Radically open dialectical behaviour therapy for refractory depression: the RefraMED RCT

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Scientific summary

The RefraMED RCT

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Scientific summary

Background

Major depressive disorder is a disabling condition causing substantial impairment in psychosocial functioning and quality of life – in the workplace, at home and with friends. Only two-thirds of patients respond to antidepressant medication (ADM) and only half respond to psychological treatment. Thus, treatment resistance is a common outcome in major depression. The personal, social and economic burden of depression is substantial, especially for treatment-resistant depression.

Research on psychological interventions for refractory depression, defined as chronic depression or recurrent depression with two or more previous episodes, is sparse; most studies focus on acute or episodic depression and pharmacological or somatic treatments. Historically, psychotherapy trials avoided patients with refractory depression because these treatments were not designed to meet their needs. More recently, treatments that were developed specifically for refractory depression have achieved small to moderate effect sizes.

One potential reason why treatments work for only some patients with refractory depression is comorbidity with other mental disorders, especially personality disorders (PDs). Current treatments neglect the role of emotional overcontrol in refractory depression. However, many adults with chronic depression show overcontrolled traits, including greater self-criticism, impaired autonomy, rigid internalised expectations, excessive control of spontaneous emotion and inordinate fear of making mistakes. Radically open dialectical behaviour therapy (RO DBT), a novel transdiagnostic psychotherapy, aims to address this rigid coping style and the associated emotional loneliness. Earlier versions of RO DBT showed promise in two small randomised trials of patients with refractory depression and comorbid PDs.

Objectives

The primary objective of this trial was to estimate the efficacy of RO DBT plus treatment as usual (TAU) for refractory depression compared with TAU alone. The relative cost-effectiveness of RO DBT plus TAU compared with TAU alone was also estimated. Furthermore, the study aimed to explore the mechanisms of RO DBT treatment and moderators of treatment efficacy using novel statistical methods that exploit instrumental variables. These novel statistical methods aim to ameliorate bias caused by unobserved confounding, which can distort conventional analyses.

Methods

The Refractory depression: Mechanisms and Efficacy of RO DBT (RefraMED) trial was a multicentre, parallel-group, randomised trial in which participants were randomised to receive either 7 months of RO DBT plus TAU or TAU alone. RO DBT comprised 29 weekly individual sessions lasting 1 hour and 27 weekly skills classes lasting 2.5 hours. Patients allocated to TAU could access any treatment offered by the NHS or privately.

Participants were recruited from three secondary care NHS organisations in the UK: in Dorset, Hampshire and North Wales. Patients were eligible if they were aged $\geq$ 18 years, had a Hamilton Rating Scale for Depression (HRSD) score of at least 15 points, had a current diagnosis of major depressive disorder in the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) Axis I, were suffering either refractory or chronic depression and, in their current episode, had taken an adequate dose of ADM for at least 6 weeks without relief. Patients were excluded who met

criteria for dramatic–erratic PD (cluster B), bipolar disorder or psychosis or who had a primary diagnosis of substance dependence or abuse.

Once eligibility was confirmed and consent received, the Swansea Trials Unit used an adaptive algorithm to allocate participants at random to treatments and therapists. Three stratifying variables were used to ensure that there was balance between groups: (1) early or late onset of depression, (2) a HRSD score of < or > 25 points and, presence or absence of PDs. Trained assessors, who were blind to these allocations, assessed participants at 7, 12 and 18 months after randomisation. The primary outcome measure was the severity of depressive symptoms, as measured by the HRSD, at 12 months.

To aid interpretation of the primary outcome, the number of patients achieving a 'meaningful' reduction in symptoms was estimated, and full and partial depression remission rates were computed for each group. These remission criteria accounted for both depressive symptoms (evaluated using the HRSD) and quality of life [evaluated using the Longitudinal Interval Follow-up Evaluation – Range of Impaired Functioning Tool (LIFE-RIFT)]. Other secondary outcome measures included suicidal ideation and behaviour. The cost-effectiveness of RO DBT was estimated by cost per quality-adjusted life-year (QALY). Causal analyses were conducted to explore the mechanisms by which RO DBT changes prognosis.

Results

In the trial a total of 250 participants were allocated by adaptive randomisation: 162 participants to RO DBT plus TAU and 88 participants to TAU. Patients reported substantial comorbidity: 96% met the criteria for at least one comorbid disorder, 86% for at least one DSM-IV Axis-I disorder and 78% for at least one DSM-IV Axis-II disorder. A total of 183 patients (73%) after 7 months, 190 (76%) patients after 12 months and 167 (67%) patients after 18 months provided data on the primary outcome. There was no significant difference between treatment groups in the proportion of participants who contributed data to the analysis.

The trial did not show a statistically significant difference between RO DBT and TAU for the primary outcome at 12 months. By 7 months, RO DBT had substantially and significantly reduced depressive symptoms relative to TAU by 5.40 HRSD points [standardised mean difference 1.03, 95% confidence interval (CI) 0.94 to 9.85 points; $p = 0.02$]. Although this advantage for RO DBT continued, the reduction was no longer statistically significant at 12 months (2.15 HRSD points, standardised mean difference 0.41 points; 95% CI –2.28 to 6.58 points; $p = 0.29$) or at 18 months (1.69 HRSD points, standardised mean difference 0.32 points, 95% CI –2.84 to 6.22 points; $p = 0.42$). However, the TAU group achieved surprising improvements from month 12.

Full remission rates were low in both groups: 1%, 8% and 7% for the RO DBT group and 0%, 0% and 1% in for TAU group at 7, 12 and 18 months, respectively. Partial remission rates were higher in the RO DBT group participants (23%, 26% and 33% at successive assessments) than in the TAU participants (6%, 22% and 24% at successive assessments). Other indicators of improvement also showed superiority for RO DBT. The proportion of participants achieving a 'reliable improvement' or a 'worthwhile' change from the participants' perspective – at least a 17.5% reduction in symptoms – was consistently higher for RO DBT group participants than for TAU group participants. To aid patients and clinicians in future treatment choices, and to set realistic expectations for probable outcomes, data were simulated from the primary outcome model. It was found that for every 100 new patients, 32 would experience 'worthwhile' improvements in symptoms after 12 months by choosing RO DBT rather than TAU.

We found significant advantages for RO DBT participants in both emotional approach coping [as assessed by the Emotional Approach Coping scale (EAC)] and psychological inflexibility [as assessed by the Acceptance and Action Questionnaire (AAQ-II)] throughout the trial. In the RO DBT group participants, the EAC mean score and the standardised mean difference between groups increased over time at month 7 by 1.50 EAC points (standardised mean difference 0.32 points, 95% CI 0.09 to 2.90 points; $p < 0.05$); at month 12 by 3.55 EAC points (standardised mean difference 0.76 points, 95% CI 2.14 to 4.95 points; $p < 0.001$); and

at month 18 by 2.98 EAC points (standardised mean difference 0.64 points, 95% CI 1.14 to 4.82 points; $p < 0.01$). The mean AAQ-II scores decreased over time and all standardised mean differences were medium to large (month 7: –3.37 AAQ-II points, standardised mean difference 0.49 points, 95% CI –5.92 to –0.82 points; $p = 0.01$; month 12: –4.94 AAQ-II points, standardised mean difference 0.72 points; 95% CI –7.53 to –2.36 points; $p < 0.001$; and month 18: –5.48 AAQ-II points, standardised mean difference 0.79 points, 95% CI from –8.74 to 2.22 points; $p = 0.001$). However, we found no significant advantage for RO DBT group participants in impaired functioning (as assessed by the LIFE-RIFT), suicide ideation scores [as assessed by the Modified Scale for Suicidal Ideation (MSSI)] or perceived social support (as assessed by the Social Support Questionnaire). Both trial groups showed substantial reductions in LIFE-RIFT scores from baseline; mean MSSI scores remained below 8 points throughout the trial for both groups, indicating low levels of suicidal ideation, and, although perceived social support increased in the RO DBT group, the difference between groups was not significant.

The instrumental variables that we incorporated into the design of the study yielded estimates that were large, implausible and imprecise. Even conventional analyses, which assume no unobserved confounding, were unable to divide the total effect of RO DBT into direct and mediated components. Single-mediator models suggested that the pathway, either through learning skills or through therapeutic alliance, had improved participants' HRSD scores and the all-mediators model suggested that skills had played the greater role.

Primary cost-effectiveness analysis showed that the additional cost for RO DBT of £7050 (95% CI £5822 to £8274; $p < 0.001$) was associated with an increase of 0.032 QALYs (95% CI –0.028 to 0.093 QALYs; $p = 0.30$), yielding an incremental cost-effectiveness ratio (ICER) of £220,000 per QALY. This ICER was considerably above the willingness-to-pay threshold of £30,000 set by the National Institute for Health and Care Excellence (NICE) in the UK, but comparable with ICERs reported for standard dialectical behaviour therapy. Hence, from the perspective of the NHS and personal social services, RO DBT was not cost-effective relative to TAU alone in treating patients with refractory depression. RO DBT did not achieve sufficient gains in QALYs and savings in other health and social services to justify the cost of the resource-intensive therapy delivered in this trial. This was true when productivity losses were added.

In total, 33 serious adverse events (SAEs) were reported to the trial manager during the study: four for TAU participants, 28 for RO DBT participants and one for a participant before randomisation. It was judged that 17 SAEs (including all four in the TAU group) were definitely not related to RO DBT, eight were unlikely to be related, five were possibly related and three were probably related to RO DBT. Although none of the resulting eight possible serious adverse reactions (SARs) was classed as 'unexpected', all eight occurred in the RO DBT group, which was a statistically significant finding. However, TAU participants were seen by trial assessors at only the three follow-up interviews; in contrast, RO DBT participants were seen twice a week by trial therapists. We believe that the imbalance in SARs was because of this gross difference in reporting opportunities. Indeed, the Data Monitoring and Ethics Committee agreed that there was no reason to suspect that RO DBT was harmful.

Conclusions

The study found that RO DBT is much more efficacious than TAU in reducing participants' depressive symptoms over the course of treatment. After 7 months of treatment, participants in the RO DBT group show significantly fewer depressive symptoms by having an unusually large effect size (Cohen's *d*) with a *d* of 1.03. Thereafter, TAU patients also showed reductions in symptoms, reducing the effect size to a *d* of 0.41 at 12 months and a *d* of 0.32 at 18 months. Hence, differences between trial groups were not statistically significant at 12 or 18 months. However, the mean effect of RO DBT at 12 months reached the target effect size with a *d* of 0.4 and by exceeding 2 HRSD points, which is generally regarded as clinically relevant. Rates of full and partial remission were also consistently higher in RO DBT than TAU participants, especially after 7 months. Nevertheless, RO DBT is not cost-effective according to the NICE criteria.

Although the trial participants reported moderate to severe initial depression scores and considerable comorbidity, they reported low to moderate suicidal ideation throughout the study, with no significant differences between groups. Participants in the RO DBT group achieved significantly better psychological flexibility than those in the TAU group at 7, 12 and 18 months, and significantly better emotional approach coping and expressiveness after 7 months, with the difference increasing after 12 and 18 months. This suggests that patients continue to use and improve their RO DBT skills.

However, we could not draw firm conclusions from the analysis using instrumental variables. Standard diagnostics suggested that these variables were weak; therefore, the resulting estimates were biased and unreliable. However, as this was, to our knowledge, the first trial of psychotherapy to allocate instrumental variables at random, the experience will inform others.

Implications for health care

This study has demonstrated that depressive symptoms of patients receiving RO DBT decreased significantly during the 7 months of treatment and these reductions in symptoms were maintained at 12 and 18 months. However, the difference between the RO DBT and TAU groups did not achieve statistical significance after 12 and 18 months. This lack of significance was because of, in part, a smaller analysable sample at 12 months than was sought and an improvement in depressive symptoms after 7 months in the TAU group, who received more treatment between months 7 and 12 than the RO DBT group. Despite the higher cost of RO DBT than treatments typically offered within the NHS, it can improve depressive symptoms in a highly symptomatic population who suffer from many mental health problems and PDs and who may require specialised treatment for their problems.

Unlike other treatments for depression, RO DBT does not consider depression to be the primary problem. Instead, RO DBT targets emotional overcontrol – a maladaptive personality style shown to predict the development of chronic internalising disorders, such as resistant depression. Although overcontrolled PDs, including obsessive–compulsive PD, are more common than undercontrolled PDs, patients' innate capacity to tolerate distress, delay gratification and avoid public displays of emotion make their problems less noticeable. Overcontrolled individuals are likely to play down personal distress when queried and are, therefore, less likely to seek mental health treatment.

Implications for future research

The RefraMED trial was the first multisite trial of RO DBT. RO DBT improved depressive symptoms over time, and mediational analyses provided preliminary support for hypothesised mechanisms of change. Future studies should investigate variations on RO DBT that have the potential to be clinically effective but are less costly, for example by reducing the length of treatment or using stepped care that starts with group skills training and reserves one-to-one treatment for non-responsive patients. However, patients such as those who were studied by the RefraMED trial are difficult to treat and unlikely to benefit from short-term solutions. Although the RefraMED trial has investigated some mechanisms underpinning RO DBT, a more thorough investigation of which RO DBT skills are most clinically effective will be critical for developing a shorter version of the treatment, suitable for health-care systems with limited funding.

It is important to develop and test programmes that incorporate feedback from users and, thus, address tapering, online support, 'graduate groups' and other forms of continuing support. Given the recurring nature of depression, and the emphasis in RO DBT on changing maladaptive personality, future studies should extend assessment to investigate long-term differences between RO DBT and other treatments. Finally, the transdiagnostic approach of RO DBT supports testing RO DBT across a wider range of conditions, including eating disorders, overcontrolled PDs, anxiety disorders and autism spectrum disorders.

Trial registration

This trial was registered as ISRCTN85784627.

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