Title – How effective is augmentation with psychotherapy as a next-step option for patients with treatment resistant depression?

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Biography:

Daniel Silman is a core psychiatry trainee working within Oxford Health NHS Foundation Trust in the Thames Valley region. He has an interest in research in the area of psychotherapy.

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SUMMARY

Determining the optimum next-step treatment for the numerous patients with depression who do not adequately respond to an initial trial of medication remains a source of uncertainty in clinical practice. Whilst numerous psychological treatments are known to be effective for depression, their relative merits in the treatment-resistant group have not been ascertained. Cochrane has recently published a meta-analysis of the evidence available for the use of various psychotherapies as an adjunct to antidepressant compared to antidepressant alone in treatment-resistant depression. This month’s Cochrane Corner provides a commentary and appraisal of the clinical utility of these findings.

DECLARATION OF INTEREST

None.

KEYWORDS

depression; psychotherapy; cognitive behavioural therapies; statistical methodology

Evidence suggests the majority of depressed patients fail to adequately achieve remission after an initial trial of antidepressants (Thase2007 & Trivedi2006). Together with issues of medication acceptability, the challenges in achieving and sustaining recovery from depressive illness present a major burden to patients, at great societal cost (McCrone2008).

 This article addresses the ongoing need to optimise selection of the “next-step” options following initial antidepressant failure – referred to here as Treatment Resistant Depression (TRD). Current APA, NICE and BAP guidelines suggest clinicians may consider any selection out of increasing the dose of the initial medication, switching to an alternative antidepressant (within or from a different class) or augmenting with a drug (such as antipsychotics or lithium) or psychological intervention.

Psychological therapies can work by varied mechanisms in depression (explained below) and it is hoped their benefits and those from medication may be optimised when received together. Whilst certain therapies have been shown to be effective for depression more broadly (e.g. such as cognitive behavioural therapy (CBT) as a first line treatment (Cuijpers2011)), prior to this Cochrane review there had been no rigorous analysis collating recent trial data for psychotherapies in the TRD patient group, for which there has been greater focus on pharmacological strategies (Shelton 2008; Papakostas 2008; Trivedi2006). Previous systematic reviews in this area have not yielded clear recommendations for practice. This has been due to lack of a stringently defined clinical condition (McPherson2005, Trivedi 2011), inclusion of uncontrolled or inappropriate interventions (McPherson2005), or failure to find sufficient studies for meta-analysis (McIntyre2014; Cooper2011; Stimpson, 2002). Given also the suggested preference for psychological therapies over medication in certain patient groups (McHugh2013), this is a pressing research question .

SUMMARY OF THIS MONTH’S COCHRANE REVIEW

The review by Ijaz et al (2018) in this month’s Cochrane Corner includes six RCTs involving 698 participants with TRD. The results showed that patients receiving augmentation of their index antidepressant treatment with psychotherapy had favourable outcomes for depressive symptoms, and for response and remission rates, over continued drug treatment alone, and no indication of poor acceptability. The strongest evidence was over short-term follow-up and further research is needed to guide clinical practice.

AN OVERVIEW OF PSYCHOTHERAPY IN TREATMENT RESISTANT DEPRESSION

This review aimed to determine the effectiveness of psychological therapy as part of next-step treatment strategies in adults (18 – 74 years) with TRD through meta-analysis of relevant randomised controlled trials (RCTs) that specifically tested this patient group.

 There is surprisingly limited consensus in defining treatment resistance in depression.

This review applied a consistent definition for included trials of non-response to at least 4 weeks treatment with therapeutic dose of antidepressant medication - in line with the World Psychiatric Association earliest definition of TRD (non-response to 150mg per day of imipramine or equivalent drug). This may seem unfamiliar to some clinicians more acquainted with other classification systems for TRD considering non-response to multiple courses of treatment (Fava 2003; Fekadu2009). The extent to which someone treatment-resistant seems more accurately considered multi-dimensional, i.e. a non-dichotomous entity (see Ruhé2012). Failure to respond due to medication intolerance is not considered treatment resistance and this review was stringent in excluding such studies not making this distinction.

As well as being the remit of psychiatrists, TRD is also frequently managed within primary care (Thomas2013) and this review included studies from both settings. This review was restricted to examining psychotherapy in those with unipolar depression, with bipolar illness and other major psychiatric comorbidities excluded.

 Psychological treatments for depression may be first-line in the acute treatment (particularly for mild-moderate episodes) but are also recommended as an augmentation strategy in major guidelines (Cleare2015). This review also sought to determine the evidence-base for switching from medication to psychotherapy in TRD which, in addition to not being in line with current guidance, could also be considered improbable in clinical practice after single treatment failure – more feasibly associated with initial treatment intolerance. Perhaps not surprisingly, no RCTs could be identified comparing continued antidepressant treatment against switching to psychotherapy alone.

As succinctly summarised by the review authors, psychological treatments for depression may be categorised according to their proposed mechanism: 1) Psychodynamic/ psychoanalytic - focuses on unconscious processes to improve understanding of past experiences on current thoughts and behaviours; 2) Cognitive-behavioural - targeting unhelpful negative thoughts and maladaptive patterns of behaviour; 3) Humanistic - focused on enhancing self‐awareness; and 4) Integrated therapies (combining components of different models) which includes Interpersonal Therapy (IPT) and Cognitive Analytic Therapy (CAT). Evaluating psychotherapies in clinical trials will ideally take into account participant engagement and fidelity to the model where appropriate to maximise validity of the proposed findings (Alvarez-Jimenez2008). These factors were recorded in this review where possible.

METHODS

The search strategy principally reviewed the Cochrane Common Mental Disorders Group (CCMD) Clinical Trials Register which is collated from routine searches of multiple databases (MEDLINE, Embase, PsycINFO, Central) and authors also checked international trials registries for ongoing or unpublished studies. There were no date or language restrictions. A total of 4705 records were returned from the initial search with a further 4 studies through complementary searches of references and study author contacts. After initial screening of abstracts to remove obviously irrelevant papers, 102 full papers were reviewed for inclusion with 20 articles pertaining to 6 studies ultimately included (Feldman2009; Nakagawa2017; Souza2016; Town2017; Wiles2008; &Wiles2016).

 Study selection was appropriately reported using a PRISMA flow diagram with characteristics of excluded studies also listed, including some well-known studies. STAR\*D (Thase2007) for example was excluded for progressing patients to level 2 treatments if initial citalopram treatment had been poorly tolerated – comprising some 56% of those enrolled in medication switch options – in addition to those lacking adequate clinical response. Somewhat spuriously though, STAR\*D was also flagged for not re-applying diagnostic criteria before randomisation to a next-step treatment despite participants clearly meeting clinical case definition. Overall however, the study selection matched appropriately with the defined clinical question.

 In keeping with best practice recommended by Cochrane, full-text article screening, data extraction from included studies and application of the “Risk of bias” tool (Higgins *et al.* 2011 & 2017) was independently assessed by two authors, consulting a third author to resolve discrepancies and contacting study investigators were where necessary.

The primary outcome for clinical effectiveness was defined as changes in symptom severity on both self-reported (BDI, PHQ9) and clinician-rated (HAMD, MADRS) depression scales over the duration of follow-up, most commonly reported at 6 months following treatment, though longer-term follow-up was reported in some included studies. Effect size was determined by calculating mean difference (MD) or standardised mean differences (SMD, where different measures were used for the same outcome e.g. all self-reported measures) with 95% confidence intervals (CIs). For the secondary dichotomous clinical outcomes, the review authors indicated they would accept the original studies definition, but these are generally standardised as: response, quantified as >50% reduction in depression scores; remission, absolute scores of 7 or less on HAMD, or 10 or less on BDI. These were reported as risk ratios (RRs) and number needed to treat for an additional benefit (NNTB), also with 95% CI.

Number of all-cause dropouts was the primary indicator of acceptability with reasons summarised where possible. Disappointingly, this review did not identify at baseline certain clinically relevant participant characteristics, in particular educational attainment and family history of mood disorder, which may influence acceptability of certain psychotherapies (Wisniewski 2007). Other secondary outcomes in this review included data on social functioning, quality of life (QoL), economic outcomes and specific adverse events when reported in the original study.

Given that the meta-analysis pooled results from different modalities of psychotherapy (i.e. the intervention arm was not uniform between studies), it was appropriate that the review authors used a random-effect model for all analyses which accounts for between-study variation in estimating the true effect. Heterogeneity of included studies was formally assessed with Chi² test and the I² statistic, and the GRADE approach was used to denote evidence quality for each finding (see box 1).

RESULTS

Of the six studies meeting all inclusion criteria, all were parallel‐group randomised trials studying a psychological treatment as an adjunct to treatment as usual (TAU) versus TAU alone. Three studies evaluated individual CBT and a further study each assessed group dialectical behaviour therapy (DBT, incorporating change‐oriented cognitive‐behavioural strategies), IPT and intensive short‐term dynamic psychotherapy (ISTDP). Participants continued antidepressant treatment as part of TAU but further conditions, such as changes in management and contact with professionals may inevitably vary according to the setting and were not strictly defined. For example, the majority (469 / 698) of participants included in this review came from the UK multi-centre CoBalT study (Wiles2016) where TAU was overseen by the patients GP who could amend management including referral to secondary care in line with standard guidelines. Secondary care settings and other countries (USA, Canada, Japan and Brazil) were represented in the other studies.

 At the key 6 months follow-up timepoint where all studies collected self-reported depressive symptoms (either BDI or PHQ9, n=635), the pooled mean difference favoured the addition of psychotherapy to usual care when combining data from these scales (SMD ‐0.40, 95% CI ‐0.65 to ‐0.14,) and considering the more commonly applied BDI alone (5 studies, MD ‐4.07, CI ‐7.01 to ‐1.07). These findings were moderate-quality evidence with little heterogeneity – I2 of 37% and 27% respectively. A slightly lower but still significant reduction (MD ‐3.28, 95% CI ‐5.71 to ‐0.85, I2 30%) was seen in the observer-rated HAMD, but this was deemed lower-quality evidence as this aggregated data from 4 of the smaller studies (and not the large CBT trial) and covered all three therapy subtypes.

 All six studies reported on remission rates which showed an almost two‐fold higher likelihood of remission (RR 1.92, 95% CI 1.46 to 2.52) in the intervention arms over the short term (6 months) with a reported NNTB of 6.5. The response rate was similar but only collected in four studies and therefore deemed a lower-quality indication of favourable outcome with adjunctive psychotherapy. One study reported response and remission rates without declaring such *a priori*, which in individual trials may raise suspicion of selective reporting.

With only two studies collecting data at later timepoints, evidence for treatment effect here was generally considered of low quality, with mean difference of score reductions not consistently sparing the null value. RR of remission appeared preserved at 12 months (RR 1.97, 95% CI 1.51 to 2.56) and this was moderate-quality evidence.

 Stratifying the analysis by therapy type highlighted the relative dominance of the CoBalT study in the pooled result with the MD in BDI scores for adjunctive CBT closely reflecting the overall result (MD ‐4.56, 95% CI ‐7.49 to ‐1.63). The findings for the other modalities based on single small studies seemed imprecise and benefits found were inconsistent: ISTDP reporting only with observer-rated HAMD indicated favour towards the intervention (MD ‐5.84, 95% CI ‐11.22 to ‐0.46); group DBT showed a large reduction in mean BDI score but with even wider CI crossing the null value (MD ‐10.79, 95% CI ‐23.83 to 2.25); and IPT showed no difference to TAU (MD 0.80, 95% CI ‐6.70 to 8.30). Ideally, a network meta-analysis would have provided a more enriched comparison of the therapy subtypes, but this requires a lot more trials than have thus far been identified.

 The all-cause dropout from treatments showed no significant differences between intervention arms and TAU with zero heterogeneity, which was therefore considered high-quality evidence of good acceptability. Unfortunately, without data on reasons for study withdrawal, in particular those due to adverse events, assessment of tolerability was not possible from this review. Two studies did record serious adverse events (SAEs) and these were only observed in the control arm.

 Of the other secondary outcomes, QoL data was the most widely collected (5 studies) though all used different scales. No significant differences were found between treatment groups in any study, bar an improvement on the mental subscale of Short Form 12 in one study treatment arm. A marginal improvement in social functioning was seen in certain domains in the one study collecting this data but this was not consistent across observer‐rated and self‐rated scales.

Interestingly, the CoBalT study (Wiles2016) conducted cost-utility analysis which indicated a cost per quality‐adjusted life‐year (QALY) gain of £14,911 (ranging £13,006 to £29,626 based on sensitivity analyses). Based on the societal willingness to pay of £20,000 per QALY, this yielded a high probability (0.92) of cost-effectiveness, which adds weight to its adoption in UK clinical practice.

DISCUSSION

Overall, this review found moderate-quality evidence that adding psychotherapy to usual care with antidepressant in TRD was beneficial for depressive symptoms and for response and remission rates over the short term, and high-quality evidence that augmentation has good acceptability. A closer evaluation of these findings is merited to determine any potential implications for clinical practice.

**Assessment of reliability (bias)**

As is generally unavoidable for psychotherapy interventions due to lack of blinding (see box 2), all included studies were appropriately flagged for high-risk of performance bias and detection bias for the subjective scores, which may overestimate the treatment effect. However, similar improvements rated by blinded independent observers on the HAMD suggests this may not be such a concern.

 This review could have been vulnerable to small study effect given the relative dominance of smaller studies addressing this clinical question (3 out of the 6 included here were <50 participants). This may be predicted to be of low impact given that the pooled result favouring psychotherapy is lower than that found in the CoBalT study (Wiles2016) and one included study reported no benefit (Souza2016). Ultimately, formal evaluation of publication bias was not possible with insufficient studies for a funnel plot (see box 3) and this would be desirable as more trials are conducted. Three review authors themselves also reasonably declared a conflict of interest having led the two UK studies of CBT. Whilst this would not interfere with analysis of included studies, one possible introduction of bias could be the influence of their personal experience on the inclusion criteria and hence scope of the review.

 The other potential sources of variation in study quality such as attrition and treatment fidelity did not seem to greatly alter the effectiveness when removed from the pooled effect size in the subsequent sensitivity analysis.

**Evaluating the clinical significance of the findings**

Whilst this review reports some positive effect of psychological interventions in TRD, the clinical significance of these findings remains uncertain. The authors note that the mean reduction of depressive symptoms on the BDI (-4.7 based on the five studies that used this outcome) is indeed of greater magnitude than the minimum clinically important difference (MCID) previously defined by NICE as at least 3 points. However, this threshold has since been under challenge by more recent evidence suggesting patients themselves may place greater emphasis on larger relative (rather than absolute) changes to BDI (Button2015), and clinical significance may be better assessed by addressing changes in specific functional impairments (Saltiel 2015). Although a secondary outcome, the remission and response rates in the intervention arms do suggest improvements were likely clinically significant. Data in this review for benefits on social functioning and quality of life was scarcer and more inconsistent in its findings.

This review was able to make a confident conclusion about good treatment acceptability based on dropouts from the data available but it is becoming increasingly recognised that psychotherapy trials in general often have more limited systems for capturing adverse event data – either not reported or using guidelines developed for drug trials (Duggan2014). Weaker understanding of tolerability may pose further limitations on the clinical utility of psychotherapy trials which should readily be addressed in future studies (Linden and Schermuly-Haupt, 2014).

**Applicability of the findings**

As previously mentioned much of the evidence in this review is derived from a single large trial of CBT conducted in primary care. One key consequence for this review is that this clearly weakens the generalizability of the purported pooled result to the other modalities of psychotherapy for which effect sizes were imprecise and less consistent. Of note however, the severity of symptoms (BDI 31.8 in both the intervention and TAU) at baseline in this study was similar to included studies based in secondary care, and therefore whether results could feasibly translate between settings remains an interesting question. Addressing this would ultimately benefit from further studies of psychotherapy in TRD amongst patients under secondary care in the UK.

The treatment resistant clinical population should also be considered heterogenous - perhaps more so when defined by single antidepressant failure – with illness severity, number of treatments used and duration of episode having been laid out as potential variables within treatment resistance in the “The Maudsley Staging Method” (Fekadu 2009). For a more granular understanding of treatment effects, ideally meta-analyses would consider such factors as potential effect modifiers. To its credit, this review did identify *a priori* initial treatment duration and degree of response for subgroup analyses but this was not ultimately possible with the small number of studies. One would anticipate in clinical practice that augmentation (either psychological or pharmacological) after a single drug treatment is most likely to be attempted when there has been at least partial response to the primary antidepressant, so this analysis would have added to the review’s external validity.

Preference for psychological therapies over pharmacological treatment for psychiatric disorders is suggested to be common in a meta-analysis by McHugh 2013, though this could be challenged by the limited uptake of cognitive therapy in STAR\*D (Wisniewski 2007). Given that treatment preference may ultimately influence outcome (Mergl 2011) as well as uptake in clinical practice, it would have been useful if this review had taken into account baseline characteristics such as educational attainment and prior treatment experiences thought to effect patient preference.

CONCLUSIONS AND IMPLICATIONS FOR RESEARCH

In summary, through applying rigorous inclusion standards of case definition and controlled studies, this review provides the strongest clinical evidence yet for a benefit of psychotherapy given in addition to usual care over usual care alone for TRD.

 This review could be regarded as confirming adjunctive psychotherapy in TRD is very much a credible option amongst the various next-step choices. There remains however no great advancement in guiding the choice for clinicians and patients. NNTB calculated for the included studies here look favourable to those quoted for antidepressant switch (Papakostas 2008) and antipsychotic augmentation (Nelson and Papakostas, 2009) but cannot reliably be extrapolated to compare interventions under differing study conditions. It is noted in the STAR\*D study, CBT augmentation and medication augmentation as a next-step were similar in overall outcome but that medication augmentation worked faster (Thase2007).

This review was unable to fulfil a further aim of evaluating psychotherapy alone as a switch option after first-line treatment failure. Whether patients with moderate-severe depression would abandon a medication-containing strategy after initial treatment failure may though be unlikely, suggesting this is not such an urgent research question.

 Given that the psychological interventions vary in their mechanism of action, more evidence is needed as to the relative effectiveness of different modalities and interpreting their pooled analysis should clearly be treated with caution. Future research should also address the degree of response to the initial medication and severity of symptoms at the time of augmenting with psychotherapy. In addition, further attention in study designs is needed to other domains relevant to patient outcomes such as treatment preference, improved reporting of adverse events and long-term remission.

**BOX 1: GRADE Working Group grades of evidence.**

Pooling data from multiple clinical trials within a meta-analysis may give a more robust estimate of the treatment effect than any individual study. However, the key appraisal is then to assess confidence or certainty that the resulting estimate actually reflects the true effect of treatment. The factors to consider here are broadly acknowledged to determine the “quality” of the evidence. With many potential contributors to such a judgement, the framework introduced by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group has been widely adopted as a systematic and reproducible approach (Guyatt2008)

Within this framework, clinical outcomes assessed in RCTs begin as high-quality evidence but then may be downgraded (to moderate, low or very low quality) based on limitations in quality as assessed in five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias. Determining the extent to which any of these may compromise the results is of course subjective and requires a degree of expert intuition, including for the clinical context. The GRADE framework also allows for weaknesses identified to be mitigated though by positive indicators such as the magnitude of effect and evidence of a dose-response gradient which themselves increase certainty.

**BOX 2: Lack of blinding within Psychiatry**

 The cornerstone of high-quality studies is to eliminate as far as possible any differences between the intervention and control arms of the study other than the active ingredient of the treatments. Blinding or masking to the treatment condition (note this persists throughout the study, making it distinct from allocation concealment) minimizes participants in one group being exposed to different influences compared to another group that may alter the impact of treatment – these are broad but could include the nature of contact with healthcare professionals, or reflect a belief about a particular treatment. When such systematic differences between groups occur, it is known as performance bias. If similar different influences are present when outcome data is collected, this is known as detection bias. Failure to blind has been estimated to cause 23% exaggeration of intervention effect estimates in trials with subjective outcomes (Balk2002).

 Regrettably, there are numerous interventions with potentially vital roles in psychiatry that are practically impossible (or very difficult) to adequately blind, including psychotherapies, physical treatments such as ECT and, more experimentally, psychoactive drugs such as ketamine and psychedelics that elicit very characteristic reactions. In such instances, whilst performance bias may be hard to overcome, overall bias of the study (particularly detection bias) can be minimized by including observer rated outcomes with an independent blinded assessor or identifying clearly objective outcomes such as hospital admissions, though these may be less sensitive.

**BOX 3: Small study effect and funnel plots**

 It is well described that smaller studies sometimes show different and potentially larger effect sizes for a given intervention than larger studies (Sterne 2000). This is thought to have multiple origins. Firstly, publication bias – i.e. undue influence of the result itself on the decision to publish - may be more likely in smaller studies, as authors may be more inclined to submit smaller studies and journals themselves more likely to publish them, in instances where results are “significant”. Other factors include higher possibilities of selective reporting and recruitment of less representative samples. The net effect of cumulative biases from smaller studies may in turn affect the result of meta analyses.

The best method to test for publication bias amongst small studies is to visualise through funnel plots whether studies with small / negative effect sizes are missing. On a funnel plot (figure 1) the y-axis shows Standard Error SE (which is smaller for larger studies) in reversed scale, and effect size on the x-axis. When there is no publication bias, studies would lie symmetrically around the pooled effect size (the striped line in figure 1), 95% within the triangular region representing the CI around the central estimate.



***Figure 1*** - Illustrative example of a funnel plot

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