**Online supplementary material**



Figure 1. *Prisma Flow Diagram*

**Quality assessment strategy and results**

Kazdin [1] formulated seven central requirements for research on mechanisms of change using mediators. The first is strong associations between the intervention and the mediator and between the mediator and the outcome. Secondly, mediators should be specific: the mediator should account for therapeutic change to a greater extent than other plausible constructs. Furthermore, change in a potential mediator should always temporally precede changes in outcome and the mediator should give a plausible explanation for a possible mechanism of change that fits with current scientific knowledge. Studies should use a randomised controlled or experimental design to test mediation. With studies using a dose-response design or an experimental design, research can strengthen the evidence that changes in mediators causally lead to changes in outcome. Lastly, whenever a mediation effect is found, it should be consistently replicated across different studies, samples, and treatment groups. The more these requirements are fulfilled, the stronger the evidence that a certain mediator explains the relationship between a treatment and its outcome.

Since we exclusively considered studies that performed a formal test of mediation, we looked to what extent the analyses they used to quantify associations between the treatment, the mediator, and treatment outcome were appropriate [2] using a 3-point Likert scale. A low score (0) was assigned to analyses that used regression models with inferred effects rather than statistical tests (e.g.Baron and Kenny [3]). An intermediate score (1) was assigned to studies that used tests of indirect effects, such as the Sobel test [4], as a standalone test or as an addition to regression analyses. A high score (2) was assigned to explicit analyses estimating direct and indirect effects (e.g. Preacher & Hayes, 2008). When studies used both appropriate and less appropriate methods, the highest quality score was used.

Studies that had a temporal design received a high score (2) for temporality when they indeed investigated whether change in the mediator(s) occurred before the observed change in outcome. If temporality was not part of the investigations, the study was assigned a low score (0). No intermediate scores were awarded.

In our review we used a slightly different definition of specificity than Kazdin [1]did. On page 5 of his paper he states that *‘we would not want multiple mediators to account for change, but rather show a more specific connection.’* We do agree that the case for a certain *mechanism* is strengthened when results show that it is the only significant process among other nonsignificant plausible mechanisms, but Kazdin’s [1] specificity definition does not allow the process of change to be captured in a single model because one then has to assume that the process can be explained by a single mediator. Therapeutic change is much more complex and a model that tries to account for change will far more likely contain several significant mediators. BA effect models see both activation and environmental reward as interacting mediators. Ideally, a model will contain different mediators that allow theory-based hypotheses to be formulated and tested to thus establish whether the primary mechanism, involving one or several mediators, accounts for the therapeutic change while rival mechanisms do not. In our quality judgements, we accordingly focused on whether different plausible mechanisms rather than specific mediators are tested in the same model, awarding studies that did the highest score (2), with studies comparing plausible competing mechanisms in different models receiving an intermediate score (1), and those that did not compare mechanisms the lowest score (0).

According to Kazdin [1] a first step in exploring mechanisms of changes is to investigate mediators in RCTs. However, when a putative mediator is shown to be significant, the case for that mediator can be strengthened by manipulating the mediator in an experiment to establish its causal effect on outcome, which cannot be done within the confines of an RCT. Alternatively, we argue that in terms of *methodological quality* it does not matter whether a study has the design of an RCT or an experimental trial. In untangling the mechanisms of change, we think both designs are useful at different stages of the investigations, where a sequential combination of both designs would be the ultimate test case for a mediator. The same goes for studies that use a dose-response design in an RCT. Accordingly, RCTs or experimental designs are both assigned a high score (2) but a naturalistic design or the absence of a control group results in a low score (0), with studies that had some kind of randomisation, e.g. a multiple baseline design, were given an intermediate score (1).

Moreover, we decided to also test two quality requirements that Cooper, et al. [5] added to their checklist to assess more general topics. The first requirement concerns the representativeness of the treatment, with treatments meeting this criterion being assigned 2 points and nonrepresentative treatments 0 points (no intermediate score). We scored the representativeness of the treatment as 1 if it was based on one of the main BA protocols, such as brief Behavioural Activation Therapy for Depression (BATD) and value-based BA, or if a similar approach was used [6, 7]. We did not differentiate for protocol duration or way of delivery (individual or group therapy). Unlike Cooper et al. [5], we did not score the representativeness of the samples because the various studies differed in terms of age, comorbidity, and other distinguishing factors to such an extent that any cut-off value to decide on the samples’ representativeness seemed arbitrary.

The final general requirement concerned statistical power and missing data imputation [5]. If the sample was adequately sized (each group n >30) and its missing data were handled appropriately, studies received the highest score (2), if one of these requirements was met an intermediate score (1), and if neither was satisfied a low score (0). More information about the development of the checklist including the latter requirements can be found in the online supplement to Cooper et al.’s review on mechanisms of prolonged exposure therapy [5].

**Table 1.** *Study characteristics and review results for all studies included*

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Authors (year, country) | Intervention(s) (and sample size) | Population, Sex and age | Measure(s) of depression | Statistical method | Potential mediator(s) and results | Quality assessment |
| **Armento** et al.[8] (2012, US) RCT | BARB (n = 25) vs.  ST (n = 25) | Students with depressive symptoms  62% female  Age 20.0 (SD = 2.75) | BDI-II | Preacher and Hayes [22] | ↑Religious background and behaviour (RBB) (+)  ↑ Spiritual well-being (SWB) (+)  Religious coping (WORCS) (-) | 4 |
| **Au** et al. [9] (2019, HK)  RCT | TBA (n=56) vs. TGM (n=55) | Dementia family caregivers TBA 84% female, age: 57.43 (9.69); TGM 79% female, age: 56.75 (10.79) | CESD | Hayes [23] | ↑Self-efficacy for controlling upsetting thoughts (SE-CU) (+) | 8 |
| **Dimidjian** et al. [10] (2017, US)  RCT | BA (n=86) vs. TAU (routine obstetric care) (n= 77) | Pregnant women with depressive symptoms  100% female age BA: 28.49 (5.73)  Age TAU (29.04 (5.63) | PHQ-9 | Krull and MacKinnon [24]  Shrout and Bolger [25] | ↑Behavioural activation (BADS) (+)  ↑Environmental reward (EROS) (+) | 11 |
| **Folke** et al. [11]. (2015, SE) | BATD (n= 6) | Inpatients with MDD 66,5% female age 20-65 | MADRS-S | Mueser, et al. [26] | ↑ Approach behaviours (CUB) (+)  ↓Avoidance behaviours (CUB) (+) | 6 |
| **Gaynor** et al. [12] (2008, US) | Values based BA [27] (n=4) | Adolescents with depressive symptoms 50% female age 12-18 | BDI-II | Mueser, et al. [26] | ↓ Dysfunctional thinking (ATQ) (-)  ↑Activation (COPE; Things I Can Do To Behave Consistently With My Values Form) (+) | 6 |
| **Ho** [13] (2017, US) RCT | PEP (n= 49) vs. IS (n=51) | Dementia caregivers  PEP 83,3% female age 70.71 (7.57) IS 68% female age 70.98 (8.81) | CESD | MacKinnon, et al. [28]  MacKinnon, et al. [29] | Perceived activity restriction (The Activity Restriction Scale) (-)  Engagement in pleasant activities (-)  Personal mastery (Personal Mastery Scale) (-)  Perceived adequacy of expressive support from friends and family. (-) | 9 |
| **Hopko** et al. [14] (2016, US) RCT | BATD (n=42) vs PST (n=38) | Women with breast cancer and MDD 100% female BATD age: 56.4 (11.1) PST age: 54.3 (11.2) | BDI-II | Preacher & Hayes [22] | ↑ Environmental reward (EROS) (+)  Environmental reward significantly mediated the relationship between pre- and posttreatment depression in BA, but not at 12m follow up.  Anxiety (BAI) (-)  Perceived social support (MSPSS) (-) | 9 |
| **Moradveisi** et al. [15] (2015, IR) RCT | BA (n=50 )vs. ADM (n=50) | Outpatients with MDD BA 80% female  Age 32.62 (10.17) ADM 90% female Age: 30.12 (7.47) | BDI-II HRSD | Hayes and Preacher [23] | *↑ Belief in own coping capabilities (+)*  *↑Crediting for self-improvement (+)*  Belief in medication (-)  Indifference to tablets (-) | 10 |
| **Nasrin** et al. [16] (2017, UK) RCT | BATD (one session) (n= 22) vs. WL (n=24) | Outpatients with MDD BA: 59.1 % female Age: 34.9 (10.9) WL: 58.3% female age: 37.6 (8.4) | PHQ-9 | Preacher & Hayes [22] | ↑ Behavioural activation (BADS) (+) | 6 |
| **Okajima** et al. [17] (2017, AU) RCT | BAW (n=25) vs. WL (n=24) | Outpatients with excessive worry BAW 68% female age: 36.48 (12.30) WL 88% female age: 42,17 (13.11) | DASS | Baron and Kenny [3] | ↓ Insomnia severity (ISI) (+) | 5 |
| **Richards** et al. [18] (2017, UK) RCT | BA (n=221) vs. CBT (n=219) | Adults with MDD BA 64% female age: 43.9 (14.1) CBT 68% female age: 43.0 (14.1) | PHQ-9 | SEM | Behavioural activation (BADS, including subscales) (-)  Dysfunctional attitudes DAS (-)  Rumination (RRS) (-)  Anhedonia (SHAPS) (-)  Number of sessions (-)  *↑Treatment fidelity (+)* | 12 |
| **Rovner** et al. [19] (2014, US)  RCT | BA (n=87) vs ST (n=76) | Older adults with AMD BA 72,9% female  age: 85.2 (6.6) ST 67.4 female age: 82.7 (6.9) | PHQ-9 | SEM Iacobucci, et al. [30] | Activation (BADS) (-)  Avoidance/rumination (BADS) (-)  Work/school impairment (BADS) (-)  ↓Social impairment (BADS) (+) | 9 |
| **Ryba** et al. [20]. (2014, US) | BATD (n=23) | Women with breast cancer and MDD 100% female age 57 (11.3) | BDI-II | Selig and Preacher [31] | Environmental reward (EROS) (-) EROS does not mediate the relationship between compliance and depression outcome | 6 |
| **Takagaki** et al. [21] (2016, JP) | BA group therapy (n=61) | First year students Japan with depressive symptoms 39,3% female age 18.21 (range 18-19) | BDI-II | MacKinnon, et al. [29] | ↑Environmental reward (EROS) (+)  Environmental Reward (EROS) significantly mediated the relationship between change in behavioural activation (BADS) and change in depressive symptoms (BDI-II) | 6 |

ABBREVIATIONS: BARB = behavioural activation for religious behaviour, BA = behavioural activation, TBA = Telephone-based behavioural activation, TGM = telephone general monitoring, TAU = treatment as usual, BATD = behavioural activation treatment for depression, ADM = antidepressant medication, WL = wait list, PEP = pleasant event programme, IS = informational support, BAW= behavioural activation for worry, ST = supportive therapy, CBT = cognitive behavioural therapy, MDD =major depressive disorder, AMD = age-related macular degeneration, BDI-II = Beck Depression Inventory II, PHQ-9 = Patient Health Questionnaire 9, MADRS-S = The Montgomery–Asberg Depression Rating Scale, CESD = Center for Epidemiologic Studies Depression scale, HRSD= Hamilton Rating Scale for Depression, DASS = Depression Anxiety Stress Scale, SEM = structural equation modelling, RBB = Religious Background and Behavior questionnaire, SWB = Spiritual Well-Being questionnaire, WORCS = the ways of religious coping scale, BADS = Behavioural Activation for Depression Scale, ATQ= Automatic Thoughts Questionnaire COPE= COPE inventory EROS = Environmental Reward Observation Scale, BAI = Beck Anxiety inventory, MSPSS = Multidimensional Scale of Perceived Social Support, ISI = Insomnia Severity Inventory, RRS = Ruminative Response Scale, DAS = Dysfunctional Attitudes Scale, SHAPS = Snaith-Hamilton Pleasure Scale

**Table 2.** Quality assessment results

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors** | **A** | **S** | **RCT** | **T** | **R** | **PMD** | **Sum** |
| **Armento** et al.[8] | 2 | 0 | 2 | 0 | 0 | 0 | 4 |
| **Au** et al. [9] | 2 | 0 | 2 | 0 | 2 | 2 | 8 |
| **Dimidjian** et al. [10] | 2 | 1 | 2 | 2 | 2 | 2 | 11 |
| **Folke** et al. [11] | 0 | 0 | 1 | 2 | 2 | 1 | 6 |
| **Gaynor** et al. [12] | 0 | 1 | 0 | 2 | 2 | 1 | 6 |
| **Ho** [13] | 2 | 1 | 2 | 0 | 2 | 2 | 9 |
| **Hopko** et al. [14] | 2 | 1 | 2 | 0 | 2 | 2 | 9 |
| **Moradveisi** et al. [15] | 2 | 2 | 2 | 0 | 2 | 2 | 10 |
| **Nasrin** et al. [16] | 2 | 0 | 2 | 0 | 2 | 0 | 6 |
| **Okajima** et al. [17] | 0 | 0 | 2 | 0 | 2 | 1 | 5 |
| **Richards** et al. [18] | 2 | 2 | 2 | 2 | 2 | 2 | 12 |
| **Rovner** et al. [19] | 2 | 1 | 2 | 0 | 2 | 2 | 9 |
| **Ryba** et al. [20] | 2 | 0 | 0ᵃ | 2 | 2 | 0 | 6 |
| **Takagaki** et al. [21] | 2 | 0 | 0ᵃ | 0 | 2 | 2 | 6 |

A= Association; S = Specificity; RCT= Randomised controlled trial or experimental trial; T = temporality; R= representativeness PMD = statistical power and missing data imputation; ᵃ = only data from active condition of RCT used for analyses.

**References**

1 Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annu Rev Clin Psychol. 2007;3: 1-27.

2 Hayes AF. Beyond baron and kenny: Statistical mediation analysis in the new millennium. Commun Monogr. 2009;76(4):408-420.

3 Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173.

4 Sobel ME, Becker MP: Sociological methodology: Volume 30. Basil Blackwell, Limited for the American Sociological Association, 1999.

5 Cooper AA, Clifton EG, Feeny NC. An empirical review of potential mediators and mechanisms of prolonged exposure therapy. Clin Psychol Rev. 2017;56:106-121.

6 Lejuez CW, Hopko DR, Hopko SD. A brief behavioral activation treatment for depression: Treatment manual. Behav Modif. 2001;25(2):255-286.

7 Martell CR, Dimidjian S, Herman-Dunn R: Behavioral activation for depression: A clinician's guide. Guilford Press, 2013.

8 Armento ME, McNulty JK, Hopko DR. Behavioral activation of religious behaviors (BARB): Randomized trial with depressed college students. Psycholog Relig Spiritual. 2012;4(3):206-222.

9 Au A, Yip HM, Lai S, Ngai S, Cheng ST, Losada A, et al. Telephone-based behavioral activation intervention for dementia family caregivers: Outcomes and mediation effect of a randomized controlled trial. Patient Educ Couns. 2019;102(11):2049-2059.

10 Dimidjian S, Goodman SH, Sherwood NE, Simon GE, Ludman E, Gallop R, et al. A pragmatic randomized clinical trial of behavioral activation for depressed pregnant women. J Consult Clin Psychol. 2017;85(1):26-36.

11 Folke F, Hursti T, Tungstrom S, Soderberg P, Kanter JW, Kuutmann K, et al. Behavioral activation in acute inpatient psychiatry: A multiple baseline evaluation. J Behav Ther Exp Psychiatry. 2015;46:170-181.

12 Gaynor ST, Harris A. Single-participant assessment of treatment mediators: Strategy description and examples from a behavioral activation intervention for depressed adolescents. Behav Modif. 2008;32(3):372-402.

13 Ho JS. Mediators and moderators of dementia caregiver depression and cvd risk outcomes in the pleasant events program. San Diego. Dissertation Abstracts International: Section B: The Sciences and Engineering. 2017;78(1).

14 Hopko DR, Armento MEA, Robertson SMC, Ryba MM, Carvalho JP, Colman LK, et al. Brief behavioral activation and problem-solving therapy for depressed breast cancer patients: Randomized trial. J Consult Clin Psychol. 2011;79(6):834-849.

15 Moradveisi L, Huibers MJH, Arntz A. The influence of patients' attributions of the immediate effects of treatment of depression on long-term effectiveness of behavioural activation and antidepressant medication. Behav Res Ther. 2015;69(83-92.

16 Nasrin F, Rimes K, Reinecke A, Rinck M, Barnhofer T. Effects of brief behavioural activation on approach and avoidance tendencies in acute depression: Preliminary findings. Behav Cogn Psychother. 2017;45(1):58-72.

17 Okajima I, Chen J. The effect of insomnia on changes in anxiety, depression, and social function after a transdiagnostic treatment targeting excessive worry. Sleep Biol Rhythms. 2017;15(3):243-249.

18 Richards DA, Rhodes S, Ekers D, McMillan D, Taylor RS, Byford S, et al. Cost and outcome of behavioural activation (COBRA): A randomised controlled trial of behavioural activation versus cognitive–behavioural therapy for depression. Health TechnolAssess. 2017; 21(46).

19 Rovner BW, Casten RJ, Hegel MT, Massof RW, Leiby BE, Ho AC, et al. Low vision depression prevention trial in age-related macular degeneration: A randomized clinical trial. Ophthalmology. 2014;121(11):2204-2211.

20 Ryba MM, Lejuez C, Hopko DR. Behavioral activation for depressed breast cancer patients: The impact of therapeutic compliance and quantity of activities completed on symptom reduction. J Consult Clin Psychol. 2014;82(2):325.

21 Takagaki K, Jinnin R, Mori A, Nishiyama Y, Yamamura T, Yokoyama S, et al. Mechanisms of behavioral activation for late adolescents: Positive reinforcement mediate the relationship between activation and depressive symptoms from pre-treatment to post-treatment. J Affect Disord. 2016;204(70-73.

22 Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879-891.

23 Hayes AF, Preacher KJ. Statistical mediation analysis with a multicategorical independent variable. Br J Math Stat Psychol. 2014;67(3):451-470.

24 Krull JL, MacKinnon DP. Multilevel modeling of individual and group level mediated effects. Multivar Behav Res. 2001;36(2):249-277.

25 Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: New procedures and recommendations. Psychol Methods. 2002;7(4):422.

26 Mueser KT, Yarnold PR, Foy DW. Statistical analysis for single-case designs: Evaluating outcome of imaginal exposure treatment of chronic ptsd. Behav Modif. 1991;15(2):134-155.

27 Martell CR, Addis ME, Jacobson NS. Depression in context: Strategies for guided action. Depression in context: Strategies for guided action, New York, US: W W Norton & Co; US. 2001

28 MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annu Rev Psychol. 2007;58(593-614.

29 MacKinnon DP, Lockwood CM, Williams J. Confidence limits for the indirect effect: Distribution of the product and resampling methods. Multivar Behav Res. 2004;39(1):99-128.

30 Iacobucci D, Saldanha N, Deng X. A meditation on mediation: Evidence that structural equations models perform better than regressions. J Consum Psychol. 2007;17(2):139-153.

31 Selig JP, Preacher KJ. Mediation models for longitudinal data in developmental research. Res Hum Dev. 2009;6(2-3):144-164.