Comparing Apples and Oranges in Youth Depression Treatments?

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# 1. Abstract

**Objectives:** Should a young person receive psychotherapy or medication for their depression, and on what evidence do we base this decision? In this paper, we test whether the basic conditions required to draw valid inferences to answer this question are currently met.

**Methods:** We included 88 RCTs of psychotherapy and medication for child and adolescent depression (mean age 4-18 years). Using meta-analyses, we compared a) participant characteristics and b) trial characteristics in medication and psychotherapy trials. Lastly, we examined whether psychotherapy controls are well-matched to active conditions.

**Results:** Participants in medication RCTs had higher depression severity and were more frequently male compared to psychotherapy RCTs. There was a dramatic difference in the within-subject improvement due to placebo (SMD=-1.9 (95% CI: -2.10 to -1.70)) vs psychotherapy controls (SMD=-0.5 (95% CI: -0.75 to -0.25)). Within psychotherapy RCTs, control conditions were less intensive on average than active conditions.

**Conclusions:** Medication and psychotherapy RCTs differ on fundamental participant and methodological characteristics, thereby violating key conditions for valid comparison between them. Psychotherapy controls often involve little therapist contact and are easy-to-beat comparators. These findings cast doubt on the confidence with which psychotherapy is recommended for youth depression, and highlight the pressing need to improve the evidence base.

# 2. Key messages

Psychotherapy is recommended before medication for most cases of depression in children and adolescents, a recommendation that is based on indirect comparisons of outcomes from randomised controlled trials (RCTs) within each treatment modality. We examine the validity of these inferences by scrutinising the comparability of psychotherapy and medication RCTs. We find significant differences in sample characteristics (namely depression severity and sex composition) and trial design features, such that the within-group effect sizes of medication controls (i.e. pill placebo) are much larger than those for psychotherapy controls, and that medication RCTs feature significantly more trial sites. We also examine the quality of controls used in psychotherapy RCTs and find that they are poorly matched to active intervention arms in ways such as human contact hours, and hence represent poor and easy to beat comparators. Our findings underscore the need for a higher quality evidence base upon which to base treatment guidelines and clinical decision making.

# 3. Background

Should a child or an adolescent receive psychotherapy or medication for their depression, and what information should be used to guide decision-making?

For adolescent depression, there are limited head-to-head trials of medication and psychotherapy, and hence recommendations are derived from indirect comparisons of treatment efficacy. The National Institute of Health and Care Excellence (NICE) guidelines for adolescent depression recommend psychotherapy (specifically cognitive behaviour therapy (CBT) or interpersonal therapy (IPT)) over medication in most cases (1). This is in keeping with two sources of evidence relating to child and adolescent depression: meta-analyses of medication randomised controlled trials (RCTs) that cast doubt on the efficacy of antidepressants, with the exception of fluoxetine (2); and meta-analyses of psychotherapy RCTs that conclude psychotherapy to be efficacious (3). However, a recent network meta-analysis (NMA) (4), an established method of comparing treatments using both direct and indirect (i.e. treatment A with treatment C, via studies that directly compare A with B and B with C) evidence, concluded that only fluoxetine alone and fluoxetine administered together with CBT were significantly more effective than medication control (i.e. pill placebo) or psychotherapy controls. The only head-to-head RCT comparing modalities found that fluoxetine, alone and in combination with CBT, was superior to pill placebo, though CBT alone was not (5). Also, the addition of psychotherapy to standard care did not improve outcomes (6). Given this confusing evidence base, how should patients, carers, clinicians and policy makers make treatment decisions?

In this paper, we examine whether the existing evidence for adolescent depression treatments can offer valid answers to this question. We provide a conceptual framework and test a series of hypotheses using data from existing trials. Two points are crucial to indirect comparisons of treatment modalities. First, whether the participants in trials are comparable across modalities. Second, whether key conditions of the trial, such as the effects of control conditions or the number of sites involved, are comparable.

Starting with the first point, comparison between different trials assumes that they sample from the same population. If not, the validity of any comparisons, including those conducted through NMA (which rests on the principal of transitivity, i.e. the requirement that the different sets of randomized trials are similar on average (7)) are questionable.

The assumption that medication and psychotherapy trials sample from the same population may not be valid as patients and parents often have treatment preferences (8–10), meaning that there is likely to be a self-selection bias in who participates in psychotherapy and medication trials. Moreover, treatment preferences correlate with clinically-relevant participant characteristics, including severity and sex. Some of these characteristics, such as severity, may moderate treatment response (11,12) and if they differ across psychotherapy and medication trials they may confound comparisons.

Regarding the second point, differences in trial design may impact outcomes in a differential way between medication and psychotherapy trials (13). Most obviously, participants in psychotherapy trials are generally unblinded to treatment allocation, with the exception perhaps of trials that compare two equally plausible treatment arms (14). This creates differential expectations which may favour the psychotherapy active condition, as participants are content to be receiving the “cutting edge” treatment, whilst those in the control are dissatisfied for having missed out (i.e. “disappointment bias” (15). By contrast, in new antidepressant trials, patients (and raters) were largely unable to judge treatment allocation (16), suggesting that expectancy effects are well-matched across conditions. Since expectancy is substantially associated with treatment outcomes (17), if expectancy differs between medication and psychotherapy trials, comparisons between them, including in NMA, become questionable.

Another difference in design is the number of trial sites. The number of sites in medication trials is positively related to the magnitude of placebo response (18–20). This phenomenon may be due to lower quality of assessments in multi-site trials, with higher rates of classification errors and therefore higher apparent spontaneous remission or regression to the mean.

An inter-related issue concerns the effect of control conditions. Often psychotherapy and medication are compared on the basis of their respective effect sizes (i.e. differences between the active and control conditions for each modality). For these to be comparable, medication and psychotherapy controls ought to be equal in their effects. Otherwise, misleading conclusions could be drawn, e.g. two effect sizes of 40% would be considered equal, even if one arose from a difference of 100% versus 60% and another from a difference of 40% versus 0% (i.e. from different points of reference).

Additionally, control conditions in RCTs should generate counterfactual conditions to the intervention (21): what would have been the outcome had an individual not received the intervention, with all else being equal. Pill placebo, where the appearance of the drug is faithfully emulated, is an effort for all else to be equal. In psychotherapy trials, control conditions may not be so well matched to the intervention (e.g. in number of hours of therapist contact).

# 4. Objective

In this study we examine RCTs of psychotherapy and medication for child and adolescent depression (mean age 4-18 years). We hypothesise that there are substantial differences between psychotherapy and medication RCTs, making their comparison problematic, which we examine in the following ways. First, we conduct meta-analyses to compare sample characteristics of medication and psychotherapy trials including: a) baseline depression severity; b) percentage females; and c) mean age. Second, we examine trial characteristics including the efficacy of the control arms, using random-effects meta-regression, and the number of trial sites. Third, we examine the quality of psychotherapy control conditions by scrutinising the extent to which they are matched to the active intervention in ways such as number and frequency of sessions, and hence whether they represent fair pairings from which to draw valid efficacy inferences.

# 5. Study selection and analysis

The study protocol was registered on the Open Science Framework (OSF) and can be found at <https://osf.io/bfmc6>.

A detailed description of our methods, including formalisms on which analyses are based, can be found in the Supplement.

## 5.1 Included studies

We included RCTs identified in a recent meta-analysis of psychotherapy versus control (3) and an NMA examining the efficacy of antidepressants (2) for depression in children and adolescents. For the psychotherapy trials, we utilised open data from the previous meta-analysis (see <https://docs.metapsy.org/databases/depression-childadol-psyctr/>). For medication trials, we were unable to access the full dataset used in the NMA and hence extracted data from the included studies ourselves.

For medication trials, we also conducted a systematic search for studies published after the final search date of Cipriani et al.’s (2) review up to the final search date of Cuijpers et al’s (3) review to ensure we analysed an equivalently up-to-date database of medication trials. Two authors screened 450 titles and abstracts, and 38 full text records. Seven studies met inclusion criteria and one author completed data extraction for these papers (see [Figure 1](#fig-prisma) for PRISMA diagram).

## 5.2 Statistical analysis

### 5.2.1 Sample characteristics

We conducted random-effects meta-analyses and tested subgroup differences (psychotherapy vs medication trials) in severity of depressive symptoms, sex and age. Meta-analyses were implemented using R’s meta package.

### 5.2.2 Trial design

#### 5.2.2.1 Measures of effect

As the measure of effect of each individual study, we used the within-group Standardised Mean Difference (SMD) for the primary depression scale used (selected according to the hierarchy defined in the Supplement).

Where individual studies did not report all data required to calculate the SMD, we imputed missing data according to the methods summarised in the Cochrane Handbook (22).

For meta-analysis it is necessary to estimate a standard error of the SMD. This requires a correlation between the pre- and post-measures, a statistic typically not reported. To ensure that our results are not biased by misestimation (23), we simulated n=1000 datasets for different values (0.45 to 0.9) of this correlation and used these datasets in subsequent analyses (please refer to Supplement for full details).

#### 5.2.2.2 Multilevel model metaregression

We estimated pooled SMDs for each arm by using multilevel models implemented in R’s metafor package.

We present the SMDs of each of the four treatment arms (medication control, medication active, psychotherapy control, psychotherapy active) under investigation. The SMDs are the means across the 1000 simulated datasets.

#### 5.2.2.3 Number of sites

We also conducted a t-test to compare mean number of trial sites between psychotherapy and medication trials.

### 5.2.3 Sensitivity analyses

We conducted a series of sensitivity analyses where we excluded studies that 1) used waitlist as their control and 2) recruited participants with subclinical levels of depression. Next, we conducted two analyses where we included only trials that used the Children’s Depression Rating Scale, Revised (CDRS-R) or the Hamilton Depression Rating Scale (HAM-D) as outcome instruments. Additonally, we restricted two analyses to studies with variance below 0.02 and which reported SD at outcome respectively.

Further, we tested whether the simulated values for the standard error had a substantial influence on the estimation of the differences between the medication and psychotherapy control conditions. We plotted the z-value of the difference between the two coefficients against the number of simulations. We make inference on the stability of the difference, by counting the proportion of times that the z-value is above the critical value of z = 1.645 corresponding to an alpha = 0.05.

Finally, we examined whether differential regression to the mean may account for differences in effect for psychotherapy and medication trials.

### 5.2.4 Comparing the control and active arms of psychotherapy trials

We ran t-tests to compare the active and control arms of psychotherapy trials on key variables of interest regarding the intensity of the interventions: the number, duration and intensity of sessions, and the total cumulative hours and duration of the intervention.

# 6. Findings

## 6.1 Included studies

Data for included studies are summarised in **?@tbl-all-trials** and are also available as a csv dataframe on [<https://github.com/transatlantic-comppsych/apples_oranges>]. Please see [Figure 1](#fig-prisma) for a summary of the sources of included RCTs.

In total, there were 91 RCTs which included 48 active arms and 36 control arms of medication trials; and 64 active arms and 61 control arms from psychotherapy RCTs. Note that the number of active and control arms does not exactly match because some studies feature more than one control or active arm.

Placebo pill was the control condition for all medication trials. In psychotherapy trials, the control arm included 14 waitlist, 25 treatment-as-usual (TAU), and 19 other control conditions (e.g. relaxation training, attention control, counselling).

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| Figure 1: PRISMA chart summarising sources of included studies |

## 6.2 Sample characteristics at baseline in medication and psychotherapy trials

**?@tbl-baseline-results** summarises the results from each of the meta-analyses examining sample characteristics at baseline. The summary statistics are provided for each subgroup (i.e. medication and psychotherapy) and the p-value derives from the test for subgroup differences.

| **Subgroup** | **K** | **Mean** | **SE** | **Lower CI** | **Upper CI** | **T2** | **p-value** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Baseline Severity of Depressive Symptoms\*** | | | | | | | |
| **Overall** |  |  |  |  |  |  | **0.034** |
| Psychotherapy | 48 | 0.37 | 0.02 | 0.33 | 0.41 | 0.02 |  |
| Medication | 31 | 0.42 | 0.01 | 0.39 | 0.44 | 0 |  |
| **Excluding subclinical** |  |  |  |  |  |  | **0.294** |
| Psychotherapy | 40 | 0.39 | 0.02 | 0.35 | 0.43 | 0.02 |  |
| Medication | 31 | 0.42 | 0.01 | 0.39 | 0.44 | 0 |  |
| **Excluding waitlist** |  |  |  |  |  |  | **0.079** |
| Psychotherapy | 40 | 0.37 | 0.02 | 0.32 | 0.42 | 0.02 |  |
| Medication | 31 | 0.42 | 0.01 | 0.39 | 0.44 | 0 |  |
| **Percent Female** | | | | | | | |
| **Overall** |  |  |  |  |  |  | **0.018** |
| Psychotherapy | 48 | 61.55 | 2.35 | 56.83 | 66.28 | 264.58 |  |
| Medication | 28 | 53.72 | 2.33 | 48.94 | 58.51 | 152.15 |  |
| **Excluding subclinical** |  |  |  |  |  |  | **0.02** |
| Psychotherapy | 41 | 61.96 | 2.68 | 56.54 | 67.37 | 294.54 |  |
| Medication | 28 | 53.72 | 2.33 | 48.94 | 58.51 | 152.15 |  |
| **Excluding waitlist** |  |  |  |  |  |  | **0.026** |
| Psychotherapy | 40 | 61.61 | 2.66 | 56.24 | 66.99 | 282.33 |  |
| Medication | 28 | 53.72 | 2.33 | 48.94 | 58.51 | 152.15 |  |
| **Age** | | | | | | | |
| **Overall** |  |  |  |  |  |  | **0.243** |
| Psychotherapy | 52 | 14.27 | 0.33 | 13.6 | 14.95 | 5.78 |  |
| Medication | 28 | 13.69 | 0.37 | 12.95 | 14.44 | 3.7 |  |
| **Excluding subclinical** |  |  |  |  |  |  | **0.279** |
| Psychotherapy | 43 | 14.26 | 0.38 | 13.5 | 15.02 | 6.08 |  |
| Medication | 28 | 13.69 | 0.37 | 12.95 | 14.44 | 3.7 |  |
| **Excluding waitlist** |  |  |  |  |  |  | **0.278** |
| Psychotherapy | 44 | 14.26 | 0.37 | 13.52 | 15 | 5.91 |  |
| Medication | 28 | 13.69 | 0.37 | 12.95 | 14.44 | 3.7 |  |
| Abbreviations: K = number of studies, SE = standard error, CI = 95% confidence interval, T2 = estimate of between-study heterogeneity\*These are baseline depression scores transformed to reflect percentage of a scale range (see Supplement for detailed description).To take an example, the CDRS gives a possible total score from 17 to 113 (i.e. range of 96). Mean severity was 0.36 for psychotherapy studies and 0.42 for medication studies, which would translate to 51.56 (17 + 0.36 x 96) and 57.32 (17 + 0.42 x 96), respectively, as equivalent scores on the CDRS. | | | | | | | |

**?(caption)**

### 6.2.1 Baseline severity

On average, depression severity at baseline was significantly higher in medication trials compared to psychotherapy trials (see **?@tbl-baseline-results**). When excluding RCTs that used waitlist as their control, baseline severity remained significantly higher in medication trials compared to psychotherapy trials. This difference did not reach statistical significance when excluding studies that recruited samples with sub-clinical depression.

To ensure that this was not an artefact of variable transformation, we also compared means at baseline in the two instruments, CDRS and HAM-D, on which there was a sufficient number of studies to metanalyse. As can be seen in **?@tbl-hamd-baseline** and **?@tbl-cdrs-baseline** (see Supplemental Materials), the number of studies is much smaller, but the pattern of differences is the same for the HAM-D and the CDRS, though it does not reach statistical significance for the latter.

### 6.2.2 Sex

For this analysis, we excluded the two psychotherapy trials which included entirely female samples (Moeini, 2019; Shomaker, 2016; see **?@tbl-all-studies-percfemale-results** in Supplement for results with full sample). As can be seen in **?@tbl-baseline-results**, psychotherapy trials featured a significantly higher percentage of females when compared to medication trials. On average, samples were 61.55% (*SE* = 2.35) female across psychotherapy trials and 53.72% (*SE* = 2.33) female across medication trials. Excluding sub-clinical and waitlist control studies yielded similar results.

### 6.2.3 Age

As can be seen in **?@tbl-baseline\_results**, mean age was 14.27 (*SE* = 0.33) across psychotherapy trials and 13.69 (*SE* = 0.37) across medication trials, with no significant between group differences. There were no significant differences in mean age between modalities on further sensitivity analyses.

## 6.3 Trial design

### 6.3.1 Standardised mean differences of control conditions in psychotherapy and medication studies

We applied metaregression to obtain the SMDs and confidence intervals of each of the four study arms. As seen in [Figure 2](#fig-plot-means-all) there were substantial differences between the four arms of the meta-analysis with striking differences between the medication and psychotherapy control arms. In particular, pill placebo had an SMD = -1.88 (95% CI: -2.1 to -1.67) whereas psychotherapy controls had an SMD = -0.58 (95% CI: -0.85 to -0.31 ).

|  |
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| Pre-Post Standardised Mean Differences (SMD) of Control Arms |

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| Figure 2: Meta-analytic estimates of within-group changes for overall sample |

##### 6.3.1.0.1 Sensitivity analyses

We conducted a series of sensitivity analyses (all figures in the Supplement). Excluding waitlist control studies (see **?@fig-plot-means-no-wl**) and sub-clinical studies (see **?@fig-plot-means-clin**) yielded a pattern of results very similar to the overall analyses. Next, we examined the data including only those studies that used the CDRS (see **?@fig-plot-means-cdrs**) or the HAMD (see **?@fig-plot-means-hamd**). Medication control and psychotherapy control conditions remained significantly different, though the small number of studies resulted in less precise estimates of the SMDs. Conversely, restricting the analysis to studies with variance below 0.02 yielded a similar pattern of results, but with increased precision in SMD estimates across conditions (see **?@fig-plot-means-var2**). Finally, we showed that different values for the pre-post measure correlation had minimal effect on the estimated outcomes (see **?@fig-stab-sims**).

##### 6.3.1.0.2 Addressing regression to the mean

We addressed potential regression to the mean by including the baseline score for each depression scale in the linear regression model as per equation 3 in (24) (see **?@tbl-de-meaned** in the Supplement). The difference between the medication control and psychotherapy control arms remained significantly different.

### 6.3.2 Number of trial sites

Average number of trial sites was significantly higher in medication trials (*M* = 35.96, *SD* =25.16) compared to psychotherapy studies (*M* =3.07, *SD* =3.16)(*t* (27.53) = 6.89, *p* =< 0.001). Of those studies with data available, 26 of 28 (93%) medication trials were multisite, compared to 24 of 45 (54%) psychotherapy studies.

## 6.4 Comparing the nature and intensity of control conditions in psychotherapy trials

| **Group** | **K** | **Mean** | **SD** | **Cohen's d** | **Upper CI** | **Lower CI** | **t** | **df** | **p-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of sessions** | | | | | | | | | |
| Active | 63 | 13.19 | 11.40 | 0.78 | 0.36 | 1.20 | 4.37 | 98.63 | < 0.001 |
| Control | 39 | 5.56 | 6.19 |  |  |  |  |  |  |
| **Intensity (sessions per week)** | | | | | | | | | |
| Active | 57 | 1.32 | 0.72 | 1.06 | 0.60 | 1.51 | 4.99 | 75.49 | < 0.001 |
| Control | 35 | 0.57 | 0.68 |  |  |  |  |  |  |
| **Session length (mins)** | | | | | | | | | |
| Active | 55 | 64.63 | 31.32 | 1.11 | 0.65 | 1.57 | 4.99 | 66.42 | < 0.001 |
| Control | 35 | 28.24 | 35.12 |  |  |  |  |  |  |
| **Total intervention hours** | | | | | | | | | |
| Active | 55 | 13.96 | 10.18 | 0.97 | 0.51 | 1.42 | 4.74 | 84.99 | < 0.001 |
| Control | 35 | 4.97 | 7.77 |  |  |  |  |  |  |
| Abbreviations: K = number of studies, SD = standard deviation, CI = 95% confidence interval, df = degrees of freedom. | | | | | | | | | |

**?(caption)**

As seen in **?@tbl-intensity-of-int**, active conditions featured significantly more sessions when compared to control conditions. Sessions in active conditions were longer and more frequent, resulting in significantly more intervention hours overall. Notably, many control conditions were very poorly described and their intensity could not be quantified, resulting in missing data. We performed a sensitivity analysis where we excluded trials using waitlist controls; with the exception of number of sessions, differences between active and control arms were no longer statistically significant though remained substantial, with between-group Cohen’s ds ranging from 0.41-0.54 (please see **?@tbl-intensity-of-int-no-wl** in the Supplement).

# 7. Conclusions and Clinical Implications

This paper sought to address the question of whether psychotherapy and medication can be meaningfully compared on the basis of the existing evidence, by looking at two key conditions for comparability. First, whether the participants of trials in one modality are comparable to those in another modality. Second, whether conditions of the trial, such as the effects of control conditions or the number of sites involved, are comparable.

Starting with the first question, we found that participants in medication trials are comparable on age but are more likely to be male and have more severe depression compared to those in psychotherapy trials. This indicates that different people enter medication and psychotherapy trials, thereby violating basic assumptions of comparability.

Severity is particularly important as it may moderate treatment response, with some evidence suggesting that those with higher baseline scores respond more to antidepressants (25) or that their response to pill placebo is lower (18). Other studies argue against severity as a treatment moderator (26,27), however these are within people who have chosen to be in the particular trial and modality. Moreover, severity may represent different subtypes in terms of course of depression and real-life outcomes (28,29).

We then turned to our second question about whether trial design conditions are comparable between modalities. We found that medication trials are vastly more likely to be multi-site than their psychotherapy counterparts; in the current study, 93% of medication RCTs were multisite compared to 54% of psychotherapy RCTs. Multisite trials are associated with higher pill placebo response (18), and are less common in publicly-funded trials which show lower pill placebo efficacy (19); (20). Also, in single-site trials, principal investigators are often intellectually invested in the treatment (in psychotherapy these are often treatments developed or modified by the PI); this is in stark contrast to the incentive structure in multi-site trials where the number of recruited participants is the primary unit of reimbursement.

Second, psychotherapy controls have moderate effect sizes (-0.5) whereas medication controls have very large effect sizes (-1.9). Our analysis could be critiqued as it compares within arm symptom change per trial, therefore effectively breaking randomisation. This criticism would apply if our aim were to draw inferences about the efficacy of each arm — in which case preserving randomisation to balance confounders is critical. More importantly, we do not claim that these differences are genuinely due to efficacy differences; they may well be because people who attend psychotherapy and medication trials are different and therefore respond differently. In either case (difference in efficacy vs difference in trial participant profile), the substantial disparity in the response to control conditions is reason for concern about our ability to draw inferences from comparisons of modalities. This is particularly problematic as clinicians as well as policy makers often resort to between-group effect sizes to summarise findings, which our findings make obvious is misleading.

We note that our findings are largely in keeping with those of the NMA, which is designed to preserve the randomisation structure. Indeed, in Zhou et al. (4) the estimates for psychotherapy controls, TAU and waitlist conditions favoured placebo (though CIs were broad because these were indirectly estimated), as did estimates for psychodynamic and behavioural therapy. CBT did not differentiate from placebo, a result that is likely heavily weighted by the results of their direct comparison in the TADS trial (5). We note that the Zhou metanalysis, which represents an admirable effort to synthesise the literature, reports on issues that may affect transitivity with tests of incoherence showing significant differences.

Moving beyond comparison between modalities, we examined whether psychotherapy controls are reasonable counterfactuals to receiving treatment. An obvious disadvantage of psychotherapy trials is that they are typically unblinded (and hard to blind) yet psychotherapy trials are unlikely to fulfill some other basic conditions of the “all else is equal” assumption. In order to test that a psychological treatment is effective per se (e.g. because of the specific techniques) rather than because of generic effects (e.g. pleasant human contact), aspects such as therapist contact time should be matched. Many (24%) psychotherapy RCTs used waitlist controls, which by definition do not match for hours of therapist contact, and are often associated with disappointment bias. TAU and other psychotherapy control conditions varied drastically; 9 RCTs used controls that exactly matched the active arm in total number of contact hours, though several studies used bibliotherapy or online-only control conditions which did not involve any direct therapist contact. Importantly, controls were often poorly described, resulting in difficulties quantifying their intensity and hence evaluating their adequacy as counterfactual conditions. Overall, there is poor matching of control to active treatment conditions in psychotherapy RCTs, with the latter typically featuring considerably more contact hours, which may artificially inflate estimates of the efficacy of psychological treatments.

Given all of the above, the empirical basis for comparing psychotherapy and medication for adolescent depression is weak, and hence it is difficult to generate guidelines and recommend one treatment over another. Indeed, we believe that our findings have several implications for patients, their families, clinicians and policy makers.

First, the grounds for comparison between medication and psychotherapy should be seen as shaky, rather than offering confidence, and there is a need to revisit guidelines and public information in light of the limitations.

Second, the low quality of psychotherapy control conditions should prompt consideration of how to create fair comparators. Investment should be directed into providing rigorous evidence that establishes depression psychotherapies as more efficacious than fair controls. There are examples of RCTs where such rigor has been applied (e.g. Bolton, 2007; Liddle, 1990; Rohde, 2004) in matching active and control arms on variables such as therapist time and attention, provision of homework, and small group interaction. Moreover, there is a place for comparing interventions to TAU, since these represent real-world comparators. However issues of disappointment bias should be addressed to avoid inflating treatment estimates.

Third, our findings make clear the inherent difficulties of comparing psychotherapy with medication trials (13). The first obstacle is the comparability of the populations taking part. Head-to-head comparisons of psychotherapy with medication (as done in (5)) are more favourable in this regard, yet even so these trials might sample the population of those who are indifferent to which treatment they receive (30). And even in such a design, difficulties with blinding of the psychotherapy control would have to be overcome to draw valid inferences.

In summary, the current findings give cause for consternation about the state of the evidence for treatments of youth depression. Our data question the state of knowledge about the efficacy of psychotherapies and the extent to which giving them primacy in the treatment of depression is justified and beneficial for young people. Returning to our motivating question, the stakeholders, including patients and clinicians, need better evidence on which to base their choices.

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