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Economic Impact of 'Third-Wave' Cognitive Behavioral Therapies: A Systematic Review and Quality Assessment of Economic Evaluations in Randomized Controlled Trials

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Abstract

The term third-wave cognitive behavioural therapy (CBT) encompasses new forms of CBT that both extend and innovate within CBT. Most third-wave therapies have been subject to RCTs focused on clinical effectiveness, however the number and quality of economic evaluations in these RCTs has been unknown and may be few. Evidence about efficiency of these therapies may help support decisions on efficient allocation of resources in health policies. The main aim of this study was to systematically review the economic impact of third-wave therapies in the treatment of patients with physical or mental conditions. We conducted a systematic literature search in PubMed, PsycINFO, EMBASE, and CINALH to identify economic evaluations of third-wave therapies. Quality and Risk of Bias (RoB) assessment of economic evaluations was also made using the Drummond 35-item checklist and the Cochrane Collaboration's tool for assessing risk of bias, respectively. Eleven RCTs were included in this systematic review. Mindfulness-Based Cognitive Therapy (MBCT), Mindfulness-Based Stress Reduction (MBSR), Acceptance and Commitment Therapy (ACT), Dialectical Behavior Therapy (DBT), and extended Behaviour Activation (eBA) showed acceptable cost-effectiveness and cost-utility ratios. No study employed a time horizon of more than 3 years. Quality and RoB assessments highlight some limitations that temper the findings. There is some evidence that MBCT, MBSR, ACT, DBT, and eBA are efficient from a societal or a third-party payer perspective. No economic analysis was found for many third-wave therapies. Therefore, more economic evaluations with high methodological quality are needed.

Keywords: Third-wave cognitive behavioural therapies; Mindfulness; Acceptance; Economic evaluation; Systematic review

Introduction

Description of third-wave therapies

According to Hayes (2004a), the first- and second-wave forms of cognitive behaviour therapy (CBT) emerged as attempts to develop well-specified and rigorous applied techniques based on empirically validated basic principles. Unlike earlier approaches, CBT is focused directly on symptom relief or behavior change. The "first wave" of CBT, also simply called behavior therapy, was developed in the 1950s, aimed to do this predominantly through the application of principles of classical and operant conditioning (Hayes, 2004a). However, stimulus–response associationism and behavior analysis appeared inadequate to address the role of human language and cognition in complex behavior patterns, and a need for both principles and methods that could incorporate patients' thoughts and feelings was clear (Hayes, 2016; Kahl, Winter & Schweiger,2012). Thus, second-wave forms of CBT emerged in the 1960s with a focus on assessing and intervening in relation to dysfunctional cognitions. Within these approaches negative thoughts and irrational beliefs are identified, challenged and disputed by means of techniques such as cognitive restructuring, in which the therapist and patient work together to change maladaptive thinking patterns, encouraging patients to replace these with more rational, realistic ones (e.g. Beck, 1967). From the 1960s until present, second wave forms of CBT, have been the dominant psychotherapies worldwide and are demonstrated to be cost-effective for a wide range of disorders (Mavranezouli et al., 2015; Pompoli et al., 2016; Skapinakis et al., 2016).

Second-wave CBT has succeeded in many respects, but has not been exempt from criticism (Hayes 2004a). First, effect sizes for CBT for some conditions are only modest, suggesting either weakness in the underlying model or some limits in application (e.g., Cuijpers et al., 2013). Second, hypothesised cognitive mediators frequently fail to explain

the results of CBT, casting doubt on the intended aims of conventional cognitive therapy methods (David & Montgomery, 2011). In addition, newer, constructivist, philosophical developments lead to questions with respect to the relatively mechanistic assumptions postulated by CBT. Altogether, these issues represent the breeding ground for discontent around the current mainstream. At the same time, it has been suggested that a potential avenue toward better therapy development may include a focus on the *function* of problematic cognitions and behaviors, and on a model of behavior that is more contextual, non-mechanistic, more consistent with evolutionary theory, and radically pragmatic (Hayes 2004a).

Under the broad umbrella term "third wave" there are forms of CBT that represent both an extension of and innovation within CBT. These therapies, some of them developed in the 1990s, are generally less focused on reducing psychological and emotional symptoms, although it is a consistent "side-benefit". These therapies do not have first-order change as their only objective, they are contextualistic, use experiential and indirect change techniques besides direct strategies, and have a broad focus of change (Hayes, 2004ab). Aspects of context here are broad, including environment, therapeutic relationship, and person (Pérez-Alvarez, 2012). According to Dimidjian et al. (2016), from 2004 to 2015, the "third wave" label has been linked to the following treatment approaches: Acceptance and Commitment Therapy (ACT; Hayes, Strosahl, & Wilson, 1999), Dialectical Behavior Therapy (DBT; Linehan, 1993), Mindfulness-Based Cognitive Therapy (MBCT; Segal, Williams & Teasdale,2013), Functional Analytic Psychotherapy (FAP; Kohlenberg & Tsai, 1991), and Extended Behavioral Activation (eBA; Martell, Addis & Jacobson,2001), whereas there is some discrepancy of view about others, such as Cognitive Behavioural Analysis System of Psychotherapy (CBASP; McCullough, 2000), Compassion-focused Therapy (CFT, Gilbert, 2009), Mindfulness-Based Stress Reduction (MBSR; Kabat-Zinn,

1982), Mindfulness-Based Relapse Prevention (MBRP; Bowen, Chawla & Marlatt,2011), Mindfulness-Based Eating Awareness Training (MB-EAT; Kristeller & Hallett, 1999), Metacognitive Therapy (MCT; Wells, 1995), and Integrative Behavioural Couple Therapy (IBCT; Jacobson & Christensen, 1996). Hayes, Villatte, Levin and Hildebrandt (2011), recognizing some resistance and division created by the term "third wave" (Hoffman, Sawyer, & Fang, 2010) proposed the alternative term "contextual cognitive behavioral therapies", but the term third wave has become so popular in the scientific literature that we use it here. Currently, there are contradictory opinions regarding the existence of a third wave of CBT that is replacing classical CBT. For example, for authors such as Hofmann and Asmundson (2008, p. 13), *there is no data to suggest that it (ACT) represents an entirely new treatment approach*". Of course, others would argue that the distinction is, at least initially, a philosophical one and not an empirical one (Hayes et al. 2011). A critical analysis of this issue is beyond the scope of this paper.

Third-wave therapies have obtained promising results for some conditions, but at the same time, clear superiority over other well-established treatments is infrequently demonstrated (Churchill et al., 2013; Dimidjian et al., 2016; Hoffman et al., 2010; Hunot et al., 2013; Öst, 2008; Öst, 2014). In a pioneering meta-analysis of the scientific evidence and methodological quality of third-wave CBT (including ACT, DBT, CBASP, FAP, and IBCT) for psychiatric disorders, Öst (2008) found that the total effect size for the third-wave RCTs was .56. Öst (2008) concluded that the third-wave therapies provide a significant moderate effect size, but they are limited by a lack of methodological quality of RCTs conducted to test them. More recently, Dimidjian et al (2016) carried out a search for meta-analyses of the therapies most frequently identified as third wave. Meta-analytic findings indicated that ACT showed superiority to a variety of control conditions. Regarding DBT, there was no strong indication in this study that it provides incremental

benefit over first- or second-wave CBT. Concerning MBCT, results indicated a significant

reduction of depression relapse across studies. Finally, eBA did not obtain compelling

indication that it outperforms second-wave CBT. The authors concluded that the therapies

classified as third wave offer significant clinical benefit over some control conditions, but

that more well-designed RCTs are needed. Currently, according to the definitions of "well

established" and "probably efficacious" treatments (APA Presidential Task Force on

Evidence-Based Practice, 2006; https://www.div12.org/psychological-

treatments/treatments/), only three third-wave therapies have achieved the status of "well-

established" treatments. Specifically, ACT, CBASP, and DBT have strong support for

chronic/persistent pain, depression, and borderline personality disorder, respectively.

Third-wave therapies address a wide variety of conditions, some of them extremely

difficult to manage and very costly for the healthcare system and the society as a whole.

For instance, DBT, CBASP and ACT are usually delivered to patients diagnosed of

Borderline Personality Disorder (BPD), chronic major depression and chronic pain,

respectively. Patients with BPD, chronic major depression or chronic pain consistently

show high patterns of healthcare service utilization and therefore carry high costs (Leadley,

Armstrong, Lee, Allen, & Kleijnen, 2012; Meuldijk, McCarthy, Bourke, & Grenye, 2017;

Pincus & Pettit, 2001).

How third-wave therapies are supposed to work

The second-wave of psychological therapies are based on a classical biomedical

model in four meanings (Pérez-Alvarez, 2012): internal perspective (information

processing), causal mechanism (dysfunction in psychological functioning), management

based on resolving the underlying dysfunctions, and effectiveness criteria (improvement of

symptoms). In contrast, third-wave therapies are much less based on pathology or

symptom-focused models, explaining the psychological problems in interactive, functional

and contextual terms (Kahl, Winter, & Scweiger, 2012). So, it is assumed that psychological problems emerge from the individual in his/her interaction with specific internal-external circumstances. For the contextual model of psychological therapy, the focus is not on symptom reduction. Instead the focus is on reducing experiential avoidance, increasing contact with the present moment, increasing acceptance, openness, and engagement with values (Hayes, 2004ab). Whereas in second-wave CBT the objective of identifying unwanted thoughts is to change them, in third-wave CBT the aim is to change the subject's relationship with unwanted thoughts and feelings so that experiential avoidance is decreased. They also include training in mindfulness techniques to improve awareness and a focus on the present moment. This is also intended to decrease restrictive or avoidance-coordinating effects of thoughts, and allow behaviour to be better regulated but the situation at hand. More conventional behavioural strategies also can be employed to help individuals to commit, rehearse, apply, and integrate behaviour change according to their goals and values.

The importance of economic evaluations

Economic evaluations describe the costs and effects of alternative treatments and are a useful tool for public health decision making. Policy-makers are faced with limited economic resources and routinely have to prioritize available treatments or choose among different alternatives (Haycox, 2009). In health economics, different analytic approaches are used for economic evaluation (cost-effectiveness, cost-utility, cost–benefit analysis, cost-minimization, and cost–consequences analysis) in order to compare alternative courses of action or treatments, in terms of costs and outcomes. The choice of analytic approach and outcomes used depends on the decision that analysts intend to influence (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). In *cost-effectiveness* analysis, natural unidimensional index of outcomes are used (e.g. points in a scale measuring depression severity); in *cost-*

utility analysis, the primary outcome is the cost per QALY (quality-adjusted life-years; which combine duration of life and the health-related quality of life); *Cost–benefit* analysis provides a monetary value to outcomes, and *cost–consequences* analysis includes a profile of outcomes for each alternative but does not combine the outcomes into a single unit of effect. Cost-effectiveness and cost–utility analysis are the analytic approaches most commonly used by decision-makers, being the last the alternative of choice for comparing the value of interventions that have very different health benefits (Konnopka et al., 2012).

Why it is important to perform this systematic review

Although most forms of third-wave CBT appeared 10 or more years ago, the number of well-designed economic evaluations of these therapies in RCTs is not known and may be few. The great interest in these relatively new therapies among clinicians and researchers, as evidenced by recent meta-analyses of clinical outcomes in recent years (Churchill et al., 2013; Dimidjian et al., 2016; Hunot et al., 2013), suggests a need for demonstrating whether they must be prioritized by policy-makers or regulatory bodies when deciding which option is the most efficient for the treatment of a particular patient group. As Churchill *et al.* (2013) pointed out, assessment of economic impact of third-wave therapies is a priority. To address the potential efficiency of third-wave therapies as standalone or add-on treatments is a subject of crucial importance for the implementation of these therapies in actual practice (Demarzo, Cebolla, & García-Campayo, 2015). However, as far as we know, despite the great popularity of these therapies, no systematic review of economic evaluations has been performed. In this study, we first perform a systematic literature review of economic evaluations alongside RCTs of third-wave treatments to determine whether they generate significantly greater health benefits, relative to costs, for the health care system and for society as a whole compared to usual care or other well-established treatment options. Second, we critically appraised the methodological quality and potential risk of bias of the included studies using the

Drummond's checklist for economic evaluations and the Cochrane risk of bias tool, respectively.

Material and Methods

The review protocol was registered at PROSPERO in April 1st 2016 (registration number: CRD42016037216), which is an electronic database of prospectively registered systematic reviews in health and social care. PROSPERO is funded by the UK National Institute for Health Research (http://www.crd.york.ac.uk/prospero/). We report this systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for systematic reviews (PRISMA; Moher et al., 2009).

Search strategy

We performed the literature search in the following electronic bibliographical databases: PubMed/Medline, PsychINFO, EMBASE and CINAHL. We searched manuscripts published in peer-reviewed journals at any time from the inception of the databases until May 1st 2016. Terms related to `third-wave´ therapies and economic evaluations were employed, without using limitations *a priori* (e.g. 'humans' or 'English' language). There were no restrictions related to age. For the full specific syntax in each database see Supplementary file 1. A secondary search strategy was performed by contacting experts in this field, by searching in Google Scholar, and by consulting tables of contents for journals that usually publish evaluations of third-wave CBT and reference lists of identified economic studies.

Inclusion and Exclusion Criteria

A consensus was reached among coauthors on which therapies should be included or excluded. As Hunot *et al.* (2013) pointed out, one key feature of these therapies certainly it their predominant focus on modifying the *function* of thoughts and feelings rather than on modifying the frequency or form of these thoughts and feelings, or their *content*. For the purposes of the current systematic review, the following therapies were included: ACT, DBT,

MBCT, FAP, eBA, CBASP, CFT, MBSR, MBRP, MB-EAT, MCT, and IBCT. An outline of these therapies is provided in Supplementary file 2.

The obtained titles and abstracts were separately screened for eligibility by two coauthors (A.F-S and J.V.L). Full text of all potentially related manuscripts where the abstract did not provide enough details to confirm eligibility, were downloaded, examined, and discarded from the systematic review if they did not meet the inclusion criteria. References of systematic reviews and references of the included papers, were also examined in depth and cross-checked. After duplicates were removed, data extraction of included papers was made by two independent researchers (A.F-S and J.V.L) using a standardised data extraction form with any disagreements resolved through discussion. Disagreements not resolved by the two coauthors were arbitrated by a third coauthor (F.D). Only published randomized controlled trials (RCTs) incorporating economic evaluations of `third-wave´ CBT (ACT, eBA, CFT, DBT, MCT, CBASP, FAP, IBCT, MBCT, MB-EAT, MBRP, and MBSR), compared with a passive or active control group, were included. Non-randomized studies, such as quasi-experimental designs or pre–post comparisons were excluded to maximize study quality and due to the high risk of selection bias associated with non-randomised study designs. RCTs had to have an adequate control condition: waiting-list, treatment-as-usual (TAU), sham intervention, a pharmacological treatment, or an alternative psychological treatment such as conventional CBT. Only full economic evaluations in which both the cost and consequences of two or more treatments are compared were included. Modelling studies were not included due to methodological differences with economic evaluations in RCTs (estimated and synthesized data instead of obtained raw data) that could threaten the internal validity of the present review. Literature reviews, books, dissertations, commentaries, conference abstracts, study protocols, case-reports, qualitative studies, non-peer-reviewed manuscripts and non-English or non-Spanish papers were also excluded. We excluded unpublished dissertations,

master's theses, or conference presentations because restricting our analyses to RCTs

published in peer-reviewed journals increased the likelihood that studies would be of at least

minimal acceptable quality and relatively accessible.

Study measures

Quality assessment for the economic evaluations. Quality assessment was based on

the *Drummond 35-item checklist* (Drummond & Jefferson, 1996). This checklist is

recommended by the Cochrane Handbook for Systematic Reviews of Interventions for

critical appraisal of the methodological quality of health economic evaluations and is the

most widely employed tool (Frederix, Severens, & Hövels, 2015). It is crucial to use this

type of quality assessment tools in the field of economic evaluation because they enable

decision-makers to know the reliability and validity of data. It comprises 35 items divided

into 3 sections: study design (7 items), data collection (14 items) and analysis and

interpretation of results (14 items). Each item can be completely satisfied (Yes) or not

(No), not clearly reported (Not clear) or Not applicable. Given that we excluded modelling

studies, items 20 and 21 focused on 'modelling' were not appropriate. One author (J.V.L)

completed the 35-item checklist for each study, which was subsequently reviewed by

another author (A.F-S or F.D). None of the authors assessed papers to which he/she had

participated as coauthor. All disagreements were resolved through discussion. We coded

"Yes" as a 1 and No or Not clear as 0. We did not divide the %-scores into arbitrary

categorisations of excellent, good and poor quality studies - the tool was developed as an

aid to reviewers and not as a measure of quality and 100% adherence does not indicate a

perfect study. The items concern whether particular data has been recorded and it was

possible for a poorly designed evaluation to report well. Following Donker et al. (2015), a

global adherence to the checklist equal or greater than 75% was considered to be indicative

of moderate to high-quality study (in cases where a 'not applicable' answer was logged,

the item was excluded from the denominator). Based on a systematic review of quality

assessment tools for conducting and reporting health economic evaluations the Drummond

checklist appears to possess sound inter-rater reliability and test-retest reliability (Walker

et al., 2012)

> *Risk-of-bias (RoB) assessment*. Several tools have been designed to assess the

validity/quality of RCTs. We assessed the stringency of the included RCTs using the

Cochrane Collaboration's risk of bias assessment tool (Higgins et al., 2011) because it

assesses conduct (and not reporting), is based on theoretical and empirical evidence, and

on broad consultation, and because it facilitates the transparent assessment of bias

(Jørgensen et al., 2016). This carefully designed tool involves assessment of RoB arising

from each of six domains: (a) selection bias, (b) performance bias, (c) detection bias, (d)

attrition bias, (e) reporting bias, and (f) other bias (bias related to other issues: therapist

qualifications, treatment fidelity and researcher allegiance/conflict of interest). The

selection of these domains for inclusion in the assessment tool was based on the empirical

evidence of their association with effect estimates (Higgins et al., 2011). The intention of

the developers was to assess the validity of results based on the design and performance of

the study, rather than reporting. The RoB tool was applied to each RCT independently by

two reviewers (AFS and JVL) and any discrepancies were resolved through discussion

with a third author. Each RCT was scored against the above criteria to provide a score of

between 1 and 6. RCTs were classified as *high risk* (if at least one domain was assessed as

high), *unclear* (if at least one domain was assessed as unclear and the other domains were

low), or *low risk* of bias (if all individual domains were low). The Cochrane

Collaboration's risk of bias assessment tool has been employed in many Cochrane reviews,

yielding a range of inter-rater agreement for the individual domains from poor (kappa κ =

.13 for selective reporting) to substantial (κ = .74 for sequence generation) (Hartling et al.,

2009). Our raters used the Cochrane Handbook guidelines for risk of bias assessments to standardize the decision-making process (Higgins & Altman, 2008).

Outcome measures. Any economic evaluation needs to consider carefully which outcome measures are important when evaluating treatments. In this field, a good practice is to use generic (non-disease-specific) outcome measures so as to help decision-making on resource allocation across diseases or disorders (Drummond et al., 2005). In general, the most recommended and common outcome measure for cost-utility analysis (CUA) is the quality-adjusted life years (QALYs) (Vergel & Sculpher, 2008). QALYs represent an effort to take into account measures of both mortality and morbidity generated by healthcare interventions. A QALY places a weight on time in different health states. Thus, a year of perfect health is worth 1 and a year of less than perfect health is worth less than 1. QALYs provide a common metric to assess the extent of the benefits gained from different treatments in terms of HRQoL and survival for the patient. Outcome measures for the cost-effectiveness analysis (CEA) are very heterogeneous and might include reduction of psychological symptoms, somatic symptoms, alcohol use, sleep disorders, self-harm behaviours, etc., as assessed with standardized instruments with sound psychometric properties. Other outcome measures can be the years lived with disability (YLD), health-adjusted life expectancies (HALEs), and disability-adjusted life years (DALYs).

Economic evaluation estimates

CEA results are commonly expressed in cost-effectiveness ratios (CER) while CUA are usually summarized in cost-utility ratios (CUR), where the costs in the numerator are combined to a specific common measure of effectiveness or utility in the denominator (Van Hout, Al, Gordon, & Rutten, 1994). When two interventions are compared using these ratios, there are called incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR). ICER provides an estimate of the cost for one additional unit of

improvement when administering the new treatment compared to the control using the formula: (Cost test intervention – Cost control intervention) / (Effect test intervention – Effect control intervention). ICUR indicates the cost of 1 QALY gained with the new treatment compared to the control treatment.

In health economics, costs can be determined from different perspectives including the societal perspective, the funding source perspective, the patient/family perspective, or the clinician perspective (Gold, Siegel, Winstein & Russell, 1996). It is crucial to determine which perspective is taken in the evaluation to know what costs have to be included in the analysis. For instance, from the societal perspective all costs and outcomes that affect everyone in society, regardless of who pays, are included (total medical costs for resource use, productivity losses and out-of-pocket expenditures). Another important index is the willingness to pay (WTP), an indicator for the acceptability of the new treatment compared to the control treatment. Society's WTP establishes the threshold to consider the new treatment as cost-effective. This WTP or investment ceiling is country-specific (Shiroiwa et al., 2010). To deal with uncertainty in the estimates, it is usual to show cost-effectiveness acceptability curves (CEACs), which represent the probability that the intervention is cost-effective compared to the control condition, given a varying threshold for the WTP for a clinical outcome or a QALY.

Data analyses

Main results of economic evaluations are provided in local currency units, which are the most relevant to local decision-makers. Additionally, for the purpose of ICURs comparisons, local currency were inflated to the year 2014 and converted into international dollars (Int$) using purchasing power parity (PPP) exchange rates (http://wdi.worldbank.org/table/4.16). PPP indicators are calculated by comparing the cost of living, domestic goods and services in countries across the world. Given the

heterogeneity of the costing methods and the therapies, a meta-analysis was not conducted. We computed inter-rater agreement using kappa (κ) statistics for inclusion/exclusion of studies, global quality assessment, and overall RoB assessment. Agreement was graded as follows: poor (.00), slight (.01–.20), fair (.21–.40), moderate (.41–.60), substantial (.61–.80), and almost perfect (.81–1.00).

Results

Selection and inclusion of studies

The systematic literature search identified 1,342 articles (765 abstracts in total, after removal of duplicates). 730 articles were excluded in the process of title and abstract screening. 35 potentially eligible full-text papers were examined in detail for further consideration, and 24 of these were excluded. Finally, 11 RCTs met the inclusion criteria. There was an "almost perfect" inter-rater agreement between the two raters (kappa: κ = 0.85). See Figure 1 for a flowchart of the process.

Insert Figure 1

Characteristics of included RCTs

Table 1 shows a summary of study characteristics. The eleven RCTs included a total of 1,794 outpatients. The sample sizes of the study arms ranged from 19 to 221 participants. The included RCTs were carried out in six different countries: the UK (n = 6), the Netherlands (n = 1), Australia (n= 1), Sweden (n= 1), Spain (n= 1) and the USA (n= 1). The studies analysed five types of third-wave therapies: MBCT (n= 5), ACT (n= 2), eBA (n = 2), DBT (n= 1), and MBSR (n= 1). The treatment lengths varied from six weeks to 12 months. Time horizons for economic outcomes were three to 26 months. Studies used maintenance antidepressant medication (n= 2), TAU (n= 4), waiting-list (n= 2), active monitoring (n= 1), applied relaxation (n= 1), CBT (n= 1) or recommended pharmacological treatment (n= 1), as control comparison conditions. Target diseases and

disorders were history of major depression (n= 3), active major depression (n= 2), somatoform disorders (n= 1), multiple sclerosis (n= 1), unspecific chronic pain (n= 1), fibromyalgia (n= 1), personality disorders (n= 1) and history of breast cancer (n= 1). All studies performed *full* economic evaluations[1] and four studies "discounted"[2] costs.

Insert Table 1

Economics evaluations

A summary of main cost-effectiveness/cost-utility outcomes of the included RCTs is provided in Table 1. It is important to point out that only 3 studies reported both CEA and CUA (Bogosian et al., 2015; Ekers et al., 2011; Kuyken et al., 2015), whereas 4 studies computed only CEA (Kemani et al.*,* 2015; Kuyken et al., 2008; Priebe et al., 2012; Shawyer, Enticott, Özmen, Inder & Meadows, 2016) and four studies only CUA (Lengacher et al., 2015; Luciano et al., in press; Richards et al., 2016; van Ravesteijn et al., 2013). All CUA studies calculated QALYs as their primary outcome measure, the majority assessed with the European Quality of Life (EuroQol) instrument (EQ-5D-3L; EuroQol group, 1990). Only two studies used other measures: the Short-Form Six-Dimension (SF-6D; Brazier, Usherwood, Harper, & Thomas, 1998) and the 12-Item Short Form Survey Instrument (SF-12v1; Ware, Kosinski, & Keller, 1996). As shown in Table 1, the CEA studies employed heterogeneous instruments for clinical outcomes.

MBCT

The five economic evaluations based on RCTs of MBCT for adults with different conditions are presented in Table 1. All studies focused on specific populations: non-

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[1]In *partial* economic evaluations only the costs of at least two treatment alternatives are compared. This type of evaluation is also called cost analysis. A *full* economic evaluation does not only compare costs of at least two alternatives but also their effects measured in natural units (e.g. self-harm events avoided), artificial units (quality-adjusted life years or disability-adjusted life years) or monetary units.

[2]Discount= Converting future costs and effects to present values. It reflects the conventional view that individuals put a higher value on resources used today than at some point in the future (Detskie & Naglie, 1990)

depressed individuals with three or more previous major depressive episodes, somatoform disorders, and multiple sclerosis. The time horizon of the studies ranged from 3 months to 26 months. Regarding combination therapy, combination of MBCT and antidepressant discontinuation was a cost-effective option in Kuyken et al. (2008), but these results were not replicated with a larger sample in Kuyken et al. (2015). In this well-designed full RCT with MBCT delivered during eight 2.25 h group sessions + four refresher sessions, all implemented in different settings (research clinical facilities, hospital sites, and the community), the ICER and the ICUR indicated that MBCT-TS had a low probability (below 60%) of being cost-effective in comparison to maintenance antidepressant medication. MBCT was even dominated in the cost-utility analysis. In contrast, compared to relapse monitoring (self-monitoring using the Patient Health Questionnaire-2 and -9), the combination of MBCT (eight 2-hour group sessions *plus* 3-monthly optional 'booster sessions') and depressive relapse monitoring showed a high probability of cost-effectiveness from a mental health perspective in a recent Australian study (Shawyer et al., 2016). A Dutch study by van Ravesteijn et al. (2013) reported on results of an RCT to assess the cost-effectiveness of MBCT (eight 2.5-hour sessions plus a silent retreat delivered by MBCT experienced instructors) for a group of patients with heterogeneous medically unexplained symptoms. The participants were frequent attenders (top 10% most frequently attending patients of the participating family physicians). MBCT had a low probability (below 60%) of being cost-effective taking different investment thresholds into account. More recently, a pilot study (Bogosian et al., 2015) based on a skype-delivered MBCT approach adapted for patients suffering multiple sclerosis (eight one-hr group sessions by videoconference over an eight-week period) was "dominant"[3] in comparison to

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[3]Dominant= when intervention A results in improved clinical outcomes and lower resource utilization than intervention B, it is considered that A is dominant and should be adopted (Detskie & Naglie, 1990).

waiting-list using both clinical units (GHQ scores) and QALYs as treatment outcomes. These findings showed a high probability (> 90%) of cost-effectiveness at 3-month follow-up.

ACT

Kemani et al. (2015) randomized Swedish adults with unspecific longstanding pain to ACT or applied relaxation (AR), both treatments delivered during 12 weeks (12 weekly group sessions of 90 min.), with pain disability the primary outcome measure. These authors assessed cost-effectiveness by computing the quotient of the difference in mean changes in costs and pain disability in ACT and AR. ICERs revealed that ACT was more cost-effective than AR after treatment and three-month follow-up, but these results were not maintained at six-month follow-up. Of interest are also the results of ACT as stand-alone therapy published by Luciano et al. (in press), who found that a group-based form of this therapy (eight 2.5h sessions) was cost-effective for Spanish FM patients recruited in primary care centres in comparison to recommended pharmacological treatment (RPT; pregabalin + duloxetine in case of comorbid major depression) regardless of whether the type of analysis performed [intention-to-treat (ITT), completers or per protocol] or the economic perspective (healthcare system or societal). To sum up, in comparison to active psychological treatments (AR) and recommended medications (RPT), there are promising cost-effectiveness findings for ACT in chronic pain patients.

eBA

A pilot RCT (Ekers et al., 2011) showed results for the comparison of eBA (delivered by qualified mental health nurses with no previous formal psychotherapeutic training or experience) with TAU in a small sample of UK adults with persistent severe depression associated with substantial functional impairment. Compared with TAU, 12 one-hour face-to-face sessions of eBA were more cost-effective in two possible scenarios

(scenarios A and B were proposed on the basis of two estimates of workload taking Improving Access to Psychological Therapy, or IAPT, service specifications into account). The authors concluded that eBA is both clinically effective and cost-effective over a short period of 3 months (> 95% probability at a UK threshold of UK£20,000). In a recent large-scale non-inferiority RCT (the COBRA trial), Richards et al. (2016) showed that eBA (delivered by junior mental health workers) was non-inferior to CBT (delivered by highly trained professionals) in reduction of depression symptoms, depression status, depression-free days and anxiety diagnoses. From the UK NHS/personal social services perspective, costs were lower and QALY outcomes better in the eBA study arm, therefore eBA was cost-effective in comparison to CBT. eBA remained cost-effective in all sensitivity analyses (e.g. including productivity losses).

DBT

Priebe et al. (2012) examined whether DBT delivered during 12 months was cost-effective in UK patients referred to the DBT service in the London Borough of Newham, who had personality disorders characterized by self-harm behaviours (the majority had borderline personality disorder). Self-harm was "any act which the individual performed with the intention of self-harm, and caused tissue damage". Compared to TAU delivered free of charge under the NHS, at 12 months there was a non-significant trend towards higher total costs (including lost employment costs) and significant better outcomes for DBT. Specifically, the authors found an ICER of $55 per one percent point reduction of self-harm. As there are no accepted threshold values for cost per percent point reduction of self-harm incidence we abstain from an interpretation.

MBSR

Among US breast cancer survivors with a previous diagnosis of stage 0, I, II, or III and who had completed treatment within two years prior to study enrolment, Lengacher et

al. (2015) compared MBSR (six-weekly two-hour format, excluding the one-day, eight-hour retreat) with TAU, which consisted of standard post treatment clinic visits, with patients specifically asked not to use or practice mindfulness/meditation. At three-month follow-up, MBSR was more cost-effective than TAU from the provider and patients' perspective. However, in the absence of any data on WTP, it is difficult to draw conclusions regarding the cost-effectiveness of MBSR.

Quality assessment of economic evaluations

Information about the quality of the identified RCTs is shown in Table 2. Overall, the methodological quality of the economic evaluations was acceptable to good, but there was some heterogeneity among studies. On average, the global adherence to the checklist was 78.1%. The minimum percentage of adherence fulfilled was 58.3% (Ekers et al., 2011) and the maximum percentage of adherence met was 100% (Kuyken *et al.,* 2015). Seven of the included studies (64%) adhered to ≥ 75% of the guideline and achieved a rating of good quality. Agreement regarding global adherence/non adherence to the checklist was "almost perfect" (κ= .90).

Most studies, with the exception of Ekers et al. (2011), had a well-defined research question, but the economic importance of the research question was not generally provided (Bogosian et al., 2015, Ekers et al., 2011; Kuyken et al., 2008). All studies mentioned the economic perspective but the viewpoint of the analysis was not clearly justified in all cases (Bogosian et al., 2015; Kemani et al., 2015; Kuyken et al., 2008; Shawyer et al., 2016; van Ravesteijn et al., 2013). All authors reported on the effectiveness of the third-wave therapy being tested, identified the most important costs and consequences for each condition, measured costs and consequences accurately, and valued the costs using reliable sources. Not all studies included a comprehensive description of the competing alternatives (Ekers et al., 2011; Shawyer et al., 2016). Only two studies provided sufficient information on

quantities of health service utilization (Kuyken et al., 2015; Priebe et al., 2012). Similarly, only thee studies justified the choice of variables for the "sensitivity analysis"[4] as well as the ranges over which the variables were varied (Ekers et al., 2011; Lengacher et al., 2015; Richards et al., 2016). These were the least frequently fulfilled criteria. Finally, two studies were rated unfavourable because of the absence of major outcomes presented in aggregated and disaggregated form (Bogosian et al., 2015; Lengacher et al., 2015).

Insert Table 2

Risk-of-bias assessment

Figure 2 shows risk of bias for each included RCT. We reached a "substantial" level of agreement between raters ($\kappa= 0.75$). All of the studies (11/11) reported an adequate random sequence generation. However, the majority of the trials (6/11) provided insufficient information on the method of allocation concealment from patients. Authors made a great effort for blinding research staff and outcome assessors, but given the nature of the interventions, blinding of participants from knowledge of which intervention they were receiving was not possible at all. Incomplete outcome data were adequately managed by six included RCTs. All of the included trials were rated as free from selective outcome reporting bias (11/11), but a vast majority presented other sources of bias (unclear or high risk of bias in this item). Taking into account that is almost impossible to blind participants in a RCT testing a psychological treatment, only two studies (Kuyken et al., 2015; Richards et al., 2016) demonstrated a low global risk of bias. The overall RoB of the other constituent studies were unclear or high.

Insert Figure 2

Discussion

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[4]Sensitivity analysis= method for testing the stability of a cost-effectiveness/cost-utility ratio over a range of estimates and assumptions. A range of ratios is calculated by substituting a range of estimates for each of the variables of the cost-effectiveness/cost-utility ratio (Detskie & Naglie, 1990).

The first main finding is that there is a need for further economic evaluations of third-wave therapies given that only eleven RCTs focusing on five of these therapies (MBCT, MBSR, ACT, DBT, and eBA) were found. As Edwards, Bryning and Crane (2015, p. 491) pointed out, "*An intervention cannot be cost-effective if it is not first clinically effective*". The clinical effectiveness of three of the five third-wave therapies (ACT, CBASP, and DBT) is currently well-established for some conditions (APA Presidential Task Force on Evidence-Based Practice, 2006). In the health economics arena, the number of economic evaluations of MBCT far outnumber those focused on the other third-wave therapies.

Comparative cost-effectiveness determines if implementation of a treatment option is likely to be efficient or not. Disease-specific cost-effectiveness tables, along with assessments of the methodological quality of the included studies, represent the most important tool for policy makers in order to decide the most recommendable treatment. An inspection of available evidence indicates that compared to applied relaxation or recommended medications, ACT is a dominant treatment option for chronic pain patients (Kemani et al., 2015, Luciano et al., in press). In the case of Luciano et al's study (in press), it might have been also very interesting to assess ACT as an aggregated component of usual care rather than as an alternative to recommended pharmacological treatment. The same can be said in the case of some MBCT trials (Kuyken et al., 2008; Kuyken et al., 2015). A more appropriate real-world question could have been whether receiving MBCT in addition to maintenance antidepressant drugs is cost-effective compared to maintenance antidepressant drugs as standalone treatment. Focusing on MBCT, findings are inconclusive because of the presence of very positive results in some trials (Bogosian et al., 2015, Shawyer et al.*,* 2016) and modest results in others (Kuyken et al., 2015; van Ravesteijn et al., 2013). In the specific case of relapse prevention in major depression,

MBCT was dominated by maintenance antidepressant medication in the cost-utility analysis performed by Kuyken et al. (2015). The other mindfulness based treatment (MBSR) obtained support for the care of breast cancer survivors taking a reasonable investment threshold into account (Lengacher et al., 2015). DBT was superior to usual care in the management of self-harm behaviours from a societal perspective (Priebe et al., 2012). eBA delivered without the need of experienced and highly trained professionals was cost-effective compared to usual care for adults with depression (Ekers et al., 2011) and CBT (Richards et al., 2016).

An important finding is the total absence of economic evaluations of MCT, CBASP, FAP, IBCT, CFT, MB-EAT, and MBRP. So, it seems necessary to begin to include and report on the costs and cost effectiveness of these third-wave therapies. In comparison to second-wave CBT, economic analyses of third-wave therapies are considerably underdeveloped. Selecting depression as target condition, Brettschneider et al. (2015) identified 22 studies performing cost-utility analyses of CBT. Their results showed that individualized CBT can be a cost-effective treatment from the perspective of a third-party payer at short-term for the acute treatment and prevention of major depression in an adult population and also obtained some evidence that the use of a societal perspective enhanced cost-effectiveness. Focusing on the effectiveness and cost-effectiveness of CBT interventions delivered via internet, Hedman, Ljotsson, and Lindefors (2012) found that of the 108 RCTs included in their review, eight provided data on cost–effectiveness of the treatments in adult patients. Therefore, even narrowing the focus of interest (internet CBT), the number of economic evaluations alongside RCTs of second wave CBT is relatively high. We suspect that grant funding might be a plausible explanation for the fewer number of economic evaluations of third-wave therapies. We agree with Gaudiano (2009, p. 1067) when he stated that *"…ACT and CBT interventions*

are at very different stages of clinical trial testing, and thus ACT studies have historically had less funding to support this early research. In contrast, CBT clinical trials are in the most advanced stage of any psychotherapy outcome research to date". This reasoning in favour of ACT can be extended to the other third-wave therapies.

For the present review, we decided to exclude non-randomized studies owing to their susceptibility to bias. Unpublished studies were also excluded as numbers enrolled may vary between unpublished data and final publications. According to an anonymous reviewer this is a potential limitation. Due to the expected low number of economic evaluations alongside RCTs, the inclusion of non-randomized or unpublished studies could have provided additional interesting data in this nascent field.

It appears interest in economic evaluations of third-wave CBT is growing. There are numerous upcoming economic evaluations that will reinforce the available evidence about MBCT, MBSR, ACT, DBT, eBA, and CBASP (for the first time). Ten references reporting on protocols for ongoing RCTs that seem to meet the inclusion criteria for a future third-wave CBT systematic review (see supplementary file 3). A future update of the present review we will be able to include findings from the ten ongoing studies that perform economic evaluations alongside a RCT: two are focused on MBCT, three on ACT, one on eBA, two on MBSR, one on DBT and one on CBASP. Of the ten studies that are currently assessing the cost-effectiveness of a third-wave therapy, nine have decided to adopt a societal perspective, as the target disorders are very heterogeneous. We can observe in this table that the well-established EQ-5D-3L, that is currently considered the leading generic measure of HRQoL worldwide is being replaced in some cases by the five-level version (EQ-5D-5L) with the expectative of increasing sensitivity to change (Agborsangaya, Lahtinen, Cooke, & Johnson,2014).

The quality and risk of bias assessment revealed important shortcomings that temper the promising findings reported until now. The RCTs included in this systematic review present important limitations in terms of small sample sizes and absence of long-term follow up. As pointed out by Shean (2014), sample sizes in psychotherapy trials are "*frequently justified by power estimates based on questionable effect sizes reported in previous non-double-blind psychotherapy efficacy studies. These estimates are likely to be inflated by the effects of "therapist allegiance.*" Third-wave therapies are no exception in this. We found small sample sizes (n< 50 by study arm) in 45% of the included RCTs. Regarding follow-ups, 64% of the trials were commonly limited to 12 months or less and the benefits of third-wave therapies may extend or diminish beyond these follow-up periods. In contrast, the cost-effectiveness of CBT has been compared to other equally active treatment options, including large samples, and long-term follow-ups. For instance, Egger et al. (2016) have demonstrated the cost-effectiveness of CBT at 30 months compared to psychodynamic therapy in the management in a large sample (n > 200 per study arm) of patients with social anxiety disorder. Another limitation is that most third-wave treatment providers are not integrated into the existing health care systems. As is evident from this systematic review, the majority of studies do not address the generalizability and actual implementation of these therapies, a subject that is currently under debate (Demarzo et al., 2015). Some third-wave CBTs are challenging to implement in routine care. For example, the half-day retreat required by MBSR or the shortage of trained CBASP teachers represent serious obstacles for implementation. It would be very interesting if future studies address the staffing costs, training costs, venue overheads, and materials needed to implement third-wave treatments. Of great interest is also to know what is the cost of delivering third-wave CBT vs. first- or second-wave CBT, which may involve comparing the training of the teacher/instructor, running costs, including

supervision of clinicians and continuous professional development training; space needed

to make the intervention; materials such as books or CDs for home practice; administrative

support, and so forth. These comparisons are relevant to those wanting to make a case for

the funding of third-wave CBT in the future and potential integration into routine care

(Edwards et al., 2015).

The economic analysis of third-wave therapies can be performed under the

perspective of integrated care, assuming that they constitute complex interventions that

need to be evaluated in "realist RCTs" (Fletcher et al., 2016). The main of our systematic

review is not to provide lessons for how to design definitive, fully powered economic

evaluations of third-wave therapies alongside RCTs for the future. Edwards et al (2015)

have focused their efforts on this issue. The ten methodological considerations for the

economic evaluation of mindfulness-based interventions described by these authors can be

aptly extended to all third-wave cognitive behavioural therapies. For instance, these

authors recommend "*A cost utility or cost-effectiveness analysis embedded in a wider cost-consequence analysis*" (p. 494) in order to acknowledge the wider range of outcomes from

a mindfulness-based intervention. As these authors pointed out, researchers should use the

same conventional outcomes as those used in most studies for the sake of comparability

(e.g. QALY estimates), but is also crucial to include measures that capture the particular

shift in functional performance outcomes, which are the core focus of acceptance and

mindfulness-based training. We are aware that the inclusion of this type of outcomes in

cost-effectiveness analysis is far from being easy because, for example, there are certainly

no accepted threshold values for cost per point increase in aspects of psychological

flexibility. Finally, last but not least, one common flaw in the economic evaluation of

psychological therapies in general is that sample size per study arm is determined by

clinical outcomes and not by economic outcomes. Unfortunately, a full economic analysis

needs a larger sample size than that needed for clinical analysis. The inclusion of health economists within multidisciplinary teams prior to beginning of the trials could help researchers to produce better quality economic studies.

Conclusions

To sum up, this is currently the only systematic review of the literature on the economic evaluation for third-wave CBT for the management of different physical and mental health conditions. This review also incorporated a quality and risk of bias assessment. There is economic data supporting some of the interventions usually labelled as "third-wave" CBT. However, our review suggests that further research with higher methodological quality is needed on the relative efficiency of different forms of "third-wave" CBT compared to other active treatments.

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Acknowledgements

Table 1

Full Economic Evaluations of 'Third-Wave' Cognitive and Behavioural Therapies

Author (year); country	'Third wave' psychotherapy	Target condition	Treatment arms (n); Delivery period	Cost categories included (cost-perspective)	Clinical effect or utility outcome	Results of the economic evaluation	Time horizon
Kuyken *et al.* (2008); UK	MBCT	Non-depressed adults with three or more previous major depressive episodes	(a) MBCT + antidepressant discontinuation (n= 61) (b) maintenance antidepressant medication (m-ADM; n= 62) Delivery period: 8 weeks	Societal perspective. It included all hospital (inpatient, outpatient, emergency department) and community health and social services (e.g., primary care, social work, complementary therapies), plus productivity losses resulting from time off work due to illness. Discount rate: 0%	SCID-I (proportion of patients who relapse)	Cost-effectiveness analysis (ITT) ICER= $962 per relapse/recurrence prevented and $50 per depression-free day. From the healthcare perspective, the ratios were $439 and $23, respectively. WTP MBCT showed a 42% probability of being cost-effective compared to m-ADM if the society would pay €0 for preventing and additional relapse/recurrence. MBCT has a high probability (> 80%) of being more cost-effective than has m-ADM for WTP ≥ $10,000	15 months
van Ravesteijn *et al.* (2013); Netherlands	MBCT	Undifferentiated somatoform disorder	(a) MBCT (n= 64) (b) Enhanced Usual Care (EUC; n= 61) Delivery period: 8	Societal perspective. It covered employment participation, health care use per day, medication use, number of attended MBCT sessions. Discount rate: 0%.	SF-6D	Cost-utility analysis (completers) ICUR= €56,637 for a QALY gain, that is, MBCT was more costly and more effective than EUC (inflated and converted	12 months

			weeks			ICUR= Int\$81,700) WTP MBCT had a 28% probability of being cost-effective compared to EUC if the society would pay €0 for one gained QALY. And at a threshold of €40.000 and €80,000 this is 48% and 57%, respectively.	
Bogosian *et al.* (2015); UK	MBCT	Primary and secondary progressive multiple sclerosis	(a) Skype distant-delivered MBCT (n= 19) (b) Waiting-list control group (n= 21) Delivery period: 8 weeks	Societal perspective. Direct intervention costs (resources and time spent by professionals providing the mindfulness sessions), health and social care costs (admission days, consultations, etc.) and informal care costs. Discount rate: 0%	GHQ-12 EQ-5D-3L	Cost-effectiveness analysis (ITT) ICER not reported. Authors indicate lower costs and larger clinical effects (GHQ scores) in MBCT compared to waiting-list control at 3 months. Cost-utility analysis (ITT) ICUR not reported. Equal health gains in terms of QALY gained were generated for less costs by MBCT compared to waiting-list control at 3 months. WTP MBCT ≥ 90% probability of being cost-effective vs. waiting-list control if society were willing to pay £20,000 for one additional QALY.	3 months
Kuyken *et al.* (2015); UK	MBCT	Non-depressed adults with three or more previous	(a) MBCT + antidepressant discontinuation	Primary analysis from the health and social care perspective. Secondary analyses included	SCID-I (proportion of patients	Cost-effectiveness analysis (completers) ICER= £4,955 from the	24 months

		major depressive episodes	(MBCT-TS; n= 212) (b) maintenance antidepressant medication (m-ADM; n= 212) Delivery period: 8 weeks	productivity losses and out-of-pocket expenditure. Discount rate: 3.5%	who relapse) EQ-5D-3L	NHS/Personal Social Services perspective and £10,604 from the societal perspective (including productivity losses and patient costs). These values would need to be invested in order to generate a unit reduction in the percentage of participants who relapse. WTP The probability of MBCT-TS being more cost-effective than m-ADM did not rise above 43%. Cost-utility analysis (completers) ICUR not reported. MBCT-TS is dominated by m-ADM, that is, MBCT-TS costs were higher and outcomes worse, on average, than m-ADM. WTP The probability that MBCT-TS was more cost-effective than m-ADM did not rise above 52%.	
Shawyer *et al.* (2016); Australia	MBCT	Non-depressed adults with a history of three or more major depressive episodes	(a) MBCT + DRAM (depressive relapse active monitoring; n= 101) (b) Control (DRAM; n= 102)	Analysis from the mental healthcare, health care, and societal perspectives. Costs included were delivery of MBCT, prescribed medications, hospital, community health and social service contacts, productivity	CIDI 2.1 (days in MDEs) ICD-10	Cost-effectiveness (ITT; societal perspective) ICER= -AUD156. This value reflects savings (less costs) achieved by MBCT compared to the control to avert a day of major depression in one person.	26 months

			Delivery period: 8 weeks	loses, and out-of-pocket expenses. Discount rate: 3%		In addition, MBCT produced -AUD164,758 as saving per person each year by averting a DALY. WTP Not reported from the whole of society perspective. From the mental health care perspective, MBCT= 81% probability of being cost-effective vs. control if decision makers were willing to pay AUD0 for an extra point increase in DALY.	
Kemani *et al.* (2015); Sweden	ACT	Unspecific, longstanding pain.	(a) ACT (n= 30) (b) Applied Relaxation (AR; n= 30) Delivery period: 12 weeks	Analysis from the societal perspective. Data obtained in 3 different domains: (1) direct medical costs, comprising costs related to healthcare utilization, medication use + intervention costs (2) direct non-medical costs, and (3) indirect nonmedical costs (employment status, sick leave, and reduced capacity at work and domestically) Discount rate: 0%	PDI	Cost-effectiveness (ITT; societal perspective) ICER at 6.months not reported. No differences in costs or effectiveness between the two treatments. ICER (3 months) = -$648. Each incremental improvement on the PDI for ACT participants relative to AR yielded a societal earning of $648 at 3 months. WTP Not reported	6 months
Luciano *et al.* (in press); Spain	ACT	Fibromyalgia	(a) ACT (n= 51) (b) Recommended pharmacological treatment (RPT; n=	Analyses performed from the healthcare (self-reported data collection about medication consumption, medical tests, use	EQ-5D-3L	Cost-utility analysis (ITT; societal perspective) ICURs not reported. ACT was found to be dominant when	6 months

			52) (c) Waiting-list (WL; n= 53) Delivery period: 8 weeks	of health-related services, and cost of the staff running the ACT intervention) and from a restricted societal perspective (productivity losses). Discount rate: 0%		compared against RPT and WL. The average incremental cost for the comparison ACT vs. RPT was €-389.5. The incremental effect for QALYs was found to be around 0.01. WTP Not reported
Ekers *et al.* (2011); UK	eBA	Major depression	(a) eBA (n= 24) (b) TAU (n= 23) Delivery period: 12 weeks	Health care perspective. It included therapists' costs, training costs, supervision costs, and total services use. Discount rate: 0%	BDI-II EQ-5D-3L	Cost-effectiveness analysis (ITT; health care perspective) ICER (Scenario A)= £9.45 per BDI-II point reduction ICER (Scenario B)= £11.04 per BDI-II point reduction Cost-utility analysis (ITT; health care perspective) ICUR (Scenario A)= £5006 per QALY (inflated and converted ICUR= Int$7644,7) ICUR (Scenario B)= £5756 per QALY (inflated and converted ICUR= Int$8790,2) WTP >95% probability that eBA is more cost-effective than TAU at a threshold value of £20 000 in both scenarios.	3 months
Richards *et al.* (2016); UK	eBA	Major depression	(a) eBA delivered by junior mental health workers (n= 221)	Primary analysis from the UK National Health Service perspective. Sensitivity analysis	EQ-5D-3L	Cost-utility analysis (completers; UK NHS perspective) ICUR= –£6865 for a QALY	18 months

			(b) CBT delivered by professional therapists (n= 219) Delivery period: 16 weeks	from the societal perspective (including productivity loses). Data collection on patients' use of eBA and CBT from clinical records. Measurement of all other health and social care services used (community health and social care contacts, medication prescription and use), and productivity losses (absenteeism and presenteeism questions). Discount rate: 3.5%		gain, that is, eBA costs were lower and QALY outcomes better compared to CBT (converted ICUR= -Int$9807) WTP eBA had a 75-80% probability of being cost-effective compared to CBT if the UK NHS would pay £20,000–30,000 per QALY. Cost-utility analysis (ITT; UK NHS perspective) Multiple imputation increased the ICUR= –£16,951 (converted ICUR= -Int$24,216)	
Priebe *et al.* (2012); UK	DBT	Personality disorders with self-harm	(a) DBT (n= 40) (b) TAU (n= 40) Delivery period: 12 months	Societal perspective. Service use included the number of days spent in hospital, outpatient visits, contacts with general practitioners and other community-based health providers, prescribed medication, and lost work time for those in employment. Discount rate: 0%	SCI	Cost-effectiveness analysis (ITT; societal perspective) ICER= £36GBP per one percentage point reduction in the incidence of self-harm rate as a result of using DBT (per 2-month period). WTP Not reported	12 months
Lengacher *et al.* (2015); USA	MBSR	Breast cancer survivors	(a) MBSR (n= 49) (b) TAU (n= 47) Delivery period: 6 weeks	Provider and patient perspective. Accounting for both direct medical costs of the intervention and patient opportunity costs (time spent participating in the MBSR, time spent traveling to and from the intervention site,	SF-12v1	Cost-utility analysis (ITT) ICUR= $22,200 is the cost to provider per incremental gain in QALYs. $19,733 is the out-of-pocket cost per incremental gain. The incremental gain during the 12-week period was 0.03	3 months

	participant transportation, childcare, meals and lodging for patients who travelled long distances) Discount rate: 0%	QALYs. WTP Not reported

Note: BDI-II= Beck Depression Inventory (); CIDI 2.1= Composite International Diagnostic Instrument 2.1 Auto Lifetime version; EQ-5D-3L= European Quality of Life (EuroQol) instrument in 5 dimensions (three level version); GHQ-12= General Health Questionnaire; SF-6D= Short Form Health Survey in 6 dimensions. Preference-based single index measure of general health based on the SF-36 and SF-12. The SF-6D enables the calculation of QALYs. PDI= Pain Disability Index; SCID-I= Structured Clinical Interview for DSM Axis I Disorders. SCI= Self-harm structured interview; SF-12v1= first version of the 12-item Short-Form Health Survey.

Table 2

Quality of Studies Computing Cost-effectiveness/Cost-utility Analyses of 'Third-Wave' Cognitive and Behavioural Therapies.

Quality checklist (Drummond & Jefferson, 1996)	Kuyken *et al.* (2008)	van Ravesteijn *et al.* (2013)	Bogosian *et al.* (2015)	Kuyken *et al.* (2015)	Shawyer *et al.* (2016)	Kemani *et al.* (2015)
Study design						
The research question is stated.	Yes	Yes	Yes	Yes	Yes	Yes
The economic importance of the research question is stated.	Yes	Yes	No	Yes	Yes	Yes
The viewpoint(s) of the analysis are clearly stated and justified.	No	N.C	No	Yes	Yes	N.C.
Selection of alternatives						
The rationale for choosing alternative programmes or interventions compared is stated.	Yes	No	No	Yes	Yes	Yes
The alternatives being compared are clearly described.	Yes	Yes	Yes	Yes	Yes	Yes
Form of evaluation						
The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	No	Yes	Yes	Yes
Effectiveness data						
The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes	Yes
Details of the design and results of effectiveness study are given (if based on a single study).	Yes	Yes	Yes	Yes	Yes	Yes
. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Benefit measurement and valuation						
. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes	Yes
. Methods to value benefits are stated.	Yes	Yes	Yes	Yes	Yes	Yes
. Details of the subjects from whom valuations were obtained were given.	Yes	Yes	Yes	Yes	Yes	Yes
. Productivity changes (if included) are reported separately.	Yes	Yes	N.A.	Yes	No	Yes
. The relevance of productivity changes to the study question is discussed.	No	No	N.A.	Yes	No	No

	Luciano et al. (in press)	Ekers et al. (2011)	Richards et al. (2016)	Priebe et al. (2012)	Lengacher et al. (2015)
Costing					
. Quantities of resource use are reported separately from their unit costs.	No	No	No	Yes	No	No
. Methods for the estimation of quantities and unit costs are described.	Yes	Yes	Yes	Yes	Yes	Yes
. Currency and price date are recorded.	Yes	Yes	Yes	Yes	Yes	Yes
. Details of currency of price adjustments for inflation or currency conversion are given.	Yes	No	No	Yes	No	No
Modelling					
. Details of any model used are given.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A
. The choice of model used and the key parameters on which it is based are justified.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A
Adjustments timing of costs & benefits					
. Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes	Yes
. The discount rate(s) is stated.	No	N.A.	N.A	Yes	Yes	N.A.
. The choice of discount rate(s) is justified.	No	N.A.	N.A	Yes	Yes	N.A.
. An explanation is given if costs and benefits are not discounted.	No	N.A.	N.A	N.A	N.A	N.A.
Allowance for uncertainty					
. Details of statistical tests and confidence intervals are given for stochastic data.	Yes	Yes	Yes	Yes	No	Yes
. The approach to sensitivity analysis is given.	No	Yes	N.A.	N.A.	Yes	N.A.
. The choice of variables for sensitivity analysis is justified.	No	No	N.A.	N.A.	No	N.A.
. The ranges over which the variables are varied are justified.	No	No	N.A.	N.A.	No	N.A.
. Relevant alternatives are compared.	Yes	Yes	Yes	Yes	N.C.	Yes
Presentation of results					
. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes	Yes
. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	Yes	No	Yes	Yes	Yes
. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes	Yes
. Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes	Yes
. Conclusions are accompanied by the appropriate caveats.	Yes	Yes	No	Yes	Yes	Yes

Study design					
The research question is stated.	Yes	N.C.	Yes	Yes	Yes
The economic importance of the research question is stated.	Yes	No	Yes	Yes	Yes
The viewpoint(s) of the analysis are clearly stated and justified.	Yes	Yes	Yes	Yes	Yes
Selection of alternatives					
The rationale for choosing alternative programmes or interventions compared is stated.	Yes	N.C.	Yes	Yes	No
The alternatives being compared are clearly described.	Yes	No	Yes	Yes	Yes
Form of evaluation					
The form of economic evaluation used is stated.	Yes	Yes	Yes	Yes	Yes
The choice of form of economic evaluation is justified in relation to the questions addressed.	Yes	Yes	Yes	Yes	Yes
Effectiveness data					
The source(s) of effectiveness estimates used are stated.	Yes	Yes	Yes	Yes	Yes
Details of the design and results of effectiveness study are given (if based on a single study).	Yes	N.C.	Yes	Yes	No
. Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies).	N.A.	N.A.	N.A.	N.A.	N.A.
Benefit measurement and valuation					
. The primary outcome measure(s) for the economic evaluation are clearly stated.	Yes	Yes	Yes	Yes	Yes
. Methods to value benefits are stated.	Yes	N.C.	Yes	Yes	Yes
. Details of the subjects from whom valuations were obtained were given.	Yes	No	Yes	Yes	Yes
. Productivity changes (if included) are reported separately.	Yes	N.A.	Yes	Yes	N.A.
. The relevance of productivity changes to the study question is discussed.	No	N.A.	N.C.	No	N.A.
Costing					
. Quantities of resource use are reported separately from their unit costs.	No	No	No	Yes	No
. Methods for the estimation of quantities and unit costs are described.	Yes	Yes	N.C.	N.C.	Yes
. Currency and price date are recorded.	Yes	Yes	Yes	Yes	No
. Details of currency of price adjustments for inflation or currency conversion are given.	Yes	No	No	No	N.A.
Modelling					

. Details of any model used are given.	N.A.	N.A.	N.A.	N.A.	N.A
. The choice of model used and the key parameters on which it is based are justified.	N.A.	N.A.	N.A.	N.A.	N.A
Adjustments timing of costs & benefits					
. Time horizon of costs and benefits is stated.	Yes	Yes	Yes	Yes	Yes
. The discount rate(s) is stated.	N.A.	N.A.	Yes	N.A.	Yes
. The choice of discount rate(s) is justified.	N.A.	N.A.	Yes	N.A.	Yes
. An explanation is given if costs and benefits are not discounted.	N.A.	N.A.	N.A	N.A.	N.A.
Allowance for uncertainty					
. Details of statistical tests and confidence intervals are given for stochastic data.	Yes	Yes	Yes	Yes	Yes
. The approach to sensitivity analysis is given.	Yes	N.A.	Yes	No	Yes
. The choice of variables for sensitivity analysis is justified.	No	N.A.	Yes	No	Yes
. The ranges over which the variables are varied are justified.	No	N.A.	Yes.	No	Yes
. Relevant alternatives are compared.	Yes	Yes	Yes	No	Yes
Presentation of results					
. Incremental analysis is reported.	Yes	Yes	Yes	Yes	Yes
. Major outcomes are presented in a disaggregated as well as aggregated form.	Yes	No	Yes	Yes	No
. The answer to the study question is given.	Yes	Yes	Yes	Yes	Yes
. Conclusions follow from the data reported.	Yes	Yes	Yes	Yes	Yes
. Conclusions are accompanied by the appropriate caveats.	Yes	Yes	Yes	Yes	No

N.A., Not applicable.

N.C., Not clear

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)

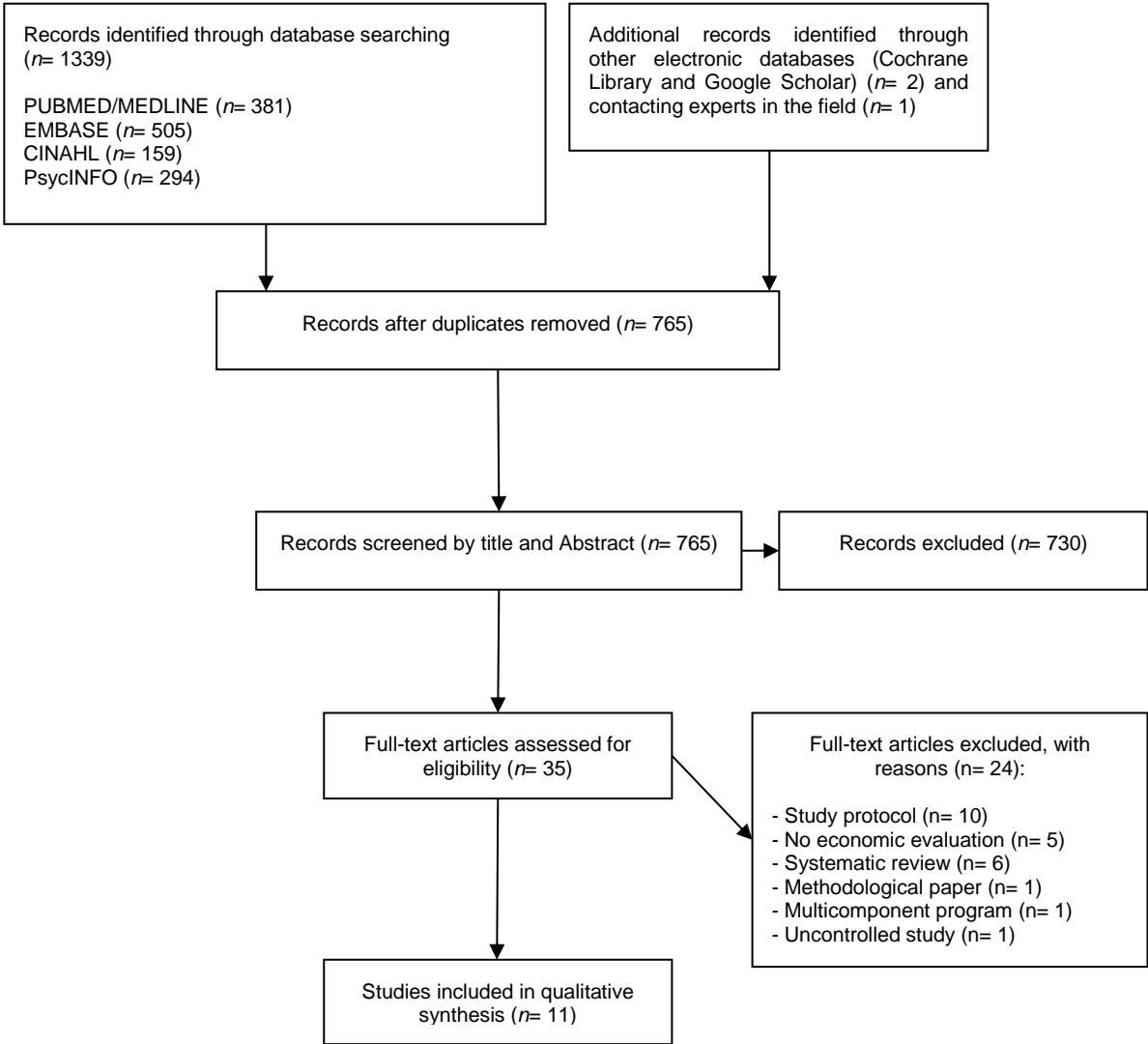flow diagram from record identification to study inclusion.

Figure 2. Risk of bias assessment for each included study using the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011)

Key: + indicates low risk of bias, − indicates high risk of bias, and ? indicates unclear risk of bias.

	Kuyken et al. (2008)	van Ravesteijn et al. (2013)	Bogosian et al. (2015)	Kuyken et al. (2015)	Shawyer et al. (2016)	Kemani et al. (2015)	Luciano et al. (2016)	Ekers et al. (2011a)	Richards et al. (2016)	Priebe et al. (2012)	Lengacher et al. (2015)	
Random sequence generation (selection bias)	+	+	+	+	+	+	+	+	+	+	+	
Allocation concealment (selection bias)	?	+	+	+	?	?	?	+	+	?	?	
Blinding (performance bias and detection bias)	-	-	-	-	-	-	-	-	-	-	-	
Incomplete outcome data (attrition bias)	+	-	+	+	+	-	+	-	+	+	?	
Selective reporting (reporting bias)	+	+	+	+	+	+	+	+	+	+	+	
Other bias	?	-	-	?	?	?	?	-	?	-	?	

Other bias:

Kuyken *et al* (2008, 2015). The antidepressant medication was not fully controlled.

van Ravesteijn *et al* (2013). The authors did not systematically evaluate the treatment integrity and therapist competency. They did not keep a record of their compliance with the patients' homework exercises.

Bogosian *et al* (2015). One of the authors notified participants of their group allocation and was the mindfulness instructor that delivered all the mindfulness courses.

Kemani *et al* (2015). High amount of missing economic data. Therapists in the ACT condition were more familiar with the treatment method.

Luciano *et al* (in press). The authors cannot dismiss the possibility that patients from the GACT condition concealed the use of medications, for example the use of opioids or anxiolytics as rescue medication. In contrast, participants in the RPT can claim to have taken their prescribed medication, when this is not the case.

Ekers *et al* (2011). Lack of follow-up and small sample size (underpowered RCT). Quality of behavioural activation administered was not measured.

Richards et al (2016). Missing data for the primary outcome measure was substantial.

Priebe *et al* (2012). RCT carried out in a relatively small sample size (underpowered RCT). One of the coauthors evaluated the adherence to DBT. The authors assessed indirect costs caused by sickness absence exclusively

Lengacher *et al* (2015). It is unclear whether more than one MBSR instructor delivered the MBSR program. The original MBSR program was modified to a 6-week format and excluded the recommended one-day retreat.