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Acceptance and Commitment Therapy – Do we know enough? Cumulative and Sequential meta-analyses of randomized controlled trials

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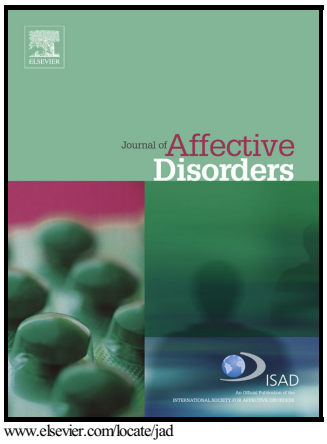

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Acceptance and Commitment Therapy. A sequential meta-analysis of randomized controlled trials

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Running Head: Acceptance and Commitment Therapy – Do we know enough? Cumulative and Sequential meta-analyses of randomized controlled trials

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Abstract: Acceptance and Commitment Therapy (ACT) has accrued a substantial evidence base. Recent systematic and meta-analytic reviews suggest that ACT is effective compared to control conditions. However, these reviews appraise the efficacy of ACT across a broad range of presenting problems, rather than addressing specific common mental health difficulties. Focussing on depression and anxiety we performed a meta-analysis of trials of ACT. We incorporated sequential meta-analysis (SMA) techniques to critically appraise the sufficiency of the existing evidence base. Findings suggest that ACT demonstrates at least moderate group and pre-post effects for symptom reductions for both anxiety and depression. However using SMA findings are more qualified. There is currently insufficient evidence to confidently conclude that ACT for anxiety is efficacious when compared to active control conditions or as primary treatment for anxiety. Similarly, using SMA, there is currently insufficient evidence to suggest a moderate efficacy of ACT for depression compared to

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active control conditions. To stimulate further research we offer specific estimates of additional numbers of participants required to reach sufficiency to help inform future studies. We also discuss the appropriate strategies for future research into ACT for anxiety given the current evidence suggests no differential efficacy of ACT in the treatment of anxiety compared to active control conditions.

Keywords: sequential meta-analysis, acceptance and commitment therapy, mental health, treatment efficacy, anxiety, depression

Word count: 4422 (excl. references, tables and figures).

1. Introduction

Within the last decade third wave treatment approaches (Hayes, 2004) have widened the spectrum of evidence-based psychological treatments, particularly in relation to mental health conditions deemed longstanding, complex or treatment resistant. 'Third wave' therapies have gained currency as an alternative to more established models of cognitive behavioural therapy (CBT) (e.g. Beck, 1963) via a relatively greater emphasis on context and experiential facets of psychological experience.

Third wave cognitive behavioural therapies include among others Dialectical Behavioural Therapy (DBT, Linehan, 1995), Mindfulness Based Cognitive Therapy (Segal, Williams, & Teasdale, 2012), Compassion Focused Therapy (Gilbert, 2004), and Acceptance and Commitment Therapy (ACT, Hayes, Strosahl, & Wilson, 1999). The third wave therapies also make explicit attempts to balance a coherent theoretical underpinning with a commitment to empirical testing.

Controlled trials have suggested efficacy for ACT in the treatment of depression, mixed depression and anxiety, physical health problems and psychotic disorders. Meta-analyses of randomized controlled trials of ACT have suggested a moderate to large effect size on primary outcomes measures after treatment and at follow-up (Hayes, Luoma, Bond, Masuda, Lillis, 2006; Ost, 2008; Powers, Zum Vorde Sive Vording, & Emmelkamp, 2009, Ruiz, 2010, 2012). A recent meta-analysis of ACT by Ruiz (2012) concluded that ACT outperformed CBT (Hedges g = 0.4). However, the debate regarding the differential efficacy of ACT compared to other evidence-based psychological interventions is ongoing (e.g. Hoffman & Asmundsen, 2008, 2010; Ost, 2009). The proliferation of third wave approaches raises questions for clinicians and policy makers (and clients/service users) regarding which therapeutic intervention is of optimal benefit for a given disorder or difficulty. This is especially important to the development of clear guidelines for the evidence-based practice of psychological interventions.

Existing evidence from systematic and meta-analytic reviews provide qualified support for the effectiveness of ACT as a psychological intervention when compared with no intervention (Ruiz, 2012; Powers et al., 2009). However, the data with regards to ACT in comparison to other psychological therapies are more equivocal. Therefore, clinicians, health

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service commissioners and policy makers at present must judge whether the evidence base for ACT is sufficient to make a confident recommendation regarding its efficacy. Borrowing from public health research (Muellerleile & Mullen, 2006; Wetterslev, Thorlund, & Gluud, 2008), a novel statistical approach to this question is the appraisal of the sufficiency of the available cumulative knowledge. Where the total cumulative knowledge is still emerging, meta-analytic findings are at risk of false positives or false negatives due to methodological weaknesses such as power, random errors or systematic error (e.g. Kuppens, Heyvaert, Van den Noortgate, & Onghena, 2011). Sequential meta-analysis (SMA; Pogue & Yusuf, 1997) uses group sequential boundaries based on the alpha spending function to measure the accumulation of knowledge across studies, enabling decisions on the sufficiency of knowledge to recommend treatment to be made based on statistical properties. This approach, commonly used in the evaluation of medical interventions (e.g. Devereaux, Beattie, Choi, Badner, Guyatt, Villar et al. 2005; Wetterslev et al., 2008) is under-utilized in the evaluation of psychological therapies. Although of potential benefit to evaluation of all evidence based psychological therapies we choose in this review to focus on ACT as an example of an emerging psychological therapy with a commitment to evidence-based practice.

In view of the above, our primary aim was to quantitatively review outcomes of ACT interventions for anxiety and depression using two complementary statistical approaches. Firstly, using cumulative meta-analytic techniques (CMA), we reviewed the evidence for ACT as a psychological intervention for anxiety and depression in group and pre-post comparisons. Secondly, we reviewed the evidence for the same conditions using sequential meta-analytic techniques (SMA). Use of SMA enabled us to make an estimate of the sufficiency of the evidence base for ACT. Secondary aims were to investigate the efficacy of ACT when compared against active treatments and when anxiety or depression were predetermined target outcomes. Regarding the primary aims we hypothesise that there is sufficient evidence to suggest that ACT is efficacious in the treatment of anxiety and depression. With regards to SMAs, to the best of our knowledge, this is the first time that a sequential meta-analytic approach has been used to appraise the sufficiency of evidence of ACT. Therefore no specific hypotheses were made.

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2. Method

Our quantitative review followed two stages. Firstly the literature was systematically searched to identify the study sample and to extract data. Secondly, the data was analysed using meta-analytic techniques. This stage incorporated conventional cumulative meta-analyses for ACT for anxiety or depression in group and pre-post comparisons, sequential meta-analyses for these conditions and lastly, subgroup analyses in which ACT was compared with active treatments and in conditions were anxiety or depression were predetermined treatment outcomes.

2.1 Literature search

2.1.1 Eligibility criteria

A systematic literature search was conducted to identify potential studies, following PRISMA guidelines (Moher, Schulz, & Altman, 2008). Studies were included if they (1) investigated a manualised ACT approach, (2) used a randomised control design, (3) assessed anxiety or depressive symptoms using standardised outcome measures.

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Studies were excluded if they (1) were not published in English, (2) did not include a standardised measure of anxiety or depression, (3) did not use an RCT methodology, or 4) were not published in a peer-reviewed publication, e.g. conference abstracts, book chapters, dissertations.

2.1.2 Information sources

Studies were identified by searching several database namely: PsycINFO 1840 to June 2015, MEDLINE 1966 to June 2015, SCOPUS 1841 to June 2013, Cochrane Central Register of Controlled Trials for 2014.

2.1.3 Search

We used search terms incorporating conjunctions of therapy and trial design terms: 'acceptance and commitment therapy' or 'acceptance', 'random', 'randomly', 'randomise', 'randomize', 'randomised', 'randomized', 'clinical trial', or 'trial'. These words were searched as key words, title, abstract, and MeSH subject heading terms. Also, we examined citation maps and used the 'cited by' search tools. Limits were then implemented to further refine the scope and ensure quality: databases were de-duplicated; searches limited to peer-reviewed articles; searches limited to human studies; and searches limited to adult studies. Reference lists of all relevant articles and existing systematic reviews (e.g. Powers et al., 2009) were screened by the authors to ensure no studies were overlooked.

2.1.4 Data collection

The data was extracted into an electronic data extraction sheet by the first author and independently reviewed by the second author. Information extracted from the studies included (1) trial characteristics (including first author, publication year, and participant number), (2) control group characteristics (including active or non-active control), and (3) outcome characteristics (outcome measures).

2.1.5 Risk of bias measurement

To minimise the risk of data selection biases we included data pertaining to all reported anxiety and depression outcomes.

2.1.6 Summary measures

Standardised mean differences with heteroscedastic population variances (SMDH) for independent groups and for dependent groups were calculated (Bonett, 2008, 2009). Additionally, considering the small study samples Knapp and Hartung's adjustments (Knapp & Hartung, 2003) were calculated, yielding closer to nominal standard errors of the estimated parameters.

2.1.7 Study selection

Inclusion, exclusion criteria and search terms were specified a-priori.

The literature search identified initially 1865 studies. Study titles and abstract were screened against inclusion and exclusion criteria. Two independent reviewers conducted screening (first and second authors). Studies were assessed by considering the eligibility by the second author and revised by the first author. Disagreement was resolved through discussion.

In cases where insufficient data was reported in the primary study to apply meta-analytic methods we attempted to retrieve additional information from the first author of the

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published paper. Five authors were contacted to retrieve additional information. One author provided additional information. The review flowchart is illustrated in Fig. 1.

[Insert Fig. 1 about here]

Quality assessments of the studies were evaluated using the 34-item Consort 2010 checklist (Moher et al., 2010). Each item is rated on a 3-point scale from 0 to 1, where 0 = absent, 0.5= partial, 1= complete. Overall, Consort checklist scores range from 0 to 34. Higher overall scores suggest superior methodological rigour. The second and third author independently assessed a randomized subset of 10 % of studies to check for inter-rater reliability. All studies were randomised using www.random.org list randomizer. Where there were ambiguities between the reviewers, the studies were jointly reviewed to reach a unanimous decision. If further ambiguities remained a third reviewer had the ultimate decision. All remaining studies were randomised and divided amongst the two reviewers for independent evaluation. Overall the inter reviewer concordance was Kappa = 0.85, suggesting an excellent agreement (Banerjee, Capozzoli, McSweeney, & Sinha, 1999).

2.2 Literature appraisal

2.2.1 Meta-analytic approach

All meta-analytic procedures were conducted using the R-software package 'metafor' (Viechtbauer, 2015). Conducting consecutive meta-analyses that incorporate the same or virtually the same study sample can significant increase the risk of both type I and type II errors (Higgins, Thompson, Deeks, & Altman, 2008; Borm & Donders, 2009). Findings may be erroneously deemed positive when they may be due to chance findings or false-positives. Similarly, findings might be rejected as negative or neutral due to lack of precisions or statistical power. A sequential meta-analysis method offers a statistical approach to manage these risks (Wald 1947; Pogue and Yusuf, 1997).

In this analysis we used a four-steps analytic approach described by Kuppens and Onghena (2012) including the calculation of the optimal information size, conducting cumulative meta-analyses, constructing sequential boundaries, and determining statistical sufficiency. These steps will be described in detail in the ensuing sections.

Computing optimal information size (OIS)

Arguably the level of convincing evidence for a meta-analysis should be no less than that of a well-designed single trial. To determine the threshold level of sufficiency Pogue and Yusuf (1997) proposed that conventional sample size calculation methods can be used. The optimal information size (OIS) is the sample size required to detect a presumed pooled effect whilst minimising type I and II errors. However, this approach does not control for heterogeneity between studies when using meta-analytic methods. Therefore a heterogeneity adjusted method for hierarchical designs can be used to control for the degree of between study variability (Higgins, Whitehead, & Simmonds, 2010; Kuppens & Onghena, 2012). The heterogeneity adjusted OIS (HOIS) can be readily calculated as follows:

$$HOIS = \frac{OIS}{(1 - I^2)}$$

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Conventionally, the I^2 index measures the extent of true heterogeneity dividing the difference between the Q value and its degrees of freedom (k-1) by the Q value, and multiplied by 100 (Borenstein, 2009). To render authorities conclusions regarding the evidence base for ACT we chose more stringent criteria for alpha, power and proposed effect sizes (α=.01, 1-β=.9) as recommended by Kuppens and Onghena (2012). Considering the moderate to high heterogeneity reported in previous meta-analyses (Ruiz, 2012) the authors also elected to use a high heterogeneity estimate (e.g. I^2=75%) in their HOIS calculations. Lastly, considering currently reported effect size estimates a medium effect size (e.g. d=.5) was selected to be a reasonable estimate for the HOIS calculations. We used the open-source program G*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) to calculate heterogeneity adjusted OIS's (Table 3).

Cumulative meta-analysis

To obtain pooled cumulative estimates of effect sizes over time cumulative meta-analyses were conducted on a chronologically ordered study sample (e.g. publication year). Random models were used to calculate pool effect sizes at interim analysis points.

Independent meta-analyses were conducted for anxiety and depression in order to conform to the assumption of independent effect sizes that underline meta-analytic procedures (Borenstein, 2009). When several relevant outcome measures were reported, the outcomes yielding the most conservative effect size estimate per study were included in the analyses.

Sequential boundaries

The optimal information size can be used to calculate the group sequential boundaries b using the alpha-spending function by Lan and DeMets (1983). This function α^* is a monotonically non-decreasing function which allocated the allowable Type I error through a function based on the information fraction t. The information fraction t in turn is the proportion of (heterogeneity adjusted) optimal information size (HOIS) that has been accumulate at a particular interim analysis point q thus $t_q = i_q/HOIS$. Several functions can be fitted into the Lan and DeMets (1983) alpha spending function including the O'Brien Fleming used in this analysis (Reboussin, DeMets, & Lan, 2000):

$$\propto^*(t) = \begin{cases} 0, & t = 0 \\ 2\left(1 - \Phi\left(Z_{\propto/2}/\sqrt{t}\right)\right), & 0 < t \leq 1 \end{cases}$$

Φ is the standard nomal distribution function. The function thus allows for the calculation of sequential boundaries b_q. This statistic corresponds to the critical Z-value for the allocated α at each step of the interim analysis.

Sufficiency

At each interim point of the analysis q we obtain two standardized test statistics Zq and b_q that denote the Z values of the pooled effect size and allocated α respectively. Sufficiency is determined by comparing the Zq and $b_q$scores at each step of the interim analysis. As long as $[Zq] < b_q$ sufficiency has not yet been attained and further studies are needed. However, if

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the criterion of $\lceil Zq \rceil \geq b_q$ is reached at an interim point of the analysis sufficiency of evidence indicates that a predetermined treatment effect exists. In turn, if the optimal information size has been reached and $\lceil Zq \rceil < b_q$, sufficiency of cumulative evidence is achieved to refute the effectiveness of the intervention in relation to the predetermined effect size, α and power.

3. Results

3.1 Literature search

The systematic literature search identified k=28 and k=39 eligible randomized controlled trials studies of ACT for anxiety and depression respectively. Study characteristics including trial characteristics, control group characteristics, and outcomes are described in Table 1-3.

[Insert Tables 1 - 3 about here]

The total participant sample in this quantitative review was n=1628 and n=1987 participants in anxiety and depression trials. The sample size for participants within both anxiety and depression treatment trials varied from n=6 to n=125 per group. All papers were published between 1989 and 2015. Within the reviewed sample the modus of published trials for anxiety treatment were in 2011, 2013 and 2014 (k=8). In turn, for depression the modus of published depression treatment trials was in 2011 and 2012 (k=8). For both anxiety and depression outcomes the majority of trials compared ACT against a waiting list control (WL; k=17 and k=22 studies for anxiety and depression respectively). The majority of anxiety treatment trials used CBT as bona fide treatment comparator (k=7). Similarly, the most frequent bona fide control treatment condition in depression treatment trials was CBT (k=9). The most frequently used anxiety outcome measure was the Depression Anxiety and Stress Scale (DASS-A, k=9). In turn, the most frequently used depression outcome measure was the Beck Depression Inventory (BDI, k=18). Less than a third of anxiety trials (k=10) employed an active control condition compared to 38% of depression trials (k=15). Eighteen per cent of anxiety trials (k=5) and 31% of depression trials (k=12) predetermined the primary target outcome.

3.2 Literature appraisal

3.2.1 Optimal information size (OIS)

The calculated heterogeneity adjusted optimal information size was n=220 and n=848 for pre-post and group comparisons respectively.

3.2.2 Cumulative meta-analyses

A series of random-effects cumulative meta-analyses were conducted. Findings are listed in Table 4. Regarding the primary aims the cumulative meta-analysis yielded large significant effects for pre-post treatment reduction in anxiety (d= .95, p<.001) and depression (d=.92, p<.001) scores. Analyses also revealed a small significant effect for group treatment changes for anxiety (d= .45, p<.05) and a medium effect size for depression (d=.54, p<.001) favouring ACT.

[Insert Table 3 about here]

Regarding the secondary aims, for ACT for anxiety the pre-post comparison suggested a large significant effect (d=1.85, p<.01) when anxiety was predetermined as primary treatment

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target. In turn, ACT for anxiety in active control conditions revealed no effect (d= -.04, n.s.). Similarly, findings for ACT for anxiety in group comparisons when anxiety was the primary treatment target revealed a non-significant large effect (d= .77, n.s.). In pre-post comparisons for ACT where depression was the primary treatment target findings suggested a large significant effect (d= 1.22, p<.001). Group comparisons for ACT for depression as a primary treatment target suggested also large significant effects (d= .73, p<.001). In group comparisons for ACT versus an active control conditions findings suggested a small non significant effect (d=.26, n.s.)

3.2.3 Sequential meta-analyses

In relation to sufficiency, findings will initially be described for ACT in both pre-post and group comparisons for the whole study sample. We will then continue to describe findings comparing ACT when anxiety or depression was specified a-priori as target outcome and against active control conditions. Lastly, findings from auxiliary analyses will be described.

As illustrated in (Figs 2a,c,d), sufficiency was reached for all SMAs for anxiety and depression with the exception of ACT for anxiety in group comparisons (Fig. 2b). In this comparison, although statistical sufficiency (HOIS) was reached, the threshold boundary was not crossed thus based on these data it cannot be assumed that ACT is moderately effective in treatment of anxiety in group comparisons. It is of note that for ACT for depression in pre-post comparisons, the intermittent Z-value crossed the threshold boundary at some point in the analysis (Fig. 2c). However, at the end point when the accumulated alpha has been reached (i.e. t≥1), the sequential boundary was not crossed ($Z_{\alpha=.01}$=2.46, $Z_{t\geq=1}$=2.17). Although at the end point of the analysis the sequential boundary has not been crossed, nonetheless statistical criterion for ACT as an efficacious intervention has been met.

Our analyses suggest that ACT for anxiety as an a-priori comparator in pre-post comparisons is at least moderately effective as the threshold boundary was crossed at some point in the analysis (Fig. 3a). In contrast, findings from the SMAs of ACT for anxiety in group comparisons when a-priori determined as treatment or when compared with active control conditions, suggest that there is currently insufficient evidence to indicate a medium effect (Fig. 3b & 3c). . As described in Table 3 additional samples of n=573 and n=290 participants respectively would be required to reach the predetermined heterogeneity adjusted optimal information size for group comparisons when anxiety has been predetermined or compared to an active control condition.

In relation to ACT for depression findings suggest that there is sufficient evidence of a least a medium effect in studies where depression was a-priori specified as a target outcome. This is the case for both pre-post and group comparisons (Fig. 4a & 4b),. Conversely, our findings suggest that ACT for depression in group comparisons with active control conditions there is currently insufficient evidence to indicate a medium effect as sufficiency (HOIS) has been reached (HOIS) (Fig. 4c). An additional samples of n=93 would be required to reach the predetermined heterogeneity adjusted optimal information size for group comparisons with active controls in depression.

3.2.4 Auxiliary analyses

To further explore the differential efficacy of ACT and CBT we conducted additional post-hoc meta-analyses. For anxiety findings from a cumulative meta analysis (k=8) suggest that there is currently no differential effect between these two treatment modalities (d=.08, n.s.). An

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additional n=260 participants would be required to be able to determine the sufficiency of cumulative evidence.

Similarly the cumulative evidence (k=10) of ACT for depression revealed no differential effect between ACT and CBT (d=-.01, n.s.). An additional n=314 participants would be required to be able to confidently appraise the statistical sufficiency of the cumulative evidence.

3.2.5 Publication Bias Analysis

As we did not include unpublished work in our meta-analyses we tested for publication bias in the following ways. Firstly, funnel plots were examined. demonstrating no systematic publication biases (tables available from first author on request). Secondly..Fail-safe N (Rosenthal, 1979) values ranged from k=2048 to k=6708 studies for the primary study aims, suggesting absence of publication bias. For the secondary study aims Fail-safe N values ranged from k=288 to k=671 studies, again suggesting absence of publication bias.

4. Discussion

The aim of this paper was to quantitatively review the cumulative evidence for ACT as a treatment for anxiety and depression. In doing so we generate sample size estimates for ACT trials in which there is currently insufficient evidence to determine the sufficiency of the evidence for ACT. Our novel statistical approach enables us to confidently appraise the treatment literature from a standpoint of statistical sufficiency. In contrast to conventional meta-analysis our approach controls for typical threats to statistical techniques in the evaluation of evidence based psychological therapies e.g. type I and II statistical errors; and between-sample heterogeneity – thereby enhancing the statistical basis for determining treatment sufficiency.

In total we included k=28 and k=439 studies for anxiety and depression respectively. The cumulative pooled effect sizes for ACT for anxiety for both pre-post and group comparisons ranged from d= .45 to d=.95. In turn, the cumulative pooled effect sizes for depression in trials comparing ACT in pre-post and group comparisons ranged from d= .54 to d=.92. Our findings suggest that there is currently cumulative evidence for the efficacy of ACT versus controls in the treatment of anxiety and depression. All four cumulative meta-analyses for anxiety and depression were statistically significant. Equally findings from SMAs suggested sufficiency of evidence of an at least moderate effect for these conditions with the exception of ACT for anxiety in group comparisons. Thus one can conclude that with respect to the efficacy of ACT versus control conditions statistical sufficiency is reached and no further randomized clinical trials are required. Findings are thus in keeping with the previous literature for the overall cumulative efficacy of ACT (e.g. Hayes, Luoma, Bond, Masuda, Lillis, 2006; Ost, 2008; Powers et al., 2009; Ruiz, 2010, 2012). However, applying an SMA approach suggests that although sufficiency has been reached in terms of clinical trials (as exemplified by above-threshold HOIS values), we conclude that the effect size of ACT for anxiety in-group comparisons is below a moderate effect.

However, findings are more qualified when considering the evidence for ACT compared to active control conditions i.e. existing evidence-based therapies, and when anxiety or depression were the primary treatment targets. For anxiety, although cumulative evidence

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suggest a strong significant effect in pre-post comparisons (d=1.85, p<.001) other cumulative meta-analyses for ACT for anxiety were not significant. Similarly, SMAs of ACT for anxiety for group comparisons failed to reach sufficiency (Figs 3b&c). There is currently insufficient evidence to confidently infer a moderate effect between these intervention conditions (Fig. 3). However ACT for anxiety in pre-post comparisons, where ACT has been specified a-priori as the primary outcome, there is sufficient evidence to infer that ACT has a moderate effect. With respect to the analyses that fail to reach sufficiency two factors might account for these findings. Firstly, these SMAs for anxiety were underpowered; thus findings may have been erroneous. Secondly, Z values for the cumulative evidence suggest that, although HOIS has not yet been reached, there is no differential benefit for ACT in group conditions when ACT was predetermined as a treatment outcome or when compared to an active control (Z_{active}=-.46; Fig. 3c). Equally, there is little differential benefit for ACT for anxiety in group comparisons when primarily targeting symptoms ($Z_{group,\ primary}$=1.22; Fig. 3b). Findings therefore seem to indicate similar outcomes are obtained irrespective of the active intervention. It is thus not likely to assume that additional clinical trials will reveal differential efficacy. These findings may inform treatment planning in settings or healthcare structures where estimates of differential efficacy are practically relevant to operationalizing treatment programmes.

Conversely, where ACT for depression was the primary outcome the cumulative evidence suggest large significant effects in both group-($d_{group,\ primary}$ =.73, p<.01) and pre-post comparisons ($d_{pre\text{-}post,\ primary}$=1.22, p<.001). Findings from SMAs for these comparisons also suggests that sufficient evidence exists to indicate an at least medium effect (Fig. 4a & 4b). However, cumulative evidence of ACT for depression against active controls suggests a small non significant effect ($d_{group,\ active}$=.26, n.s.). However. the SMA for this comparison (Fig. 4c) failed to reach statistical sufficiency. Consequently, the same issues raised above with regard to the anxiety comparisons that failed to reach sufficiency also apply to the effect of Act for depression when compared against normal controls.

It is noteworthy that careful consideration should be given whether and how additional randomized control trials meaningfully add to the existing knowledge base. For example in our study, when appraising the effect size of ACT for anxiety in active control conditions (i.e. d=-.04, n.s.), a difference in treatment gains might not become readily apparent. A possible explanation for this may be that ACT and CBT share therapeutic techniques, particularly exposure strategies.

Overall, the findings suggest that ACT is effective in the treatment of common mental health difficulties; however not more so than traditional treatment approaches. For instance, within the theoretical literature on ACT there has been discussion of the treatment mechanisms by which ACT leads to change in clinical presentations e.g. psychological flexibility. Our analysis does not evaluate these questions of process. Therefore, it may be a productive line of enquiry for future studies of ACT to emphasise the unique components of the intervention that may generate change in particular presentations (Arch & Craske, 2008). From this perspective, future research might thus attempt to answer questions of optimising treatment matching i.e. 'what works for whom' (Roth & Fonagy, 2006).

We acknowledge that the review is subject to several caveats. Efforts were made to retrieve grey literature in relation to ACT RCTs to minimise the impact of publication biases. Results of the analyses indicate no significant file drawer effect, thus publication errors are not likely to have significantly biased our results.

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The heterogeneity indexes suggest a significant level of between study variance in the sample. Therefore it could be argued that the study sample is too diverse to meaningfully infer general conclusions regarding the evidence base as a significant proportion of between study variance has not been explained. However, our findings are in keeping with previous quantitative reviews and as such offer additional support for the veracity of our findings. In addition, the observed heterogeneity may be considered an accurate reflection of the scope of the application of ACT and as such might be suggestive of the external validity of our findings. We also acknowledge that our study set out to explore the efficacy of ACT for anxiety and depression. Consequently, the current analyses cannot comment on the efficacy of ACT for other complex mental health conditions e.g. psychosis (White et al., 2013) or physical health conditions such as chronic pain (McCracken, Sato, & Taylor, 2013).

The use of SMA has introduced discussion around the use stop criteria in research considerations (Higgins et al., 2010; Pogue & Yusuf, 1997). As noted our intention in using the method has been to inform future research. Although historically SMA has been used to inform decision on research funding in clinical trials (Wetterslev et al., 2008) we caution against the indiscriminate application of SMA for such sole purpose. Whether or not individual trials proceed is a complex decision making process of which sufficiency considerations might comprise one aspect of multiple evidence strands, e.g. in conjunction with Disability Adjusted Life Years (DALYs).

Lastly, it is important to note that symptom reduction is not the primary intervention objective of ACT interventions; instead ACT aims to improve psychological flexibility (Harris & Hayes, 2009; Hayes et al., 2011). Future studies might want to investigate other outcome domains consistent such as function or quality of life which may be more germane to third wave interventions.

Acknowledgment

Kuppens et al. (2012) whose previous publications introduced us to SMA and thus enabled us to use the method for the purpose of this meta-analysis.

Conflict of Interest

The authors report no conflicts of interest in the preparation of this article. Dr MacBeth was supported by an NHS Research Scotland Career Research Fellowship while preparing the article. The funder was not directly involved in the conduct of the research or the write-up.

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Figure 1: Flow diagram of the study selection process.

Figure 2: Sequential meta-analyses of ACT for Anxiety and Depression (pre-post, group comparisons).

Fig. 3. Sequential meta-analyses of ACT for Anxiety (primary outcome, active control condition).

Fig. 4: Sequential meta-analysis of ACT for Depression (pre-post primary outcome, group primary outcome, group active control comparisons).

Table 1: Characteristics of studies included in the meta-analyses

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Study Reference	Country and Type of Sample	Recruitment	Initial Sample Size (Analysed Sample)	Mean age (s.d)	Male/Female (n)	Ethnicity %	Education	Problem & severity	Treatment Dosage for ACT intervention
Studies Measuring Depression as outcome of interest									
Zettle & Rains 1989	USA Community	Self-selecting Volunteers via media	31 (31)	41.3 (N/R)	0/31	N/R	Mean 14.1 yearsof education; All at least High School Level	Clinical Depression	12 weekly group sessions
Bond & Bunce., 2000	UK Business	Self-selecting volunteers via flyers	90 (65)	36.43 (9.72)	45/45	N/R	Primarily University Graduates	Stress Management	3 group sessions over 14 weeks
Hayes et al., 2004	USA – Clinical: Substance Misuse in Treatment	Recruitment from 3 Methadone Clinics	138 (78)	42.2 (N/R)	67/72	Ethnic Minorities = 13%	N/R	Participants met DSM-IV criteria for Substance Abuse or Dependence	16 week protocol, 48 sessions – 32 individual +16 group
Lappalain et al., 2007	Finland – clients seeking psychotherapy	Self-selecting from media adverts	28 (28)	41.8 (13.2)	3/25	N/R	N/R	Common difficulties predominatly depression, interpersonal and anxiety problems	10 individual sessions
Wicksell et al., 2009	Sweden – Clinical sample of Adolescents with chronic pain	Chronic idiopathic pain referred to specialist Pain Treatment Service	32 (32)	14.8 (2.4)	7/25	N/R	N/R	Chronic pain of >3 months	10x weekly 1 hour individual sessions + 1-2 sessions with parents (90 mins)
Hinton et al ., 2010	USA – University Students	Self selecting volunteers via flyers	22 (22)	20.09 (2.56)	6/16	Euro/American = 86.5% African/American = 4.5% MultiEthnic = 9 %	96% full time college students	Evidence of low-self esteem or negativity AND scoring as Distressed on standardised	3 weekly, 1 hour individual sessions

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								measures	
Smout et al., 2010	Australia – Clinical sample of Methamphetamine Users	Recruited from Drug and Alcohol Services, plus media recruitment	104 (31)	30.9 (6.5)	57/47	N/R	7–10 years =25% 11–13 years =49% Vocational education =17% University =9%	Met DSM-IV criteria for methamphetamine abuse or dependence; Use at least once weekly over past 3 months	12x weekly 1 hour individual sessions
Twohig et al., 2010	USA – Community sample of individuals presenting with OCD	Recruitment from Health Professionals and via media	79 (79)	37 (15.5)	31/48	Caucasian =88.6% African American =1% Asian American=2.5% Latin American=5% Native American=2.5%	Mean = 14.9 years of schooling (*SD* □ 2.0)	Met DSM-IV criteria for OCD	8x weekly 1 hour individual sessions
Hayes et al., 2011	Australia – Clinical Sample of adolescents	Recruitment from public child and adolescent psychiatric services	38 (30)	14.9 (2.55)	11/27	N/R	71% of sample attending school	Moderate to severe depressive symptoms via DAWBA	Individual sessions (no number of sessions given)
Folke et al., 2012	Sweden – Individuals on disability or illness benefits	Recruitment from regional Social Insurance Office	34 (27)	43.24 (9.46)	4/30	All Caucasian	N/R	DSM-IV Unipolar Depression + Unemployment and Sick Leave	1 individual + 5 group sessions
Kocovski et al., 2013	Canada – Community sample of Social Anxiety Disorder	Recruitment from Health Professionals and via media	137 (137)	Tx: 34.94 (12.52)	63/74	White = 62% Asian= 20% Black= 3.6% Hispanic=3.6% Other= 10.9%	College or university = 63.5% Some post secondary education = 27.0% N/R = 9.5%	DSM-IV diagnosis of Social Anxiety Disorder, Generalized	12x weekly 2 hour individual sessions
Alonso et al., 2013	Spain – selected clinical sample in nursing care homes	Recruitment from two selected nursing homes	10 (10)	Tx: 87 (2.44)	2/8	N/R	None = 40% Primary = 50% Secondary = 20%	Chronic musculoskeletal pain of articular origin for >6 months	10x twice weekly group sessions of 2 hours per week.
Lappalainen et	Finland – community sample	Self-selecting via	24 (24)	Tx: 47.1 years	24/0	N/R	Tx: Mean duration of 7.1	"Exhaustion, stress symptoms,	Integrated progra

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al., 2013	of males	newspaper advert		(SD 4.72			years	or sleeping problems".	m of web/mobile apps, personal monitoring and software with 3x group intervention sessions
McCracken et al., 2013	UK – Community sample with Chronic Pain	Recruitment from General Medical Practices	73 (58)	58.0 (12.8)	23/50	White British = 97.3%	Mean = 12.4 years of education (SD =4.2)	Persistent pain of longer than 3 months' duration with GP consulations, Distress/Disability and use of Medication	4x Group sessions, each4 hours long. 3x one week and a further session one week later.
Clarke et al., 2014	UK - clinical sample of individuals with treatment resistant mental health problems	Referrals from Specialist personality disorder clinic in a public health setting	45 (45)	43.46 (s.d. 1/4 12.35).	20/41	N/R	N/R	Treatment resistance via > one previous 8-session episode of psychological therapy	16x weekly group sessions of 2 hours duration
Livheim et al., 2014.	Australia – community sample of young people at school	Referral via school counsellors	51 (51)	14.6 (1.03)	8/43	N/R	N/A	mild to moderate depressive symptoms	8x weekly group intervention sessions
Tamannaeifar et al., 2014	Iran – Clinical sample of women with depressive disorder	Referral to University Clinic	19 (19)	25.2 (4.2)	0/19	N/R	Diploma = 58% Master = 42%	DSM-IV diagnosis of Major Depressive Disorder	12x twice weekly group intervention sessions
Mojtabaie, et al., 2014	Iran - clinical sample of women with breast cancer	Referrals from specialist clinic	30 (30)	N/R	0/30	N/R	N/R	Depressive symptoms, no diagnostic or severity criteria	8 intervention sessions of one hour duration
Kohtala et al., 2015	Finland – community sample of individuals	Self-selecting via local media	57 (57)	46.2 (SD = 11.9	12/45	All caucasian	Comprehensive school = 9% Secondar	subjective depressive symptoms or depressed	4x group intervention sessions

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	reporting depressive symptoms						y school = 45% Higher educatio n = 43% Other = 3%	mood	of 1 hour duratio n
Studies Measuring Anxiety as outcome of interest									
Zettle et al., 2003	USA - College students	Self selecting volunteers via flyers	37 (24)	30.9 (N/R)	7/30	White= 66.6% Black = 21 %Hispanic =12.5%	N/R	Test anxiety	6 individu al weekly sessions
Brown et al., 2011	USA - University students	Self selecting volunteers from Psychology courses	16 (16)	20.2 (1.9)	5/11	White =43.7% Asian/Pacific Islander =25% Black =6.2% Caribbean/Hai tian= 6.2% Latino=6.2% Multiracial/ot her= 12.5%	N/R	Test anxiety	Single – 2 hour group session
Mo'Tamed i et al., 2012	Iran – clinical sample of female patients with headache	Self-referral from women attending specialised headache clinic	30 (30)	Tx: 34.1 8 (7.30)	0/30	N/R	Tx Group: 13.00 (2.90)	Internatio nal Classificati on of Headache Disorders diagnosis of primary chronic headache	8x weekly group sessions
Arch et al., 2012	USA – Clinical sample of Anxiety disorders	Adult Outpatient s recruited via media	128 (128)	37.9 3 (11.7 0)	61/67	White =67.2% Asian American/Paci fic Islander =8.0% African American/Blac k =8.8% Hispanic/Latin o=12.0% American Indian/Alaska n Native= 0.08%	15.41 (2.07)	DSM-IV Diagnosis of Anxiety Disorder (Panic, Social Anxiety, Specific Phobia, OCD or GAD)	12 individu al weekly 1-hour sessions
Zargar et al., 2012	Iran - Clinical Sample of GAD	Patients receiving treatment for GAD	24 (18)	Tx: 34.5 (2.41)	0/24	N/R	Guidance School = 11.1% High School = 77.8% Bachelor = 11.1%	DSM-IV Diagnosis of Generalize d Anxiety Disorder	12 x 90 minute sessions
Craske et al., 2014	USA – individuals with social phobia	Referrals from local flyers, Internet and local newspap er advertise	87/87	28.3 7 (6.76)	47/87	White=50.57 % Hispanic/Latin o=17.24% African American/Blac k=2.30% Asian American/Paci fic Islander=18.3 9%	Mean no. of years= 15.04 (1.95)	DSM-IV Diagnosis of Social Anxiety Disorder	12 weekly sessions of individu al interve ntion

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		ments, and referrals.							
Lanza et al., 2014	Spain – Forensic population of women with substance misuse disorders	Referrals from Prison Team	50 (50)	Tx: 31.1 (6.4)	0/31	N/R	N/R	DSM-IV diagnosis of substance misuse disorder	16x weekly group sessions of 90 minutes duration
Studies measuring both Depression and Anxiety as outcomes									
Gratz et al., 2006	USA – Clinical Sample of Females presenting with Borderline PD	Patients referred from clinicians at psychiatric hospital, private practice and self-referrals via advert	22 (22)	33.32 (9.98)	0/22	All White	Some college =21% College Graduate 42% Graduate school=37%	Meeting 5 or more criteria for DSM-IV BPD + at least 1 episode of DSH over previous 6 months	14x weekly group session
Woods et al., 2006	USA – Unclear sampling	N/R	28 (25)	35.0 (10.2)	3/25	Caucasian = 96.4% African American = 3.6%	Mean years of education = 15.0 (2.8)	DSM-IV diagnostic criteria for Trichotillomania;	10 x individual sessions across 12 weeks
Forman et al., 2007	USA – Clinical sample with "Distressing Symptoms"	Clients presenting to University Counselling Center	101 (99)	27.87 (7.25)	20/81	Caucasian =64.4% Asian =10.9% Black =12.9% Latino=3.0%	N/R	DSM-IV diagnostic criteria for depressive, anxiety or adjustment disorders	Mean of 15.27 individual sessions
Roemer et al., 2008	USA – clinical sample with Generalized Anxiety Disorder	Clients seeking treatment at specialist centre for anxiety disorders	31 (31)	33.59 (11.74)	9/22	White = 87% Latino/Latina = 6.5 Black = 3.25% Asian =3.25%	N/R	DSM-IV Diagnosis of Generalized Anxiety Disorder	4x 90 minute individual sessions + 12x individual weekly 1-hour sessions
Wicksell et al., 2008	Sweden – Clinical sample of chronic pain and whiplash	Self-selecting via Patient Organisation in one geographical area of Sweden	22 (20)	Tx: 48.2 (7.8)	5/16	N/R	N/R	Pain duration of >3 months	10 individual sessions over 8 weeks
Johnston et al., 2010	New Zealand – Clinical sample	Referral via contact with Clinical	24 (14)	Median age = 43	10/14	N/R	N/R	No severity criteria	Self-Help intervention

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	with chronic pain	Psychology and Pain Clinics							via book and workbook
Bohlmeijer et al., 2011	Netherlands – Clinical sample with depressive symptoms	Self-referral via targeted recruitment from mental health institutions	93(93)	49.02 (10.70)	17/76	White Dutch = 85% Other = 8% N/R = 7%	<13 Years of education= 26.9% 13-16 Years of education = 33.3% >16 Years of education = 39.8%	Mild to moderate psychological distress	8x 2-hour group based intervention.
Fledderus et al., 2011	Netherlands – Community sample with depressive symptoms	Self-referral via media adverts	376 (376)	42 (N/R)	113/263	White Dutch = 93% Other = 7%	Low Level = 1.5% Middle Level =12% High Level = 86.5%	Mild to moderate depressive symptoms	9-week protocol with Self-help book + weekly email support with guided questioning
Muto et al., 2011	USA – Japanese students studying at overseas University	Self-referral via flyers on campus and email to students	70	23.6 (N/R)	26/44	N/R	N/R	No severity criterion	Self-help workbook completed over 8 weeks.
Thorsel et al., 2011	Sweden – clinical sample of individuals with chronic pain	Recruitment from specialised pain clinic	90(90)	46.0 years (SD 12.3)	32/58	N/R	N/R	Chronic pain with no severity criterion	1x initial individual face to face session; workbook + 7 weeks of 30 minute phone support ; 1x 90 minute concluding face to face session
Westin et al., 2011	Sweden – Clinical sample of individuals with	Recruited from audiology departments and self-	64 (62)	50.9 years (SD= 12.9	34/30	N/R	N/R	Tinnitus of duration of > 6 months	Up to 10x individual sessions

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	tinnitus	referral via adverts							, mean number of session = 8.38 (1.56)
Wetherell et al., 2011	USA – community sample with chronic pain	Recruited via clinics, advertisements, media, pain support groups, other studies, referrals from other participants	114 (114)	54.9 (12.5)	56/58	N/R	44.7% had at least a bachelor's degree	Chronic non-malignant pain > 6 months duration, with significant severity and interference	8x weekly group sessions
Jeffcoat et al., 2012	USA – sample of teachers and staff of educational district	Self-referral after mail drop via staff support office	236 (186)	N/R	N/R	N/R	N/R	No severity criterion	Self-help workbook completed over 8 weeks.
Jensen et al., 2012	Sweden – clinical sample of women with Fibromyalgia	Referral via Primary Care Physicians	43 (34)	45.6 years (SD 6.4)	0/43	N/R	N/R	Meeting 1990 American College of Rheumatology diagnostic criteria for fibromyalgia	12 weekly sessions (90 minutes each), conducted in groups of 6 patients.
Morton et al., 2012	Australia – clinical sample of individuals with Borderline PD	Referrals from specialist public sector mental health service	41 (28)	Tx: 35.6 (9.33)	3/38	N/R	Did not complete high school = 29% Completed high school = 34%Some tertiary/ has degree = 37%	Individuals with 4 or more of the 9 criteria for DSM-IV diagnosis of BPD	12x 2-hour group intervention sessions
Buhrman et al., 2013	Sweden – clinical sample of individuals with chronic pain	Recruitment from specialised pain clinic	76 (76)	49.1 (10.34)	31/45	N/R	Nine-year compulsory school=9.2% Upper secondary school=4	Functional impairment caused by chronic pain with medical investigation in previous year.	7 section online treatment program with downloadable mp3

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							7.4% University education= 43.4%		files. Mean number of 4.2 (2.7) sections completed
Carlbring et al., 2013	Sweden – community sample of individuals reporting as depressed	Recruitment via newspaper advert	80 (80)	44.4 (13.5)	14/66	N/R	Elementary school= 3.8% Upper secondary school = 16.3% Vocational training = 3.8% University (ongoing) =12.5% University (completed)= 63.8%	Symptoms of mild to moderate depression on MADRS-S	Module internet-based treatment programme + 15 minutes per week acces to internet therapist
Levin et al., 2014	USA – Undergraduate college students	Self-selecting via campus and local adverts	76(76)	18.37 (.54)	35/41	Caucasian =71.1% African American =7.9% Asian =9.2% Latino/Hispanic =15.8% Native American=9.2% Pacific Islander/Hawaiian = 2.6%	N/R	No severity criterion	2x web based multimedia lessons with tailored emails
Avdagic et al., 2014	Australia – individuals presenting with GAD	Self-selecting via campus and local adverts	51 (51)	36.17 (13.1)	17/34	N/R	N/R	DSM-IV Diagnosis of Generalized Anxiety Disorder	6x weekly group sessions of 2 hours duration
Livheim et al., 2014.	Sweden - community sample of young people at school	Self-selecting sample scoring above the 80th percentile SDQ, PSS and GHQ-12 at screening.	32 (32)	14-15 years	9/22	N/R	N/A	As for recruitmen but not severe problems or suicidal ideation	6x 90 minute weekly group intervention sessions
Yadavaia et al., 2014	USA - Undergraduate	Self-selecting sample of	78 (73)	19.69 (2.66	19/54	Asian/Pacific Islander=16% African-	N/R	GHQ-10 score of <10.	1x 6 hour worksh

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	college students	psychology undergraduates meeting screening criteria		0		American/Black=7% Hispanic/Latino=12% Native American=1% White/Non-Hispanic=74%			op

Notes: N/R = Not Reported; N/A = Not Applicable; Tx = Treatment Group; DAWBA = Development and Wellbeing Assessment (Goodman et al. 2000); UK = United Kingdom; USA = United States of America; GAD = Generalized Anxiety Disorder; OCD = Obsessive Compulsive Disorder; SDQ = Strengths and Difficulties Questionnaire; PSS = Perceived Stress Scale; GHQ-12 = General Health Questionnaire – 12 item;

Table 2. Measurement characteristics of ACT studies included in the meta-analysis for anxiety.

Study Reference	Post Treatment Group Comparison N (Tx)	N (Control)	Outcome measure	Control condition	Control group	Outcome category
Zettle et al., 2003	12	12	STAI	Active	SysD	Primary
Gratz et al., 2006	12	10	DASS-A	Passive	WL	No Differentiation
Woodset al., 2006	12	13	PAI-A	Passive	WL	No Differentiation
Forman et al., 2007	55	44	BAI	Active	CT	No Differentiation
Roemer et al., 2008	15	16	DASS-A	Passive	WL	Primary
Wicksell et al., 2008	11	10	HADS-A	Passive	WL	Secondary
Johnston et al., 2010	6	8	BAI	Passive	WL	No Differentiation
Bohlmeijer et al., 2011	49	44	HADS-A	Passive	WL	Secondary
Brown et al., 2011	6	6	STAI	Active	CT	No Differentiation
Fledderus et al., 2011	125	126	HADS-A	Passive	WL	Secondary
Muto et al., 2011	30	31	DASS-A	Passive	WL	Secondary

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Thorsell et al., 2011	28	27	HADS-A	Active	AR	No Differentiation
Westin et al., 2011	21	21	HADS-A	Active	TRT	Secondary
Wetherell et al., 2011	49	50	PASS	Active	CBT	No Differentiation
Arch et al., 2012	71	57	PSWQ	Active	CBT	Primary
Jeffcoat et al., 2012	39	42	DASS-A	Passive	WL	Secondary
Jensen et al., 2012	19	15	STAI	Passive	WL	Secondary
Mo'Tamedi et al., 2012	11	15	STAI-T	Passive	WL	No Differentiation
Morton et al., 2012	14	14	DASS-A	Passive	WL	Secondary
Zargar et al., 2012	9	9	PSWQ	Passive	WL	No Differentiation
Buhrman et al., 2013	29	32	HADS-A	Passive	WL	Secondary
Carlbring et al., 2013	40	38	BAI	Passive	WL	No Differentiation
Craske et al., 2014	33	29	CSR	Active	CBT	Primary
Lanza et al., 2014	18	19	ASI	Active	CBT	No Differentiation
Levin et al., 2014	37	39	DASS-A	Passive	WL	No Differentiation
Avdagic et al., 2014	19	19	DASS-A	Active	CBT	Secondary
Livheim et al., 2014 Swedish Sample.	15	15	DASS-A	Passive	TAU	Primary
Yadavaia et al., 2014	43	39	DASS-A	Passive	WL	No Differentiation

Note. Outcome measure abbreviations: STAI – State Trait Anxiety Inventory, DASS – Depression Anxiety Stress Scale, PAI-A - Personality Assessment Inventory Anxiety, BAI – Beck Anxiety Inventory, HADS – Hospital Anxiety and Depression Scale, PASS – Pain Anxiety Symptom Scale, PSWQ – Penn State Worry Scale, AS - Control condition abbreviations: SysD – Systematic Desensitization, WL –

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Waiting List, CT – Cognitive Therapy, AR – Applied Relaxation, TRT – Tinitus Retraining Therapy, CSR = Clinical Severity Rating; ASI = Anxiety Sensitivity Inventory .

Table 3. Measurement characteristics of ACT studies included in the meta-analysis for depression.

Study Reference	Post Treatment Group Comparison N (Tx)	N (Control)	Outcome measure	Control condition	Control group	Outcome category
Zettle & Rains 1989	11	10	BDI	Active	CT	Primary
Bond et al., 2000	24	21	BDI	Active	IPP	No Differentiation
Hayes et al., 2004	42	42	BDI	Active	ITSF	Secondary
Gratz et al., 2006	12	10	DASS-D	Passive	WL	No Differentiation
Woods et al., 2006	12	12	PAI-D	Passive	WL	No Differentiation
Forman et al., 2007	55	44	BDI	Active	CT	No Differentiation
Lappalainen et al., 2007	14	14	BDI	Active	CBT	Secondary
Roemer et al., 2008	15	16	BDI	Passive	WL	Secondary
Wicksell et al., 2008	11	11	HADS-D	Passive	WL	Secondary
Wicksell et al., 2009	15	14	CES-DC	Active	MDT	Secondary
Hinton et al., 2010	10	12	BDI	Passive	WL	Primary
Johnston et al., 2010	6	8	CMDI	Passive	WL	No Differentiation
Smout et al., 2010	14	17	BDI	Active	CBT	Secondary
Twohig et al., 2010	36	32	BDI	Active	PRT	Secondary
Bohlmeijer et al., 2011	49	44	CES-D	Passive	WL	Primary
Fledderus et al., 2011	125	126	CES-D	Passive	WL	Primary
Hayes et al.,	19	11	RADS-2	Passi	WL	No

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2011				ve		Differentiation
Muto et al., 2011	30	31	DASS-D	Passive	WL	Secondary
Thorsel et al., 2011	28	29	HADS-D	Active	AR	No Differentiation
Westin et al., 2011	21	18	HADS-D	Active	TRT	Secondary
Wetherell et al., 2011	49	50	BDI	Active	CBT	No Differentiation
Folke et al., 2012	14	13	BDI	Passive	WL	Primary
Jeffcoat et al., 2012	45	44	DASS-D	Passive	WL	Secondary
Jensen et al., 2012	20	16	BDI	Passive	WL	Secondary
Morton et al., 2012	14	14	DASS-D	Passive	WL	Secondary
Buhrman et al., 2013	29	32	HADS-D	Passive	WL	Secondary
Carlbring et al., 2013	40	38	BDI	Passive	WL	No Differentiation
Kocovski et al., 2013	37	32	BDI	Active	CBGT	Tertiary
McCracken et al., 2013	31	27	PHQ-9	Passive	WL	Primary
Alonso et al., 2013	5	5	GDS-10	Passive	WL	Secondary
Lappalainen et al., 2013	11	12	BDI	Passive	WL	Primary
Clarke et al., 2014	24	15	BDI	Active	CBT	Primary
Livheim et al., 2014. Australia Sample	32	19	RADS-2	Passive	TAU	Primary
Livheim et al., 2014 Swedish Sample	15	17	DASS-D	Passive	TAU	Primary
Tamannaeifar et al., 2014	10	9	BDI	Active	CBT	Primary
Levin et al., 2014	37	39	DASS-D	Passive	WL	No Differentiation
Avdagic et al., 2014	19	19	DASS_D	Active	CBT	Secondary
Yadavaia et al., 2014	28	39	DASS-D	Passive	WL	No Differentia

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										tion
Kohtala et al., 2015	28		29		BDI		Passive	WL		Primary

Note. Outcome measure abbreviations: BDI – Beck Depression Inventory, PAI-D – Personality Assessment Inventory Depression, HADS – Hospital Anxiety and Depression Scale, CES-CD - Center for Epidemiological Studies Depression Scale for Children, CES-D - Center for Epidemiological Studies Depression Scale, RADS-2 – Reynolds Adolescent Depression Scale 2, DASS – Depression Anxiety Stress Scale, PHQ9 – Patient Health Questionnaire 9 Control condition abbreviations: CT – Cognitive Therapy, IPP – Innovation Promotion Programme, ITSF – Intensive Twelve Steps Facilitation, WL – Waiting List, CBT – Cognitive Behavioural Therapy, MDT – Multidisciplinary Treatment Approach, PRT – Progressive Relaxation Training, AR – Applied Relaxation, TRT - , CBGT – Cognitive Behavioural Group Therapy, GDS-10 = Geriatric Depression Scale; .

Table 4. Cumulative meta-analyses of ACT for Anxiety and Depression.

`	k	HOIS	At final interim analysis					Boundary crossed	Sufficiency	Additional sample required (n)
Primary Analysis			N	t	d	95% CI	I^2			
Anxiety/P	28	220	818	>1	.95***	0.55-1.36	86.1	Y	Y	0
Anxiety/G	28	848	1628	>1	.45*	0.19-0.64	84.1	N	Y	0
Depression/P	39	220	1037	>1	.92***	0.64-1.19	82.7	N	Y	0
Depression/G	39	848	1987	>1	.54***	0.34-0.73	80.6	Y	Y	0
Secondary Analysis										
Anxiety/P/Primary	5	220	146	.84	1.85**	0.05-364	93.3	N	N	74
Anxiety/G/Primary	5	848	275	.43	.77	-2.38-	93.7	N	N	573

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						0.85				
Anxiety/G/Active	10	848	558	.83	-.04	-0.21-0.14	5.3	N	N	290
Depression/P/Primary	12	220	360	>1	1.22***	0.74-1.71	74.6	Y	Y	0
Depression/G/Primary	12	848	674	.71	.73**	0.30-1.16	63.9	Y	Y	0
Depression/G/Active	15	848	755	>1	.26	-0.06-0.59	73.3	N	N	93

Note. /P – pre post comparison; /G – group comparison; /Primary – Primary target outcome; Active – Active control condition; k - number of studies; HOIS - Heterogeneity Adjusted Optimal Information Size; d- Pooled effect size; 95%CI - 95% Confidence Interval; I^2- I-squared value. As described above I^2 is defined as the ration between difference of Q and the degree of freedom by Q.

* p < .05

** p < .01

*** p < .001

Highlights

- ACT is an efficacious treatment for anxiety or depression.
- Evidence is currently insufficient to conclude that ACT is more effective than CBT.
- We report sample size estimates where sufficiency criteria have not been met.
- Use of Cumulative and Sequential Meta Analysis can increase confidence in the conclusions of quantitative reviews.

Figure 1: Flow diagram of the study selection process.

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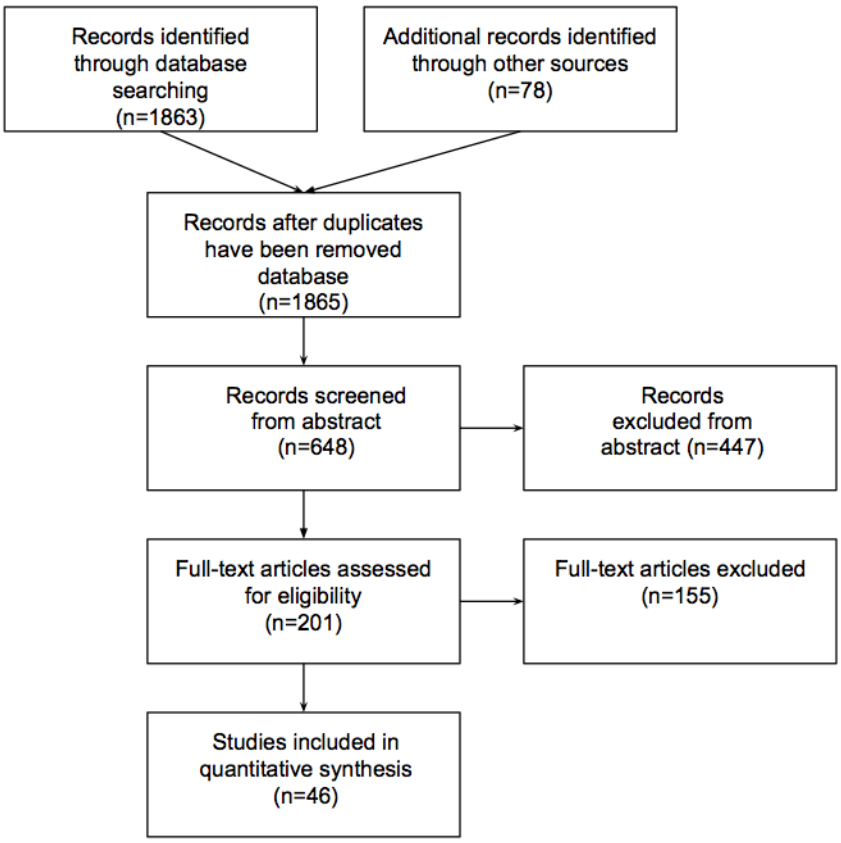

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Figure 2: Sequential meta-analyses of ACT for Anxiety and Depression (pre-post, group comparisons).

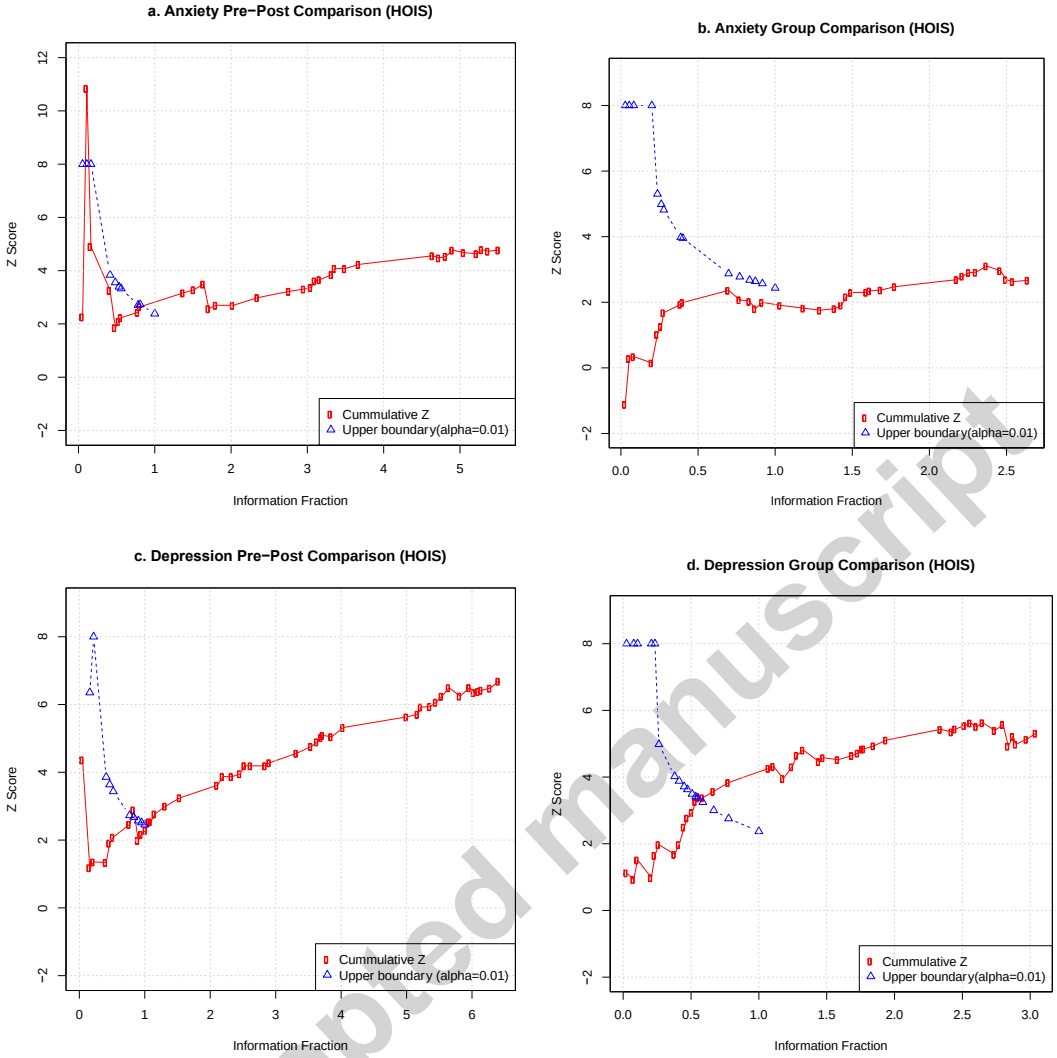

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Fig. 3. Sequential meta-analyses of ACT for Anxiety (primary outcome, active control condition).

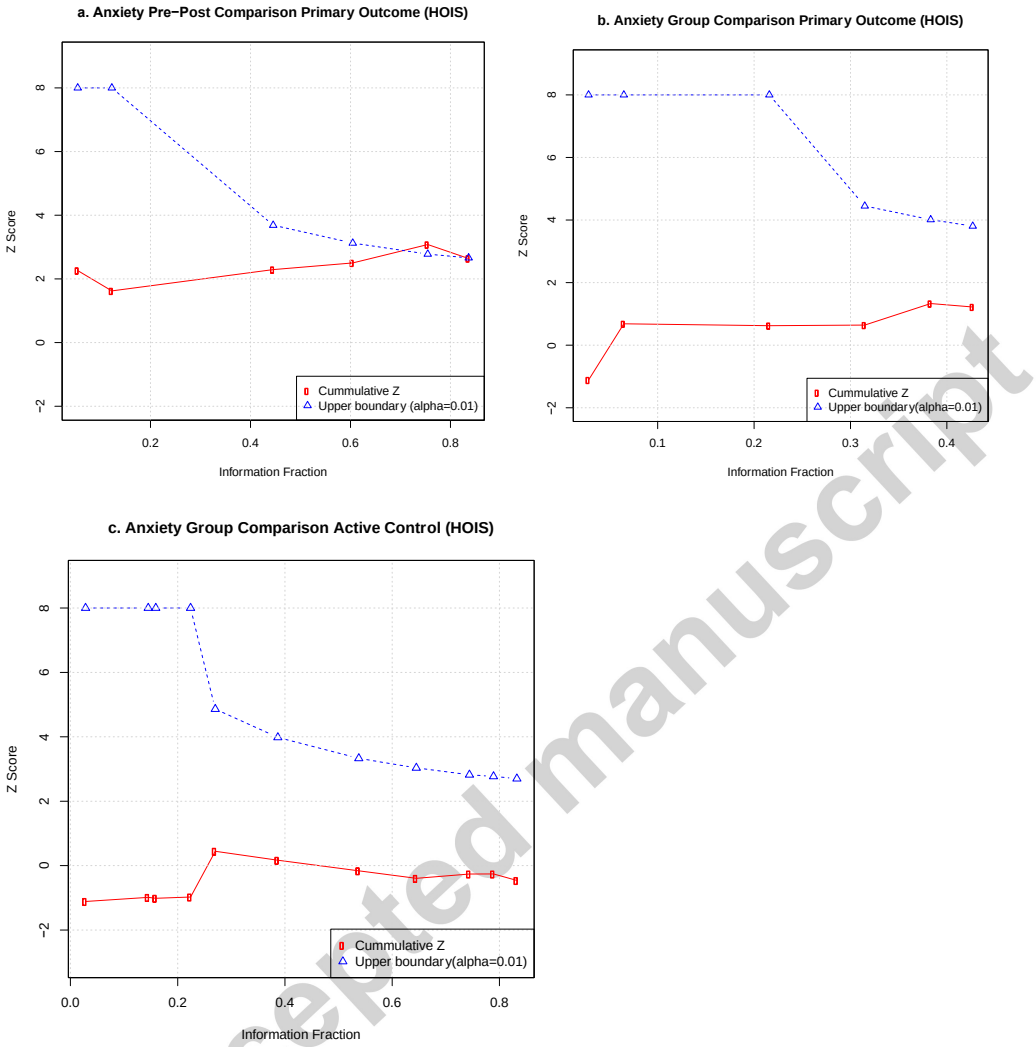

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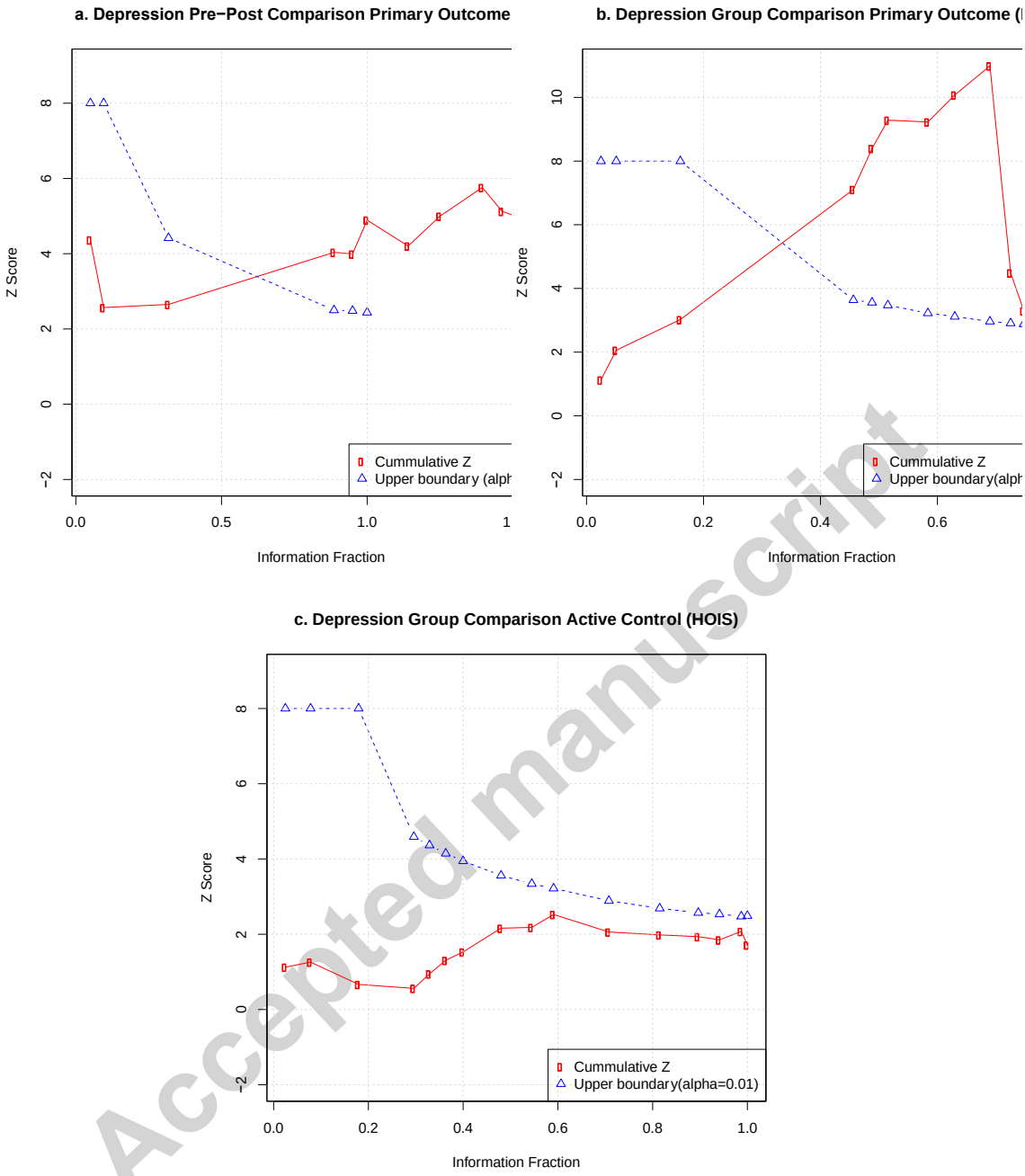
Fig. 4: Sequential meta-analysis of ACT for Depression (pre-post primary outcome, group primary outcome, group active control comparisons).



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