2*

Depressive symptoms in both groups improved continuously from baseline to 18 months. By the end of therapy at seven months, RO DBT had substantially reduced depressive symptoms relative to TAU by 5.40 HRSD points (95% CI 0.94 to 9.85; effect size = 1.03; p = 0.02). RO DBT participants maintained their improvement in depressive symptoms at 12 and 18 months, but control participants improved more after 7 months, reducing the difference between-groups. The difference of 2.15 HRSD points at 12 months exceeded our prior target of 2 points but was not statistically significant (95% CI -2.28 to 6.58; effect size = 0.41; p = 0.29). At 18 months the difference fell to 1.69 HRSD points (95% CI -2.84 to 6.22; effect size = 0.32; p = 0.42). Thus our planned contrasts revealed a statistically significant difference between RO DBT and TAU after seven months, but not after 12 or 18 months. In contrast Bayesian analysis post hoc provided evidence that RO DBT was superior to TAU across all follow-ups: the posterior odds ratio was: 46 at 7 months – suggesting "strong" evidence;[30] and 5.5 and 4.7 at 12 and 18 months respectively – suggesting "positive" evidence.[30] Figure 3 displays the posterior probability that RO DBT achieved the range of effects on the x-axis. The likely causes of the trial's reduced power was the combination of under-recruitment and unexpectedly large therapist heterogeneity, yielding an ICC of 0.14, much larger than the ICC of 0.025 postulated in our power analysis. The most and least effective therapists, judged by clinical outcomes of their participants, differed by 2.6 HRSD points, equivalent to a standardised effect size of 0.43.

→ *INSERT Figure 3*

Remission rates

Using primary criteria, full remission rates were low in both groups: 1%, 8% and 7% for RO DBT and 0%, 0% and 1% in controls, at 7, 12 and 18 months respectively; and partial remission rates were higher for RO DBT – 23%, 26% and 33% at successive assessments – than in controls – 6%, 22% and 24% at successive assessments. Using the criterion of 'worthwhile' change, namely 17.5% reduction in symptoms from baseline,[28] remission rates were: 59%, 69% and 59% for RO DBT at 7, 12 and 18 months; and 27%, 48% and 41% in controls.

To help patients and clinicians interpret our findings, we simulated likely outcomes for new patients, estimating that, for every 100 new patients, 32 would achieve 17.5% improvement in symptom scores after 12 months by choosing RO DBT rather than TAU, while ten would deteriorate by the same criterion, and 58 would remain essentially unchanged.

Secondary continuous outcomes

RO DBT participants achieved significant gains in psychological flexibility and emotional coping relative to controls throughout the trial (Table 1 and Figure 2). Mean AAQ scores, measuring psychological *inflexibility* decreased over time, especially after RO DBT; the effect size increased from 0.49 (medium) after seven months to 0.72 (large) after 12, and 0.79 after 18. EAC scores, measuring emotional coping, increased after RO DBT, but not after TAU; the effect size increased from 0.32 (small) after seven months to 0.76 (large) after 12 months and 0.64 (also large) after 18.

However Table 1 shows no significant advantage for RO DBT in functional impairment, suicidal ideation or perceived social support. Mean MSSI suicidal ideation scores remained low throughout the trial for both groups; and although mean SSQ (perceived social support) scores increased after RO DBT, the difference between groups was never significant.

Serious adverse events

We received reports of 32 serious adverse events (SAEs) – four from the 88 participants allocated to TAU and 28 from the 162 participants allocated to RO DBT;[13] none of these led to withdrawal from the trial. In the RO DBT group, 21 participants experienced a single event; two experienced two events each; and one participant experienced three events. Thus 24 RO DBT participants experienced SAEs. We judged that all four events in the TAU group and 13 in the RO DBT group were "definitely not related" to the study intervention, for example a leg fracture and one death due to natural causes. We

judged that another eight were "unlikely to be related", for example recurrent non-suicidal self-injury starting before the trial. Of the remaining eight SAEs, all from the intervention group, we judged that five were "possibly related" to RO DBT, including two overdoses, and three were "probably related", including a prevented suicide attempt. Nevertheless we classed none of those eight serious adverse reactions (SARs) as "suspected unexpected" requiring immediate reporting to the Research Ethics Committee.

Thus all eight serious adverse reactions judged as potentially related to RO DBT occurred in the intervention group (Fisher's Exact Test; one-tailed $p = 0.004$). However trial assessors saw control participants only at the three follow-up interviews, so that SAE reporting relied on their volunteering relevant information. In contrast trial therapists saw RO DBT participants twice a week, and they completed diary cards reporting on suicidal ideation and self-harm. We tried to ameliorate reporting bias by asking participants' GPs to report any SAEs they encountered. However no one outside the RefraMED team reported an SAE: control participants reported all four SAEs either during assessment or to the trial office. In the RO DBT group therapists reported 23 (82%) SAEs, and participants reported only five. We believe the imbalance was due to these gross differences in reporting opportunities and encouragement from therapists to use those opportunities.

As in both previous trials of RO DBT,[10,11] there were no suicides in this trial. For all these reasons the Data Monitoring Committee saw "no reason to suspect RO DBT had adverse effects on patients".

Discussion

Principal findings

In participants with refractory depression, Radically Open Dialectical Behaviour Therapy (RO DBT) was not statistically superior to treatment as usual (TAU) on the Hamilton Rating Scale for Depression (HRSD) at our primary endpoint of 12 months after randomisation, despite achieving the target moderate effect size of 0.40. However it was substantially better than TAU immediately after treatment, with an effect size of 1.03, much larger than reported by previous trials of psychotherapy for refractory depression.[4] The later fall in effect size stems from rapid improvement during RO DBT, and initially-slow but accelerating improvement during TAU. Bayesian analysis post hoc generated "positive" evidence of the superiority of RO DBT over 18 months; and suggests that 22% (viz 32% less 10%) more patients would experience "worthwhile change" at 12 months by choosing RO DBT over TAU.

Psychological outcomes

RO DBT aims to help individuals with rigid psychological and interpersonal styles learn flexibility. Reassuringly RO DBT participants reported significantly better psychological flexibility than the controls throughout the 18 months of follow up. RO DBT also aims to encourage appropriate expression of emotion to avoid isolation. Again RO DBT participants reported significantly better emotional processing throughout these 18 months. Both findings suggest that participants continue to use and improve their RO DBT skills. However there was no significant advantage for RO DBT in functional impairment, suicidal ideation or perceived social support. Throughout the trial suicidal ideation was low in both groups; though this decreased further over time in both groups, the difference was never significant. This finding was probably due to both groups continuing to receive treatment and support either from the trial or from the National Health Service. Though social support scores increased after RO DBT and decreased after TAU, the difference between groups was never significant.

Strengths

RO DBT is the first treatment known to us to target deficits in social signalling as the main problem underlying overcontrolled emotional loneliness. We designed RefraMED as a hybrid between a Phase 2 efficacy trial and a Phase 3 effectiveness trial. The former yielded strengths in: the consistency of both intervention and assessment; allocating therapists to patients at random rather than allocating difficult patients to the most skilled therapists.[13] The latter yielded strengths in: minimising exclusion criteria thus including a wide range of patients with depression and maximising generalisability; enabling the treatment developer to train therapists rather than provide therapy; and facilitating cost-effectiveness analysis. [13]

Limitations

Despite our best efforts to recruit 276 participants, and analyse 229 (83%) of them, we recruited only 250 and analysed only 190 (76%); we also encountered unexpectedly large therapist heterogeneity. Despite achieving our target effect size at 12 months, the resulting loss of power meant our pre-planned analyses did not achieve statistical significance beyond month 7.

Interpretation

RefraMED was the first multi-centre trial of RO DBT. Though RO DBT greatly improved depressive symptoms by the end of treatment, our planned analyses were not statistically significant thereafter. Bayesian analysis post hoc suggests that RO DBT was superior to TAU throughout, but this effect was not clinically significant after month 7.

RO DBT does not label depression as the primary problem. Instead it targets emotional overcontrol – a maladaptive personality style known to predict the development of chronic internalising disorders like refractory depression. Overcontrolled PDs, including obsessive-compulsive PD, are more common than undercontrolled PDs; and patients' innate capacity to tolerate distress, delay gratification, and avoid public displays of emotion make their problems less noticeable, and them less likely to seek mental health treatment. Hence it is reassuring that RO DBT improved psychological flexibility and emotional processing over 18 months in a highly symptomatic population, most of whom suffer several mental health problems.

Implications for future research

Given the recurring nature of depression, and RO DBT's aim of changing maladaptive personality, future studies should investigate long-term differences between RO DBT and other treatments. The high proportion of comorbid disorders in RefraMED (96%), and the evidence that patients with complex mental disorders do not benefit much from short-term psychotherapy,[31] support this proposal. RO DBT's trans-diagnostic approach justifies testing RO DBT across a range of conditions, including overcontrolled personality disorders (Clusters A and C), anxiety disorders, and eating disorders.[32]

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Authors' contributions

All authors contributed to writing and reviewing this paper.

- Sarah Byford (Professor of Health Economics) contributed to the design of the study and managed the economic evaluation.
- Rampaul Chamba (Patient and Public Representative) contributed to managing the study and to patient and public engagement.
- Paul Clarke (Professor of Social Statistics) was responsible for the design and analysis of the instrumental variable analysis.
- Susan Clarke (Visiting Professor, Consultant Clinical Psychologist; Principal Investigator and Clinical Lead for Dorset until 2014) contributed to the design of the study and clinical methods, supervised therapists and research assistants, and delivered therapy.

- Roelie Hempel (Senior Research Fellow) contributed to the design of the study and acted as Trial Manager throughout the study.
- David Kingdon (Professor of Mental Health Care Delivery; Site Principal Investigator) contributed to the design of the study, and supervised research assistants.
- Thomas Lynch (Emeritus Professor of Clinical Psychology; Chief Investigator) developed Radically Open Dialectical Behaviour Therapy and contributed to all aspects of the design and management of the study.
- Heather O'Mahen (Senior Lecturer in Clinical Psychology; Assessment Lead) trained clinical assessors, provided clinical supervision to research assistants, supported follow-up assessments, managed the study, and conducted reliability analyses.
- Bob Remington (Emeritus Professor in Psychology) contributed to writing the grant proposal and managing the study.
- Sophie Rushbrook (Consultant Clinical Psychologist, Clinical Lead for Dorset site) supervised therapists and delivered therapy.
- Ian Russell (Professor of Clinical Trials) was trial methodologist and contributed to the design and management of the study.
- James Shearer (Lecturer in Health Economics) undertook economic analyses.
- Maggie Stanton (Consultant Clinical Psychologist; Clinical Lead for Hampshire site) supervised therapists and delivered therapy.
- Michaela Swales (Consultant Clinical Psychologist; Reader in Clinical Psychology; Site Principal Investigator for North Wales site) supervised therapists and research assistants, and delivered therapy.
- Alan Watkins (Associate Professor of e-Trials Research) designed and managed the randomisation service, drafted the statistical analysis plan and reviewed its implementation, and contributed to validating data.
- Ben Whalley (Lecturer in Psychology) contributed to the design of the study and writing the grant proposal, and undertook data analyses.

Authors' competing interests

- Roelie Hempel is co-owner and director of Radically Open Ltd, the RO DBT training and dissemination company.
- David Kingdon reports grants outside the submitted work from NIHR.
- Thomas Lynch receives royalties from New Harbinger Publishing for sales of RO DBT treatment manuals, speaking fees from Radically Open Ltd, and a grant outside the submitted work from the Medical Research Council. He was co-director of Radically Open Ltd between

November 2014 and May 2015 and is married to Erica Smith-Lynch, the principal shareholder and one of two current directors of Radically Open Ltd.

- Heather O'Mahen reports personal fees from the Charlie Waller Institute and Improving Access to Psychological Therapy.
- Sophie Rushbrook provides RO DBT supervision through S C Rushbrook Ltd.
- Ian Russell reports grants outside the submitted work from NIHR and Health & Care Research Wales.
- Maggie Stanton reports personal fees from British Isles DBT Training, Stanton Psychological Services Ltd, and Taylor & Francis Ltd.
- Michaela Swales reports personal fees from British Isles DBT Training, Guilford Press, Oxford University Press, and Taylor & Francis Ltd.
- Ben Whalley was co-director of Radically Open Ltd between November 2014 and February 2015.

The remaining six authors declare no competing interests: Sarah Byford, Rampaul Chamba, Paul Clarke, Susan Clarke, Bob Remington, James Shearer and Alan Watkins

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	P1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	P2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P3
	2b	Specific objectives or hypotheses	P3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Pp4 & 6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	P4
Participants	4a	Eligibility criteria for participants	P4
	4b	Settings and locations where the data were collected	P4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Pp4 & 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Pp5 & 6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	P6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	P6

Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	P6
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	P7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	P9, Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	P9, Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P9
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Description p9 – table can be added as supplemental

			material if requested
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig 1 & p2 & p7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Pp10-11, Table 1, Figures 2 & 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	P11
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	Pp11 & 12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P13
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P13
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Pp12 & 13
Other information			
Registration	23	Registration number and name of trial registry	P1
Protocol	24	Where the full trial protocol can be accessed, if available	Reference 11
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P8

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.