



CORRESPONDENCE

Double blinding requirement for validity claims in cognitive-behavioral therapy intervention trials for major depressive disorder. Analysis of Hollon S, *et al.*, Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial [version 1; peer review: 2 approved]

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Abstract

This paper will focus on problems in the inability to double-blind cognitive-behavioral therapy (CBT) studies for major depressive disorder (MDD), and provides an analysis of a recently published study to show how this problem can lead to faulty conclusions.

A study by Hollon *et al.* published in JAMA Psychiatry that compared an antidepressant medication-only arm with a combined CBT/antidepressant arm concluded that the cognitive therapy/antidepressant combination enhanced the recovery rates compared with antidepressant alone, and that the magnitude of this increment nearly doubled for patients with more severe depression.

We propose that for subjects with greater severity, there could have been both antidepressant efficacy as well as more hope and expectation in the group who knew they had received combined cognitive therapy/medication, leading to an erroneous conclusion of greater efficacy for the combined group. The large subject number in this study could easily lead to an erroneous finding on statistical testing as a small amount of bias in the subjects adds-up.

We opine that the conclusions of unblind CBT outcome research in conditions with subjective endpoints such as MDD need to be given with great caution. The validity of CBT (and its derivatives such as dialectical behavioral therapy) for indications other than MDD is also part of a larger problem in the inability to blind outcome studies for these interventions.

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 1 published 27 Aug 2015	 report	 report
1 Rebecca Graham , Prince of Wales Hospital, Randwick, Australia		
2 Arif Khan , Northwest Clinical Research Center, Bellevue, USA		

Any reports and responses or comments on the article can be found at the end of the article.

Keywords

psychotherapy , cognitive-behavioral therapy (CBT) , outcome studies , blinding , clinical trials

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The validity of cognitive-behavioral therapy (CBT) efficacy for major depressive disorder (MDD) is widely accepted and is based largely on clinical intervention studies of CBT in MDD. However, clinical trials for CBT cannot be carried out under double-blind conditions as would be required of pharmacotherapy (or other somatic therapies), thus the rigor of CBT interventional studies is quite different from those modalities that can be studied under double-blinded conditions^{1,2}.

Treatment allocation cannot be blinded in CBT studies because the subjects have to actively participate in cognitive restructuring tasks. More than just saying a study was “blinded”, absolute concealment of what treatment was allocated is crucial in order to avoid bias³.

CBT trials are sometimes stated to be, “single-blind” because the persons who rate the symptoms that subjects report are blind to the treatment allocation of the subject. The term “single-blind”, however, should be used with caution as single-blind is defined as the condition when subjects are blind, not the raters⁴. Blind (or “masked”) raters only record whatever bias may be in the subjective reports of the subjects that can be swayed by the unblinded conditions. Emphasizing that raters are blind in a CBT study can distract from the issue that subjects and treaters are not blind.

Allocation concealment is crucial for indications with subjective outcomes as in MDD³. During a clinical trial, subjects with MDD report changes in the severity of subjective depressive symptoms that may be influenced by an expectation or hope for improvement³. Only interventional studies for indications with objective endpoints can ignore potential bias from lack of blinding. For example, mortality rates, MI incidence, stroke, etc. where random error is small¹. In this line, a meta analysis of CBT trials that controlled for blinding found treatment effects to be small in MDD⁵.

However, studies continue to report positive results of unblinded trials without voicing strong caution on the validity of the results. Hollon *et al.* in the October 2014 issue of JAMA Psychiatry compared an antidepressant medication only arm with a combined cognitive therapy/antidepressant arm⁶. All the subjects who received antidepressants did so under unblinded conditions. The cognitive therapy subjects and their treaters were also unblind to the treatment given. The study concluded that the cognitive therapy/antidepressant combination enhanced the rate of recovery compared with antidepressant alone, and that the magnitude of this increment nearly doubled for patients with more severe depression with little evidence of benefit for patients with less severe MDD. Only one line at the end of the discussion noted that the unblinded conditions could be a limitation.

An alternative conclusion could just as easily be that patients with greater severity MDD may have included more patients with a medication-responsive depression⁷. For those subjects with greater severity, there could have been both antidepressant efficacy as well as more hope and expectation in the group who knew they had received combined cognitive therapy/medication leading to an erroneous conclusion of greater efficacy for the combined group. A large sample size (N) as in this study is not necessarily a sign of robust results. A large N can create a significant finding on statistical testing as a small amount of bias in the subjects adds-up¹.

Our alternative conclusion may also be incorrect, the important issue is that the lack of allocation concealment in the study design does not allow any valid conclusion to be made either way. The antidepressant in each arm of the study provides the same amount of hope and expectation; the CBT arm has the added potential for bias from hope and expectation.

In addition, combining and comparing antidepressants that have market approval based on double-blinded placebo controlled outcome research with CBT, heretofore never studied under double-, or single-blinded conditions, in the same unblinded study is a serious problem. Handicapping one intervention group (antidepressants without the double-blinded placebo control needed for proof of efficacy), while providing advantage to another intervention group (unblinded CBT with no psychotherapy placebo which allows bias in one arm) which is then mixed with the handicapped group, confounds the study conditions and invalidates the design logic of a clinical trial.

To be sure, interventional studies for somatic therapies such as medications may also have elements of allocation non-concealment requiring caution in their interpretation. While medications can feasibly be blinded, side-effects may expose a subject to the fact that they are in the active-drug arm of a study. An exit analysis on the proportion of subjects in a study that correctly guessed the treatment arm they were in should be done, and the results of any study in an indication with subjective endpoints such as MDD that has evidence of unblinding should be suspect to have bias. Psychotherapy treatment, on the other hand, is virtually impossible to hide from the subject who is openly given the treatment. Whether medication, psychotherapy, or other intervention, no valid scientific assessment of efficacy can be made if a hurdle such as double-blinding in the study design of an indication with subjective endpoints is not rigorously implemented.

Authors must state clearly when an intervention cannot be studied with rigor, and conclusions need to be given with great caution when studies with subjective endpoints are unblinded. There is no regulatory authority like the FDA to review and approve a psychotherapeutic intervention for MDD, so that both professionals and society at large alike are dependent on the sound-bite conclusions made by authors and commentators on the results reported.

The critical problem of the inability to double-blind CBT clinical trials for MDD requires further evaluation by research groups who do not have a vested interest in CBT or related therapies. The validity of CBT (and its derivatives such as dialectical behavioral therapy) for indications other than MDD is part of a larger problem in the inability to blind outcome for these interventions.

Competing interests

No competing interests were disclosed. The author has no financial interests, activities, relationships, and affiliations other than those affiliations listed in the title page of the manuscript. There was no data collected or analyzed for this paper.

Grant information

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References

1. Piantadosi S: **Clinical Trials: A Methodologic Perspective, Second Edition**. New York: Wiley-Interscience, 2005.
[Publisher Full Text](#)
2. Hanrahan C, New JP: **Antidepressant Medications: The FDA-Approval Process and the Need for Updates**. *Ment Health Clin*. 2014; 4(1): 11–16.
[Publisher Full Text](#)
3. Schulz KF, Grimes DA: **Blinding in randomised trials: hiding who got what**. *Lancet*. 2002; 359(9307): 696–700.
[PubMed Abstract](#) | [Publisher Full Text](#)
4. Friedman LM, Furgerg CD, DeMets DL: **Fundamentals of Clinical Trials, Third Edition**. Springer; 1998.
[Reference Source](#)
5. Lynch D, Laws KR, McKenna PJ: **Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials**. *Psychol Med*. 2010; 40(1): 9–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Hollon SD, DeRubeis RJ, Fawcett J, *et al*: **Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial**. *JAMA Psychiatry*. 2014; 71(10): 1157–1164.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Khan A, Leventhal RM, Khan SR, *et al*: **Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database**. *J Clin Psychopharmacol*. 2002; 22(1): 40–45.
[PubMed Abstract](#) | [Publisher Full Text](#)

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Arif Khan

Northwest Clinical Research Center, Bellevue, WA, USA

Dr. Berger has taken to task a sacred cow in our field. Psychotherapy works and any challenges to it amount to sacrilegious position! Unfortunately for the dogmatic, Dr. Berger is right. It is not possible to truly 'blind' a psychotherapy study.

Simply put, the model of blinded raters is limited as both the patient and therapist are not blinded. Whether one likes it or not, the enthusiasm and conviction of a therapist is more than porous. The Freudian model is that a cigar smoking therapist begets a cigar smoking patient.

In the same note the sham therapist's conviction and enthusiasm (or a lack of it) will also be picked up by the patients. We have shown that the level of blinding does change expectations and expectations for the psychotherapy + pharmacotherapy results in the expected increased benefit.¹

Having said this, it would be foolish of me to suggest that psychotherapy has no value. After all, practice of medicine, psychiatry and psychology is intrinsically and intricately based on human interactions. So, training and practicing of psychotherapy is essential, just like saying you have to know anatomy before you start surgery. It is an essential skill in humanistic sciences. However, just like proving you need to know anatomy before you cut somebody up surgically cannot really be tested using current models and the same applies to psychotherapy.

In this context, it is important to note that different types of psychotherapy are better than other ones. This is like testing a surgical knife for different surgeries. All the psychotherapies (if practiced well) are effective just like all knives are effective.

It is only a poor clinician who tries to treat a patient without the understanding and application of psychotherapy principles to distressed patients. Here, I would like to note that Dr. Berger is a known psychotherapist. Thus, his position is courageous and to be lauded.

References

1. Khan A, Faucett J, Lichtenberg P, Kirsch I, Brown WA: A systematic review of comparative efficacy of

treatments and controls for depression. *PLoS One*. 2012; 7 (7): e41778 [PubMed Abstract](#) | [Publisher Full Text](#)

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 26 October 2015

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Rebecca Graham

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Overall, a reasonably well-written summary of the complexities evident in CBT intervention trials for MDD. The only suggestion I would make is that the grammar should be checked carefully prior to publication - especially the correct use of commas. Other than that - would agree with indexation.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Comments on this article

Version 1

Author Response 12 Oct 2015

Douglas Berger, Meguro Counseling Center, Tokyo, Japan

Directive psychotherapies are not more effective than non-directive psychotherapies when controlled for researcher allegiance.

We noticed that Dr. Hollon is actually one of the authors of the paper we quoted from 2012, that concluded that directive psychotherapies were not more effective than non-directive psychotherapies when controlled for researcher allegiance, and that the majority of the effect of therapy for adult depression is realized by non-specific factors¹.

This is the abstract of this paper [our bolding]:

“The effects of non-directive supportive therapy (NDST) for adult depression have been examined in a

considerable number of studies, but no meta-analysis of these studies has been conducted. We selected 31 studies on NDST from a comprehensive database of trials, examining psychotherapies for adult depression, and conducted meta-analyses in which NDST was compared with control groups, other psychotherapies and pharmacotherapy. We found that NDST is effective in the treatment of depression in adults ($g = 0.58$; 95% CI: 0.45–0.72). NDST was less effective than other psychological treatments (differential effect size $g = -0.20$; 95% CI: -0.32 to -0.08 , $p < 0.01$), but these **differences were no longer present after controlling for researcher allegiance**. We estimated that extra-therapeutic factors (those processes operating in waiting-list and care-as-usual controls) were responsible for 33.3% of the overall improvement, non-specific factors (the effects of NDST compared with control groups) for 49.6%, and specific factors (the effects of NDST compared with other therapies) for 17.1%. NDST has a considerable effect on symptoms of depression. **Most of the effect of therapy for adult depression is realized by non-specific factors, and our results suggest that the contribution of specific effects is limited at best.**"

Although Hollon and his coauthors are admitting in the above paper that the unblinded nature of therapists who have some allegiance to the therapy they are trained in can be the cause of positive findings, Hollon et al. now opine in their comment to us that blinding is not important for validation of CT efficacy, and that CT is superior to non-directive supportive therapies by referencing papers published the following year in 2013.^{2,3}

We are not sure why/how Dr. Hollon views these spins of his own conclusions over this short period of one year, nor how Dr. Hollon can state that psychotherapy studies do not require double-blinding to filter out bias.

We also noted Parker, et al.⁴ did a systematic literature search and could not find evidence that CBT was distinctively superior than other psychotherapies for major depression.

However, regardless of the issue of directiveness of a therapy, there is no way to get around the problem of not being able to blind the subjects or the treaters in any psychotherapy trial, directive or not.

That researcher allegiance is a cause of bias as concluded by a paper by Dr. Hollon himself, it is clear that conclusions must be seriously tempered in CBT trials where neither subjects nor treaters can be blinded, and where the majority of treaters trained in CBT would likely believe in CBT if they continued to be providers of this treatment.

References

1. Cuijpers P, Driessen E, Hollon SD, van Oppen P, Barth J, Andersson G: The efficacy of non-directive supportive therapy for adult depression: A meta-analysis. *Clin Psychol Rev.* 2012; **32** (4): 280-291 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
2. Barth J, Munder T, Gerger H, Nüesch E, Trelle S, Znoj H, Jüni P, Cuijpers P: Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS Med.* 2013; **10** (5): e1001454 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
3. Braun SR, Gregor B, Tran US: Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. *PLoS One.* 2013; **8** (6): e68135 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
4. Parker G, Fletcher K: Treating depression with the evidence-based psychotherapies: a critique of the evidence. *Acta Psychiatr Scand.* 2007; **115** (5): 352-359 [PubMed Abstract](#) | [Reference Source](#)

Competing Interests: There are no competing interests.

Author Response 01 Sep 2015

Douglas Berger, Meguro Counseling Center, Tokyo, Japan

Blinding and blind placebo are clearly crucial to elucidate efficacy in disorders with subjective endpoints.

We appreciate that Hollon *et al.* share our preference for double-blind controls. However, we are concerned that their logic of how to conduct and interpret the results of a clinical trial for an indication with subjective endpoints that can not be single- or double-blinded (and thus can not have a blind placebo group) does not describe the scientific needs of these kinds of trials adequately. We will address some of the most important points they describe here (we use CT (Cognitive Therapy) and CBT interchangeably to mean the same type of psychotherapy as in our article above in this comment; and Hollon *et al.* to refer to the paper discussed in our article above, and/or the comment to our paper by Hollon *et al.* above).

It is imperative that we repeat that double blinding is crucial for indications with subjective outcomes as in MDD¹. Only interventional studies for indications with objective endpoints can ignore potential bias from lack of blinding. For example, mortality rates, MI incidence, stroke, etc. where random error is small². This study on bias concluded that unblinded randomized clinical trials tended to be biased to positive effects if the outcomes were subjective as opposed to objective³.

To add additional important comment to our paper:

1. non-effective drugs and placebo pills can both show an average 30% improvement in depression scores compared to baseline (not due to improvements from waiting)⁴. Called a, “placebo effect” this is suspected to be due to the subject’s hope and expectation for improvement⁵.
2. So-called “psychological placebos” can be just as effective as standard psychotherapies in MDD⁶.

It is clear that because of the propensity of persons diagnosed with depression to improve with non-specific factors (i.e., receiving some intervention even if placebo pill or therapy, relationship with a caretaker, participation in a trial, etc.), enhanced improvement can be reported by subjects if there is even a small amount of bias to a specific intervention given in an unblinded fashion. Improvement from this bias will then be reported by the subject to the rater and can add up such that they will become significant with a large N as was the case in the study by Hollon *et al.* discussed in our paper.

We are at a loss as to how Hollon *et al.*, can argue their way out of this conundrum and make claims of efficacy without calling for serious hesitation in the interpretation of results from CBT trials such as in Hollon *et al.*

Regarding their points.

Point 1: Single-Blinding: definitions and misuse of terms.

Hollon *et al.* continue to call CBT trials “single-blind” in their comment. We noted in our paper that

“single-blind” is defined as the condition when subjects are blind, not the treaters or only the raters⁷.

See this reference in the American Psychological Association methodology data base, under, “Treatment Outcome/Clinical Trial”: “It is single-blind when the participants do not know which treatment group they have been assigned to”, (<http://www.apa.org/pubs/databases/training/method-values.aspx>, Accessed August 29th, 2015).

Using the term “single-blind” for studies that are not actually single-blind under this definition is not using the proper definition of this term and seems to be trying to suggest there is more rigor and control in a CBT study than is actually there.

The definition for single-blind is not met for a CBT trial as Hollon *et al.* acknowledge, so we are confused why they continue to use this term for trials with unblinded subjects. None of the trials they reference have a single-blind psychotherapy arm, and thus they can neither have a blind psychotherapy placebo comparison group. All the subjects and therapists know the psychotherapy provided. As we also noted in our paper, you can not logically compare blinded medications with unblinded psychotherapy and make any logical conclusions. The design of these arms are completely different, and as clearly reference in our paper, unblinded subjects in a study with subjective endpoints can not eliminate bias.

Even if Hollon *et al.* wish to redefine “single-blind” as when only raters are blind as in their study (or any study of CBT), this doesn’t change the fact that blind raters only record whatever bias may be in the subjective reports of the subjects that can be swayed by the unblinded conditions. Emphasizing that raters are blind in a CBT study can distract from the fact that this does not change the potential for bias in the subject-treater system.

Point 2: Expectancy effects: uncontrolled data, and post hoc analyses.

Their counter to our alternative interpretation of their results that , “It strains the imagination to, for example, attempt to come up with an explanation as to why expectancy effects should be limited to the third of the sample that was recurrent and non-chronic, but more severe”, is confusing because it is extremely easy to imagine the logic pitfalls in making associations here.

First and foremost is that the data is based on unblinded/non-placebo control conditions in subjective endpoints. Hollon *et al.* are trying to extract some kind of association from data born from uncontrol so that this is data on shaky ground (see the references in our paper).

Next, Hollon *et al.* have made a post hoc analysis on multiple variables (severity, acute vs chronic, recurrent or not, etc.) and thus have inflated the possibility of a type I error rate⁸.

This is because the further one looks for associations the more likely something will be found. In other words, each time an association in the data is considered, a statistical test is effectively performed. This inflates the total number of statistical tests needed and p-values need to be adjusted, which we did not see. Hollon *et al.* only did an “exploratory analysis” to determine whether severity and chronicity contributed independently to the increments observed. It is necessary to label these analyses as post hoc to avoid misleading readers that they are statistically robust when they are not.

The problems in multiple comparisons is common in the use of “data dredging” (also called “data mining”), to uncover patterns in data that can be presented as statistically significant, without first devising a specific hypothesis as to the underlying causality⁹.

The authors tried to justify the post hoc analysis problem by using a Bonferroni correction. The traditional Bonferroni tends to lack power, type II error rates are too high for individual tests, and it overcorrects for Type I error. Other modified Bonferroni approaches are available (not specified as done by the authors), but still do not fully get around the post hoc p value problem (*Portland University Data Analysis Course*, http://www.upa.pdx.edu/IOA/newsom/da1/ho_posthoc.doc, Accessed September 1, 2015).

It is hard for us to comprehend how Hollon *et al.* can call their post hoc subgroup analysis “exploratory” in the body of their text but yet claim these subgroups were clearly part of the efficacy of cognitive therapy in their Abstract conclusion: “Cognitive therapy combined with ADM treatment enhances the rates of recovery from MDD relative to ADMs alone, with the effect limited to patients with severe, nonchronic depression”.

Regardless of statistics, the Hollon *et al.* data is born from unblinded and thus uncontrolled study design so that we opine this data should not be acceptable to begin with. The FDA requires all antidepressants to have done some double-blind placebo controlled studies for approval for this reason¹⁰.

Point 3: Improved care for patients: The risks to claim improved care from unproven interventions are serious.

If an intervention is touted as efficacious in spite of having only unblinded and no placebo control, as we have outlined it is for CBT studies of depression with subjective endpoints, it is risky that patients with depression will seek out this intervention in place of treatments that have much more robust double-blind and placebo controlled data with approvals from a regulatory agency such as the FDA. These patients may sustain greater morbidity and mortality, and the financial costs to society can be large.

While few U.S. psychiatrists are unfamiliar with *Osheroff v. Chestnut Lodge*, we feel it is important enough to cite an abstract by Klerman in full here¹¹. Hollon *et al.*, will undoubtedly opine that CBT is a much more rigorously studied psychotherapy than the therapy Osheroff received, however, our paper, and other papers referenced below (references 13, 14, 18 discussed in Point 4 below), have presented strong logic to question the entire basis of CBT efficacy studies. We strongly agree with Klerman below that the, “...right of the patient to effective treatment and that treatments whose efficacy has been demonstrated have priority over treatments whose efficacy has not been established”.

Abstract from Klerman¹¹:

“Although *Osheroff v. Chestnut Lodge* never reached final court adjudication, the case generated widespread discussion in psychiatric, legal, and lay circles. The author served as a consultant to Dr. Osheroff and testified that Chestnut Lodge failed to follow through with appropriate biological treatment for its own diagnosis of depression, focusing instead on Dr. Osheroff’s presumed personality disorder diagnosis and treating him with intensive long-term individual psychotherapy. The author suggests that this case involves the proposed right of the patient to effective treatment and that treatments whose efficacy has been demonstrated have priority over treatments whose efficacy has not been established.”

Point 4: Listing of the many efficacy studies for CBT.

Hollon *et al.* list numerous studies they have done to show that CBT is efficacious. The logic here is, there are many studies with lack of single- or double-blinding control and blind placebo, these studies have shown CBT to be efficacious, thus, the data born from these studies even if not born from double-blinding

control and blind placebo is robust; i.e., data from many studies with this design problem makes up for each one of them having this design problem individually. The trouble in the logic here should be obvious.

There was no blind psychotherapy placebo, and no double-blind, nor single-blind study (as defined above) in any of the studies listed. Basing conclusions on data born from uncontrolled (unblinded and no placebo) circumstances in subjective endpoints, and then making absolute conclusions from this, and furthermore, comparing this data to medication trials born from double-blind placebo controlled studies is a tortuous argument because the data is born from such widely different level of control.

Basing results on data born without single- or double blind controls and blind placebo fits with Ioannidis' Corollary 4⁹: "The greater the flexibility in designs, definitions, outcomes, and analytical modes in a scientific field, the less likely the research findings are to be true."

The subgroup analysis Hollon *et al.*, noted in their reference #7 was also a post hoc analysis¹². The authors in this study even went to great pains to take some "middle ground" analysis in order to avoid conducting "...approximately 150 hypothesis tests, from which we could have expected to find several statistically significant results by chance". Reference #7 was also an analysis of an unblinded, non-placebo controlled psychotherapy study, and again breaking clinical trial design logic by comparing blinded medication therapy with unblinded CBT. While it is obvious that we must be very careful in concluding much from these kinds of results, Hollon *et al.*, continue to push conclusive remarks in their comment to our article.

There is considerable and growing concern that CBT is not an effective treatment for many conditions it touts itself to be. We noted the Lynch *et al.* meta analysis of CBT trials that controlled for blinding and placebo in our paper¹³. The results of this large meta analysis showed that CBT fared no better than non-specific control interventions in the treatment of schizophrenia and did not improve relapse rates, CBT showed no effect in prevention of bipolar disorder episodes, and only small treatment effects were seen in studies of MDD. We also discuss Parker¹⁴ below who found a low evidence base for the specificity and superiority of CBT over other psychotherapies.

Regarding the point that "cognitive therapy is about as efficacious as medications when adequately implemented in the acute phase of treatment and it has an enduring effect that medications cannot match" (their reference # 8)¹⁵. Long-term or prevention studies of CBT can still only be unblinded studies. CBT more clearly requires subject participation than a non-directive approach and is provided by trained therapists in an open fashion. It is obvious that bias potential is not removed from these studies. We have described above the obvious flaw of logic to compare medication arms or studies carried-out with double-blind placebo with unblinded CBT outcome results because the design of these methods are so different.

Regarding Hollon *et al.*'s comment that , "In this context, findings that CT is superior to non-directive supportive therapies (their reference #s 9,10) suggest the intervention is more than just a placebo." [ref-16-17]

A meta-analysis found no differences between directive or non-directive psychotherapy intervention when controlled for researcher allegiance, and that most of therapy effects came from by non-specific factors.¹⁸

In addition, Parker, *et al.*¹⁴ did a systematic literature search and concluded, "There is no high level evidence base suggesting or identifying CBT and IPT [Interpersonal Psychotherapy] as distinctively

superior than other psychotherapies for major depression. Claiming that they are evidence based, implicating or stating their superiority, and formalizing such differential status in therapeutic guidelines is disingenuous at best and risks distorting the value of an evidence based approach to Psychiatry. The clinical implications of over-selling CBT and IPT as specific and superior treatments for depression impact on both patients and practitioners”.

Remember, no study comparing a non-directive therapy to CBT can be blinded. The subjects and CBT practitioners would know they received CBT, and any preference for a directive approach would not be filtered by the unblinded nature of these studies.

Point 5: Use of study in Astronomy and Evolutionary Biology as an example that double-blinding and placebo control are unnecessary aspects of study design to claim efficacy in an intervention of a human disorder with subjective endpoints.

Hollon *et al.* have confused the use of data collection to make theories in natural science vs. the making of efficacy claims in a clinical trial of a human condition that has subjective endpoints. The argument about natural science theory making is not applicable to the conduct of clinical trial that is comparing the outcome of an intervention vs. some control group and then making efficacy claims. Natural scientists do not claim that their conclusions or theories should be used to treat a human disorder with subjective endpoints. This is diversionary logic that is extremely hard for us to understand in the setting of a discussion about a clinical trial of a human disorder.

Point 6: Competing Interests, potential researcher bias because of grants and academic interests.

Regarding potential researcher bias, the paper in question by Hollon *et al.*, and many of the papers referenced in the comment above by Hollon *et al.* receive research grant monies. These researchers have academic positions and have been researching CBT and comparing CBT to medications under unblinded/no blind placebo control conditions, usually reporting favorable outcomes as referenced in the Hollon *et al.* comment (see grant information sections in the Hollon *et al.* comment references, and Collorary 5 in Ioannidis⁹).

In Conclusion

1. There is really no way to get away from the problem in the inability to single- or double-blind, and have blind placebo control in a CBT clinical trial, whether in the acute, prevention, or long-term treatment phase of these trials.
2. Hollon *et al.* wrongly use the term single-blind, and do not seem to provide an understanding of the bias that can come from the subject-treater system that can not be filtered by blind raters.
3. Problems in doing post hoc analyses, and the comparing of unblinded CBT arms to blinded medication arms (the “apples to oranges” comparison of arms of completely differing control levels) run frequently in the trials noted by Hollon *et al.* who do not provide an understanding of the serious breach of scientific methodology inherent in these issues.

Hollon *et al.* also call their post hoc subgroup analysis “exploratory” in the body of their text but yet claim these subgroups were clearly part of the efficacy of cognitive therapy in their Abstract conclusion.

These points are extremely difficult for us to understand the scientific logic of, much less make strong statements of efficacy in the Abstract and Conclusions of Hollon *et al.* and related papers referenced in their comment.

4. A number of papers have noted problems in blinding of CBT trials as well as the specificity of CBT trials, and directive vs non-directive approaches, referenced in our reply here, and other papers that this comment does not have the space to discuss. Our paper here is not the only concern about the validity and claims of CBT.

We confidently stand by our assertion that the authors of these studies should use extreme caution and state clearly the problems with making any conclusions that can be drawn from CBT outcome studies that are unblinded and have no blind placebo control.

References

1. Schulz KF, Grimes DA: Blinding in randomised trials: hiding who got what. *Lancet*. 2002; **359** (9307): 696-700 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
2. Piantadosi S: Clinical Trials: A Methodologic Perspective, Second Edition. *Book*. 2005; **Wiley Series in Probability and Statistics** (New York). [Publisher Full Text](#) | [Reference Source](#)
3. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJG, Sterne JAC: Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008; **336**: 601-605 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
4. Marchesi C, De Panfilis C, Tonna M, Ossola P: Is placebo useful in the treatment of major depression in clinical practice?. *Neuropsychiatr Dis Treat*. 2013; **9**: 915-920 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
5. Rutherford BR, Mori S, Sneed JR, Pimontel MA, Roose SP: Contribution of spontaneous improvement to placebo response in depression: a meta-analytic review. *J Psychiatr Res*. 2012; **46** (6): 697-702 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
6. Wampold BE, Minami T, Tierney SC, Baskin TW, Bhati KS: The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *J Clin Psychol*. 2005; **61** (7): 835-854 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
7. Friedman LM, Furgerg CD, DeMets DL: Fundamentals of Clinical Trials, Third Edition. *Springer*. 1998. [Reference Source](#)
8. Jaccard J, Becker MA, Wood G: Pairwise multiple comparison procedures: A review. *Psychological Bulletin*. 1984; **96** (3): 589-589 [Publisher Full Text](#) | [Reference Source](#)
9. Ioannidis JPA: Why Most Published Research Findings Are False. *PLoS Medicine*. 2005; **2** (8): e124 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
10. Hanrahan C, New JP: Antidepressant Medications: The FDA-Approval Process and the Need for Updates. *Ment Health Clin*. 2014; **4** (1): 11-16 [Publisher Full Text](#) | [Reference Source](#)
11. Klerman GL: The psychiatric patient's right to effective treatment: implications of Osheroff v. Chestnut Lodge. *Am J Psychiatry*. 1990; **147** (4): 409-418 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
12. Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD: Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. *J Consult Clin Psychol*. 2009; **77** (4): 775-787 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
13. Lynch D, Laws KR, McKenna PJ: Cognitive behavioural therapy for major psychiatric disorder: does it really work? A meta-analytical review of well-controlled trials. *Psychol Med*. 2010; **40** (1): 9-24 [PubMed](#)

[Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)

14. Parker G, Fletcher K: Treating depression with the evidence-based psychotherapies: a critique of the evidence. *Acta Psychiatr Scand*. 2007; **115** (5): 9-24 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)

15. Hollon SD: Cognitive and behavior therapy in the treatment and prevention of depression. *Depress Anxiety*. 2011; **28** (4): 263-266 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)

16. Barth J, Munder T, Gerger H, Nüesch E, Trelle S, Znoj H, Jüni P, Cuijpers P: Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS Med*. 2013; **10** (5): e1001454 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)

17. Braun SR, Gregor B, Tran US: Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. *PLoS One*. 2013; **8** (6): e68135 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)

18. Cuijpers P, Driessen E, Hollon SD: The Efficacy of non-directive supportive therapy for adult depression: a meta-analysis. *Clin Psychol Rev*. 2012; **32** (4): 280-291 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)

Competing Interests: There are no competing interests associated with this comment.

Reader Comment 27 Aug 2015

Steven Hollon, Vanderbilt University, USA

[Doubling-blinding is not a requirement for validity claims: A response to Berger. Hollon, S. D., DeRubeis, R. J., & Lorenzo-Luaces, L](#)

We agree with the authors that it is virtually impossible to conduct a double-blind trial of psychotherapy. The patient typically knows what he is getting and the treating clinician knows what is being offered. Like the authors, we have more confidence in inferences drawn from placebo-controlled trials that are conducted in a double-blind fashion, all else equal.

However, the findings from so-called “single-blind” trials, like the one that we conducted, where independent evaluators were kept blind to treatment condition, should not be dismissed when they have potential clinical implications. It strains the imagination to, for example, attempt to come up with an explanation as to why expectancy effects should be limited to the third of the sample that was recurrent and non-chronic, but more severe. In our trial, those patients showed a 30% increment in recovery rates whereas patients who were chronic or less severe showed virtually no additive effect of additional CBT.¹ These findings need to be replicated before they influence clinical practice, though they echo prior findings by Thase et al.² If the findings are replicated, they have the potential to guide improved care for patients with non-chronic depression, consistent with the goals of personalized care.

We share with the authors a preference for double-blind controls. In an earlier trial we found cognitive therapy (CT) roughly comparable to medication treatment and both superior to pill-placebo, CT at the level of a nonsignificant trend.³ We also found evidence that prior CT and continuation medication reduced rates of relapse relative to medication withdrawal, triple-blinded with respect to medications and single-blind with respect to prior CT.⁴ The advantage for prior CT over prior medication is a relatively robust phenomenon but one that depends on single-blind comparisons.⁵ We also found that CT led to greater increments in employment than medication treatment, despite producing comparable reductions in depression.⁶ If the authors are correct that cognitive therapy's effects are a consequence of nonspecific expectancy effects, it is interesting that those nonspecifics reduce risk for relapse and enhance employability. Moreover, we found evidence that specific subgroups of patients exist who preferentially

responded to CT vs. medication above and beyond their average improvement (and the converse), a pattern of findings that is difficult to reconcile with the notion that CT is an inert intervention.⁷

The authors have a valid point, double-blind controls, when they are actually maintained, increase the confidence that we can have in the inferences that can be drawn. We disagree with the authors that inferences cannot be drawn in their absence; it is simply that such a design feature limits the level of certainty about the source of the benefit evidenced by patients in the CT condition. Broad findings from the meta-analytic review comparative literature are quite clear; cognitive therapy is about as efficacious as medications when adequately implemented in the acute phase of treatment and it has an enduring effect that medications cannot match.⁸

In this context, findings that CT is superior to non-directive supportive therapies^{9,10} suggest the intervention is more than just a placebo. Other directive psychological treatments are also efficacious in the treatment of depression but there is no debate among researchers that CT is the most widely studied form of psychotherapy and has the most well-established short and long-term evidence base. Confidence in these conclusions would be even greater if they had come from studies conducted using double-blind designs, but this issue echoes across the sciences. Most areas of Astronomy and Evolutionary Biology, for example, have progressed despite similar limitations. Indeed it would be good if one could conduct a double-blind study of a psychotherapy, just as it would be good if one could travel back in time to observe the evolution of the species or back to the moment of the Big Bang to observe the processes that occurred then. Even in these counterfactual fantasies one still would not be able to use some of the other tools of science, such as randomization and experimental manipulation, which would aim to rule out a variety of alternative accounts.

References

1. Hollon SD, DeRubeis RJ, Fawcett J, Amsterdam JD, Shelton RC, Zajecka J, Young PR, Gallop R: Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: A randomized clinical trial. *JAMA Psychiatry*. 2014; **71** (10): 1157-1164 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
2. Thase ME, Greenhouse JB, Frank E, Reynolds CF 3rd, Pilsbush PA, Hurley K, Grochocinski V, Kupfer DJ: Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry*. 1997; **54** (11): 1009-1015 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
3. DeRubeis RJ, Hollon SD, Amsterdam JD, Shelton RC, Young PR, Salomon RM, O'Reardon JP, Lovett ML, Gladis MM, Brown LL, Gallop R: Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry*. 2005; **62** (4): 409-416 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
4. Hollon SD, DeRubeis RJ, Shelton RC, Amsterdam JD, Salomon RM, O'Reardon JP, Lovett ML, Young PR, Haman KL, Freeman BB, Gallop R: Prevention of relapse following cognitive therapy versus medications in moderate to severe depression. *Arch Gen Psychiatry*. 2005; **62** (4): 417-422 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
5. Cuijpers P, Hollon SD, van Straten A, Bockting C, Berking M, Andersson G: Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. *BMJ Open*. 2013; **3** (4): e002542 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
6. Fournier JC, DeRubeis RJ, Amsterdam JA, Shelton RC, Hollon SD: Gains in employment status following antidepressant medication or cognitive therapy for depression. *Br J Psychiatry*. 2015; **206** (4): 332-338 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
7. Fournier JC, DeRubeis RJ, Shelton RC, Hollon SD, Amsterdam JD, Gallop R: Prediction of response to medication and cognitive therapy in the treatment of moderate to severe depression. *J Consult Clin Psychol*. 2009; **77** (4): 775-787 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)

8. Hollon SD: Cognitive and behavior therapy in the treatment and prevention of depression. *Depress Anxiety*. 2011; **28** (4): 263-266 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
9. Barth J, Munder T, Gerger H, Nüesch E, Trelle S, Znoj H, Jüni P, Cuijpers P: Comparative efficacy of seven psychotherapeutic interventions for patients with depression: a network meta-analysis. *PLoS Med*. 2013; **10** (5): e1001454 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
10. Braun SR, Gregor B, Tran US: Comparing bona fide psychotherapies of depression in adults with two meta-analytical approaches. *PLoS One*. 2013; **8** (6): e68135 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)

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