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A Systematic Review of Psychological and Pharmacological Treatments for Adjustment Disorder in Adults

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Abstract

Adjustment disorder is a common psychiatric disorder, yet knowledge of the efficacious treatments for adjustment disorder is limited. In this systematic review, we aimed to examine psychological and pharmacological interventions that target adjustment disorder in adults to determine which interventions have the best evidence for improving adjustment disorder symptoms. We performed database searches for literature published between January 1980 and September 2016 and identified studies that included both a sample majority of individuals diagnosed with adjustment disorder and findings on adjustment disorder symptom outcomes. There were 29 studies that met the inclusion criteria for qualitative synthesis; the majority of studies (59%) investigated psychological therapies rather than pharmacological treatments (35%). The range of psychological therapies tested was diverse, with the majority containing cognitive behavioral therapy (CBT) components (53%), followed by three studies that were psychodynamic-related, three studies that were behavioral therapy–based, and two studies that involved relaxation techniques. We rated individual studies using a modified National Health and Medical Research Council quality and bias checklist and then used the Grading of Recommendations Assessment, Development and Evaluation (GRADE; Grade Working Group, 2004) system to rate the overall quality of the evidence. Despite several randomized controlled trials, the quality of the evidence for positive effects of all psychological and pharmacological treatments on symptoms of adjustment disorder was ranked as low to very low. Future high-quality research in the treatment of adjustment disorder has the potential to make a significant difference to individuals who struggle to recover after stressful events.

A Systematic Review of Psychological and Pharmacological Treatments for Adjustment Disorder in Adults

Adjustment disorder is a psychiatric disorder that captures those people who fail to adjust after experiencing a traumatic or stressful event (American Psychiatric Association, 2013). Although adjustment disorder has existed in psychiatric nomenclature for several decades, the publication of the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-5*; American Psychiatric Association [APA], 2013) marked the first time it was classified under a specific category of disorders. It now sits alongside posttraumatic stress disorder (PTSD) and acute stress disorder in the Trauma- and Stressor-Related Disorders category, in recognition that a stressful event is a necessary (although not sufficient) condition for the development of the disorder. The stressful event may be a single event (e.g., ending of a significant relationship) or an ongoing stressor (e.g., chronic illness), or it may accompany a significant life event (e.g., divorce, parenthood, or retirement). Adjustment disorder can be diagnosed after a traumatic event if an individual does not meet the full diagnostic criteria for PTSD (APA, 2013). In addition to the diagnostic criteria specifying a stressful event, adjustment disorder in *DSM-5* is further conceptualized as a transient disorder, appearing in the acute phase after a stressful event and typically resolving itself in a limited period of time (usually around six months) after the stressor disappears. However, the symptoms can persist longer if they occur in reaction to an ongoing stressor or are the consequence of a stressor. The diagnostic criteria for adjustment disorder using *DSM-5* criteria are shown in Supplementary Table 1.

It is noteworthy that there is significant divergence in adjustment disorder criteria as presented in the *DSM-5* and in the proposals for the eleventh version of the *International Classification of Diseases* (*ICD-11*; World Health Organization, 2017). Research findings

indicating that intrusions, ruminations, avoidance and adaptive failure are central to adjustment disorder have led to proposals that *ICD-11* define adjustment disorder as marked by intrusions relating to the stressor as well as a failure to adapt (Einsle, Köllner, Dannemann, & Maercker, 2010). This is the first time adjustment disorder has been linked to intrusions, which are commonly associated with PTSD. This significant divergence between the current *DSM-5* and the proposed *ICD-11* criteria for adjustment disorder will have serious implications for clinical practice.

Despite concerns about the specificity of the adjustment disorder diagnostic criteria, adjustment disorder has been identified as a common diagnosis in clinical settings and especially in oncological and psychiatric settings (Huyse et al., 2001; Mitchell et al., 2011; Strain et al., 1998). Recently, in one of the few published studies dealing with longitudinal adjustment disorder, 800 survivors of severe injury were followed across time. The prevalence estimates for adjustment disorder were 18% at 3 months and 15% at 12 months postinjury, which made it the most frequently diagnosed psychiatric disorder in this population (O'Donnell et al., 2016). In addition to being a common psychiatric disorder, adjustment disorder is clinically important for other reasons. A number of studies have reported an association between adjustment disorder and self-harm and suicidality (Kryzhanovskaya & Canterbury, 2001), high levels of disability and low quality of life (Fernandez et al., 2012; O'Donnell et al., 2016), and as a gateway for other psychiatric disorders, such as depression, PTSD, and generalized anxiety disorder (O'Donnell et al., 2016).

Despite the fact that adjustment disorder in its current form emerged as a diagnosis in the third edition of the *DSM* (*DSM-III*; APA, 1980), there have been no published systematic reviews of treatments for adjustment disorder in adults to date, and the evidence-base for

treatments of adjustment disorder remains unknown. In this systematic review, we aimed to examine the available evidence in relation to psychological or pharmacological interventions that target adjustment disorder in adults.

Method

The findings for this review are reported according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement (Supplementary Table 2). We formulated the research question using the Population Intervention Comparison Outcome (PICO) framework: "Population" refers to the characteristics of the patient or population, "intervention" refers to the type of treatment, "comparison" refers to the alternatives to the intervention (e.g., placebo, another therapy, wait list, etc.), and "outcome" refers to the outcomes that are most relevant. Application of a PICO framework helps to structure, contain, and set the scope for the research question (Moher, Liberati, Tetzlaff, Altman, & Group, 2010). The population of interest was defined as adults with a diagnosis of adjustment disorder (i.e., a psychological response to stress involving marked distress and significant impairment in functioning). The intervention was defined as any psychological or pharmacological intervention that targeted symptoms of adjustment disorder. The comparison was defined as any type of control group, including active treatment, as well as any inactive or "no treatment," placebo, or waitlist alternatives. The outcome was defined as changes in adjustment disorder symptomatology and/or diagnostic status, or if these were not provided, changes in depression or anxiety symptoms.

Eligibility Criteria

Due to the general lack of research into adjustment disorder, study methodology was not restricted to randomized controlled trials (RCTs). Studies were included if they (a) investigated a psychological or pharmacological treatment that targeted adjustment disorder,

(b) were published in English and involved adults (18 years of age or greater), (c) included either a majority of participants (at least 50%) who had been diagnosed with adjustment disorder or subanalyses of those participants with adjustment disorder, and (d) reported outcome data from a psychological measure that assessed either adjustment disorder symptom severity and/or diagnosis or symptom change in anxiety or depression. Studies were excluded if (a) they were not in English, (b) full-text was not available, (c) they were validation studies, (d) they were animal studies, (e) they were "grey literature," (i.e., research that is unpublished/published in noncommercial form), (6) no quantitative data was reported (e.g., protocol-only studies), or (7) they involved children or adolescents (less than 18 years of age). Studies were not included or excluded on the basis of the type of psychological or pharmacological treatment that was provided or on the basis of the psychometric properties of the outcome measures used in the trial.

Information Sources

We searched the EMBASE, MEDLINE (PubMed), Cochrane, and PsycINFO databases for peer-reviewed literature published between January 1980 and September 2016. We selected this timeframe in order to map onto the first use of the term "adjustment disorder" (i.e., inclusive of *DSM-III*, *DSM-IV-TR*, and *DSM-5* criteria) and to ensure that the papers included in this review were reflective of current practice. Additional searches were carried out by hand-searching reference lists. Keywords were *pharmacotherapy* OR *pharmacologic** OR *drug** OR *medication** OR *antidepressant** OR *non*antidepressant** OR *antipsychotic** OR *anticonvulsant** OR *adrenergic-inhibiting agent** OR *alpha-antagonist** OR *opioid antagonist** OR *benzodiazepine** OR *antianxiety* OR *antimanic agent** OR *mood stabiliser** OR *mood stabilizer** OR *stimulant** OR *treatment** OR *therapy* OR *counselling** OR *intervention** OR *psychotherapy** AND *adjustment disorder.*

Search and Study Selection

An example of the full electronic search strategy for the MEDLINE database is presented in Supplementary Table 3. The study selection process is outlined in the PRISMA diagram (Figure 1). Two reviewers independently assessed all potentially relevant articles for inclusion, and two blinded independent reviewers checked 10% of the potential articles. There was 100% interrater agreement between the two reviewers.

Data Extraction

Data were extracted from all included studies following the full-text assessment. One reviewer (O.M.) extracted the data and one other (T.V.) checked the data, with any disagreement resolved by discussion. In order to assist the narrative synthesis of the included studies, we designed a predefined data extraction template, which included study description, intervention description, participant characteristics, measures of adjustment disorder, and main findings in relation to changes in adjustment disorder symptoms or diagnosis from pretreatment to posttreatment.

Assessment of Risk of Bias and Quality of Evidence

Whereas the Cochrane method for assessing quality and risk of bias is the "gold standard" for RCTs, there is no such scale for nonrandomized studies (Reeves, Deeks, Higgins, & Wells, 2008). Instead, we used a modified quality and bias checklist (National Health and Medical Research Council, 1999). Two reviewers (O.M. and T.V.) assessed studies for risk of bias on method of treatment assignment, control of selection bias, blinding of assessor (where relevant), and outcome assessment. When there was disagreement between the reviewers, a third reviewer (M. O.) acted as a tiebreaker. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE; Grade Working Group, 2004) system for ranking the overall quality of the evidence for specific outcomes.

The GRADE system adopts a systematic, transparent, and explicit approach to making judgements about the quality of the evidence. Outcomes of interest are identified and the evidence is evaluated, including making explicit the risk of bias and taking into account issues of inconsistency (between studies), indirectness (e.g., using evidence from a similar population), and imprecision (broad confidence intervals; rated when a meta-analysis is conducted). The GRADE system consists of four levels of evidence quality: high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and very low (we are very uncertain about the estimate). Studies are reviewed initially on study design. All RCTs begin with a high grade, and observational studies begin with a low grade. Either can be downgraded based on factors relating to the quality of the study, consistency of findings, and directness (the extent to which the evidence maps onto the population or intervention of interest). Only observational studies can be upgraded based on these factors.

Results

Study Characteristics

From a yield of 3,508 studies, we deemed 29 original studies eligible for inclusion (see Figure 1). The characteristics of each study are presented in Supplementary Table 4. There were 12 (41.3%) included studies that were published in the last 5 years (i.e., 2011–2016). Treatments lasted between 1 month and 18 months. We included 29 studies in the qualitative synthesis, which reported on data from 2,440 participants; study sample sizes ranged from one to 214. The mean age of participants ranged between 20 and 62 years; 66% of studies included majority female samples, 21% included majority male samples, and 14%

did not report on gender. In terms of types of adjustment disorders with which participants had been diagnosed, the subtype was not specified in 28% of the studies; a mix of depressed mood, anxiety, and/or disturbance with conduct was reported in the samples of 38% of the studies; 17% of the study samples reported adjustment disorder with depressed mood; and 17% of the study samples reported adjustment disorder with anxiety.

Studies were grouped according to the general focus of the treatment. The majority of studies (59%; $n = 17$) investigated the use of psychological therapy in adjustment disorder, whereas 35% ($n = 10$) of the studies were pharmacotherapy-based. A single study used plant extracts and another single study used a combination of psychological therapy and pharmacotherapy. Amongst the studies that used psychological therapies, the majority involved individual therapy (77%). The range of psychological therapies tested was diverse, with the majority containing cognitive behavioral therapy (CBT) components (53%), followed by three studies that were psychodynamic-related, three studies that were behavioral therapy–based, and two studies that involved relaxation techniques. There were 14 studies (48%) with no active comparison or control group, seven studies (24%) that compared the intervention to another intervention, and eight studies (28%) that involved an active control group.

Quality Assessment

Of the included studies, 17 (57%) were RCTs, and the remainder were less rigorous observational designs. The RCTs were generally of poor quality, with key limitations including designs that were cluster-randomized as opposed to true randomization (i.e., randomization occurring at the individual level), high percentages of dropout and/or the reporting of only completer analyses, and failure to blind or report blinding of outcome assessors. In addition, although all studies reported pre- and postsymptom change, such as

changes to depression or anxiety symptoms, almost none of the studies reported directly on the change to adjustment disorder status. The average risk of bias across interventions was high due to the low-quality designs of many studies and the methodological limitations of the few RCTs. Studies were grouped and ranked, using GRADE, according to the focus of the treatment (e.g., cognitive behavioral therapy–based, pharmacotherapy for depressive symptoms) and in relation to the posttreatment adjustment disorder outcomes (O.M and T.V.). When there was disagreement between the reviewers, a third reviewer (M.O'D.) acted as a tiebreaker. Details of the quality assessment and the GRADE results can be found in Supplementary Tables 5 and 6, respectively. Studies are discussed in detail later in this article, with studies of higher quality methodology discussed first.

Summary of the Findings

Psychological treatments.

Behavioral-based therapy versus active control. One clustered RCT investigated behavioral therapy versus an active control (Arends, van der Klink, & Bultmann, 2010). The study involved 158 Dutch employees at the start of their workplace sickness leave for mental health disorders; over half the participants had been diagnosed with an adjustment disorder (i.e., 73% of those in the intervention group and 50% of controls). Participants received either a problem-solving intervention called Stimulating Health Participation and Relapse Prevention at work (SHARP At Work) or usual care, delivered by occupational physicians according to an evidence-based guideline (Arends et al., 2010). The intervention focused on problems that the individual would face when returning to work. The researchers did not use a specific adjustment disorder measure. Both groups improved in terms of mental health complaints as measured by the Four-Dimensional Symptom Questionnaire (4DSQ) at posttreatment; however, there were no significant between-group differences. The quality of

evidence for behavioral-based therapy versus an active control for adjustment disorder symptoms was graded as "low" (moderate quality, some indirectness due to not all of the sample having adjustment disorder). Thus, we have limited confidence that there is no difference in effect for behavioral-based therapy for adjustment disorder when compared to an active control on adjustment disorder symptoms at posttreatment.

Behavioral-based therapy (no control). Two observational studies investigated behavioral-based therapy. The studies were published by similar author groups but used different samples (Hosaka et al., 2001; Hosaka, Sugiyama, Tokuda, & Okuyama, 2000). In both studies, researchers used a pre–post design with no control group and investigated changes in Japanese cancer patients with mental health disorders who received approximately five weeks of group therapy. In both instances, the group therapy included psychoeducation, problem solving, psychological support, relaxation, and guided imagery. The first study had 47 individuals, 12 of whom had an adjustment disorder, who were assessed at baseline and at the end of treatment (Hosaka et al., 2000). A subanalysis of the adjustment disorder group found that treatment made no impact on their mental health symptoms posttreatment as measured by the Profile of Mood States (POMS). A second study with a different sample added an additional three sessions of treatment, but the results were inconclusive as the authors reported contradictory findings in various sections of the study (Hosaka et al., 2001). The quality of evidence for behavioral-based therapy for adjustment disorder symptoms, without a comparator, was graded as "very low" (poor quality, serious indirectness). Thus, we have very little confidence that there is no effect for behavioral-based therapy on adjustment disorder symptoms at posttreatment.

CBT-based therapy versus CBT-based therapy. There was one clustered controlled trial (CT) that compared a CBT-based therapy to another CBT-based therapy. In the study,

Lagerveld, Blonk, Brenninkmeijer, Wijngaards-de Meij, and Schaufeli (2012) compared a modified work-related CBT (i.e., individual work-focused CBT concentrating on return to work, in addition to disorder-specific CBT treatment) to CBT (i.e., individual disorder-specific CBT based on a national protocol) in 168 Dutch employees on sick leave due to mental health problems, 67% of whom had adjustment disorder. Participants were clustered at the health-provider level, with psychotherapists assigned to perform either regular CBT or work-focused CBT. There was a significant difference between the groups posttreatment for the Stress subscale of the Depression Anxiety Stress Scales (DASS), which represented a small effect size, $d = 0.16$. There was no specific measure for adjustment disorder. The quality of evidence for CBT-based therapy versus CBT-based therapy in terms of adjustment disorder symptoms posttreatment was graded as "low" (moderate quality clustered controlled trial with some indirectness issues).

CBT-based therapy versus active control. In three RCTs, two of which were clustered RCTs, researchers investigated CBT-based therapies in comparison to an active control (Carta et al., 2012; Moorey, Greer, Bliss, & Law, 1998; Van Der Klink, Blonk, Schene, & Van Dijk, 2003). Two studies were randomized at the healthcare provider level, which encompassed general practitioners (GPs) in one study (Carta et al., 2012) and occupational physicians in the other (Carta et al., 2012; Van Der Klink et al., 2003). In a clustered RCT of 64 rural Italian patients attending their GPs, 30 patients received GP-only care and 34 received GP care plus psychologist-delivered CBT based on a manual for depression treatment for a period of 6 months (Carta et al., 2012). At baseline, 59% of the sample had been diagnosed with adjustment disorder according to *DSM-IV*. At the end of treatment, both groups had improved significantly in depression symptoms as measured by the Beck Depression Inventory (BDI), but the group that received the CBT improved

significantly more compared to the control group. Researchers did not report effect sizes, so the magnitude of this effect is unknown. A significant proportion of participants overall had been taking concurrent antidepressant medication.

In the second clustered RCT, Van Der Klink and colleagues (2003) investigated stress inoculation, which is a treatment that includes elements of CBT, and compared outcomes to those in a group that received usual care, which comprised support and education, delivered by occupational physicians. The sample included 192 Dutch workers who were on 2 weeks sick leave because of an adjustment disorder. Both groups improved significantly in mental health symptoms as measured by the 4DSQ and the Symptom Checklist 90 (SCL-90), and there was a significant between-groups difference posttreatment for anxiety on the 4DSQ (effect size calculated as $d = 0.27$).

In the third RCT, Moorey and colleagues (1998) compared 8 weeks of a problem-focused CBT treatment program called "adjuvant psychological therapy" (APT; $n = 25$) with 8 weeks of supportive counselling ($n = 22$) in cancer patients with abnormal adjustment to their disease. Adjustment disorder diagnosis was based on *DSM-III-R* criteria, modified to account for specific circumstances of cancer-related stress. Notably, these modifications were made to ensure that a patient was experiencing a minimum level of emotional distress (having scored 8 or more on either the Anxiety or Depression subscale of the Hospital Anxiety and Depression Scale [HADS]). The authors did not use a specific adjustment disorder measure. Recipients of APT reported significantly greater improvements in anxiety than recipients of supportive counselling. There was no difference in depression scores. This result was maintained at the 4-month follow-up; however, no differences were reported beyond 4 months. The authors did not report effect sizes nor did they report any adverse events or side-effects. The quality of evidence for CBT-based therapy versus an active control for

adjustment disorder symptoms, as measured at posttreatment, was graded as "low" (moderate quality studies all showing an effect, serious indirectness due to no adjustment-specific measure and modified diagnosis criteria). Therefore, further research is likely to have an important impact on our confidence in the estimate of the effectiveness of CBT-based therapy versus an active control for adjustment disorder symptoms as measured at posttreatment.

CBT-based therapy (inactive or no control). Five studies investigated interventions with CBT components in the treatment of adjustment disorder, but did not include an active control group. Four of these were observational studies (Halford, 1987; Hirsh, Sears, & Conti, 2009; Powell & McCone, 2004; van der Heiden & Melchior, 2012), whereas the fifth study was an RCT with a waitlist control group (Bachem & Maercker, 2016). In the RCT, Bachem and Maercker (2016) compared 1 month of a self-help bibliotherapy intervention (with no therapist involvement) to a waitlist control group. The study included 54 individuals who had been victims of a burglary attack and had symptoms consistent with adjustment disorder. When the authors applied the new proposed *ICD-11* diagnostic criteria for adjustment disorder, they found that 34% of the sample had an adjustment disorder diagnosis, with the remainder displaying some adjustment disorder symptoms. The intervention was found to significantly reduce the *ICD-11* criteria of "preoccupations" ($d = 0.67$) as measured by the Adjustment Disorder New Module–20; however, there were no significant differences between groups on anxiety, depression, stress, or other adjustment disorder symptoms. It should also be noted that five participants in the intervention group showed an increase in symptoms between pre- and posttreatment.

Four further observational studies, including one pre–post study with eight individuals and three case studies of single individuals with adjustment disorders, investigated CBT treatment outcomes (Halford, 1987; Hirsh et al., 2009; Powell & McCone, 2004; van der

Heiden & Melchior, 2012). The lack of control group in the pre-post study and the lack of statistical significance testing in the case studies significantly limits their interpretation. The overall quality of the evidence for CBT-based therapy versus an inactive/no control group for adjustment disorder symptoms as measured at posttreatment was graded as "very low" (poor quality studies, serious indirectness).

Brief psychodynamic psychotherapy versus intermediate psychodynamic therapy. One RCT compared brief psychodynamic psychotherapy (3 month duration) with intermediate-length (12 month duration) psychodynamic psychotherapy in 66 Israeli psychiatric outpatients with adjustment disorder (Ben-Itzhak et al., 2012). Of the 48 patients who began brief psychodynamic therapy, 13 discontinued it before the end of therapy (27%), whereas 12 of the 43 people who began intermediate therapy discontinued it before the end of therapy (28%). After 3 months, both groups had improved significantly in psychiatric symptoms as measured by the SCL-9-R; however, there were no between-group differences and the additional 9 months of treatment in the intermediate group conferred no additional benefit. Effect sizes were not reported, and a specific adjustment disorder measure was not used. The quality of evidence for brief psychodynamic psychotherapy versus intermediate psychodynamic therapy was graded as "low" (poor quality).

Psychodynamic psychotherapy (no control). Two observational studies that used pre–post designs investigated psychodynamic psychotherapy in individuals with adjustment disorder (Hofer, Holtforth, Frischknecht, & Znoj, 2010; Kramer, Despland, Michel, Drapeau, & De Roten, 2010). A naturalistic study of 32 French students with adjustment disorder by Kramer et al. (2010) and a secondary paper by Kramer, Pascual-Leone, Despland, and de Roten (2015) that reported on additional analyses involving the original sample found that, at discharge, short-term psychodynamic therapy resulted in a significant reduction in general

psychiatric symptoms as measured by the SCL-90-R as well as in depression symptoms as measured by the BDI. Participants received an average of 34 sessions (range: 24–48), including psychotherapeutic treatments, that lasted up to one year. The authors did not use a specific adjustment disorder measure nor did they report effect sizes. A second pre–post study by Hofer and colleagues (2010) sought to treat adjustment disorder in 11 individuals with acquired brain injury. Participants received an average of 20 sessions over a year; after treatment, there was a significant reduction in depression symptoms as measured by the BDI and all participants had lost their adjustment disorder diagnoses. The authors did not report effect sizes. The quality of evidence for psychodynamic therapy with no control was graded as "very low" (poor quality).

Relaxation-based therapy versus active control. One RCT, by Hsaio and colleagues (2014), investigated a relaxation-based intervention known as Body-Mind-Spirit, which was a group therapy that combined elements of relaxation, mindfulness, physical exercise, and spiritual recovery and was underpinned by Eastern philosophy. The authors compared Body-Mind-Spirit to "treatment as usual," which involved outpatient medication, psychoeducation treatment, and as-needed suicide crisis intervention. There were 70 participants with an adjustment disorder who participated, and results showed that the intervention had no effect on anxiety or depression symptoms, although the intervention group did see a reduction in suicidal thoughts, odds ratio (*OR*) = 0.34, 95% CI [0.11, 1.07]. The authors did not use a specific adjustment disorder measure. The quality of evidence for relaxation-based therapy versus an active control for adjustment disorder symptoms as measured at posttreatment was graded as "low" (poor quality).

Relaxation-based therapy (no control). In a relaxation-based, pre–post design observational study, Bos, Merea, van den Brink, Sanderman, and Bartels-Velthuis (2014)

investigated the use of mindfulness training on Dutch psychiatric patients, 14 of whom had been diagnosed with adjustment disorder. The adjustment disorder patients improved significantly after 8 weeks of mindfulness training in terms of psychiatric symptoms as measured by the Short Symptom List (SSL), $d = 0.59$. The authors did not use a specific adjustment disorder measure. The quality of evidence for relaxation-based therapy with no control was graded as "very low" (poor quality).

Pharmacological treatments.

Euphytose (EUP) versus placebo control. One clustered RCT investigated EUP, a combination of six plant extracts, versus a placebo control; the placebo was not described (Bourin, Bougerol, Guitton, & Broutin, 1997). The study involved 182 French general practice outpatients who had an adjustment disorder with anxious mood. The diagnosis of adjustment disorder with anxious mood was made using a diagnostic algorithm, and patients were required to have a score of at least 20 on the Hamilton Anxiety Scale (HAM-A). Participants received two tablets of either EUP ($n = 91$) or a placebo ($n = 91$) three times a day for 28 days. The authors reported significantly greater improvements in anxiety symptoms, as measured using the HAM-A, for the EUP group as compared to the placebo group at Week 1, Week 2, and Week 4, and although effect size was not reported, we were able to calculate the effect size at posttreatment as $d = 0.33$. Furthermore, 57% of patients treated with EUP (compared to 39% treated with a placebo) were counted as responders at posttreatment, meaning that their posttreatment HAM-A score was less than 14. Additionally, at Day 28, 43% of EUP patients scored below 10 on the HAM-A as compared to 25% of placebo patients. The researchers did not use a specific adjustment-disorder measure. Participants in the placebo group reported mild adverse effects twice as often ($n = 8$) as those in the EUP group ($n = 4$). The quality of evidence for EUP (plant extracts) versus placebo

control was graded as "low" (moderate quality, some indirectness due to no adjustment-specific measure).

Serotonin reuptake enhancer versus antidepressant versus anxiolytic. One European RCT that involved Belgian, Swiss, and French participants (N = 152) compared tianeptine, a psychotropic compound with both antidepressant and anxiolytic potentials, with both an antidepressant (mianserin) and an anxiolytic (alprazolam) for the treatment of patients with adjustment disorder with mixed emotional features (Ansseau et al., 1996). Results indicated that the three treatments had similar efficacy in reducing anxiety and depression. At the completion of the 6-week treatment period, no significant differences were found among the groups in terms of changes to anxiety and depression. Researchers did not use a specific adjustment disorder measure. Dropouts (22%) were evenly distributed between the three groups and occurred mainly due to adverse events and lack of efficacy. The quality of evidence for serotonin reuptake enhancer versus an antidepressant versus an anxiolytic was graded as "low" (moderate quality, some indirectness due to no adjustment disorder-specific measure).

Gradual-dose selective serotonin reuptake inhibitor (SSRI) versus full-dose SSRI. One RCT, by Amodeo and colleagues (2012), compared two different dosage schedules of an SSRI (paroxetine) in 30 cancer patients, half of whom had been diagnosed with depressive adjustment disorder. For the first 10 days of treatment, half of the group received a gradual-dosage schedule compared to the other half, who started on full dosage from the first day. By Day 11, both groups were receiving the same dosage. Participants received SSRIs for 8 weeks total. Both groups significantly improved in depression and anxiety symptoms at the end of the study period as measured by the SSL, d = 0.59. Researchers did not use a specific adjustment disorder measure. It should also be noted that side effects were reported in 53.3%

of participants in the intervention group (37.5% of whom rated side effects as moderate to severe) and 93.3% of those in the control group (78.6% of whom rated side effects as moderate to severe). The quality of evidence for a gradual-dose SSRI (paroxetine) versus a full-dosage SSRI for adjustment disorder symptoms as measured at posttreatment was graded as "low" (moderate quality, some indirectness).

SSRI versus benzodiazepine derivative. Two RCT studies conducted in Belgium compared an SSRI (trazodone) to a benzodiazepine derivative (clorazepate;De Wit et al., 1999; Razavi, Kormoss, Collard, Farvacques, & Delvaux, 1999). In a study by De Wit and colleagues (1999) of patients with HIV-related adjustment disorder, 10 patients received trazodone and 11 patients received clorazepate for 28 days. Results showed improvements in anxiety and depression scores for both groups at 28 days; however, there were no significant treatment effects. In a similar study by Razavi and colleagues (1999) of 18 female patients with breast cancer-related adjustment disorders, 11 patients received trazodone and seven patients received clorazepate for 28 days. Results showed improvements in anxiety and depression scores for both groups at 28 days; however, there were no significant treatment effects. Adverse events were experienced by 38.5% of trazodone recipients and 40.0% of clorazepate recipients. Researchers did not report effect sizes in either study, nor did they use specific adjustment disorder measures. The quality of evidence for an SSRI versus various controls was graded as "low."

SSRI (no control). A single case study by Özten, Hizli Sayar, Göğçegöz Gül, and Ceylan (2015) investigated the use of SSRIs in the treatment of adjustment disorder (sertraline for 1 week followed by fluoxetine for 7 weeks) and found reductions in depression levels at the end of treatment. Researchers did not undertake significance testing nor did they use a specific adjustment disorder measure. In addition, the sertraline induced an adverse

reaction, which resolved within 3 weeks. The quality of evidence for an SSRI (sertraline, followed by fluoxetine) with no control was graded as "very low" (poor quality).

SSRI and some concurrent psychotherapy (no control). A retrospective study reviewed data for 96 individuals receiving various SSRIs, 33 of whom had depressive adjustment disorder (Hameed, Schwartz, Malhotra, West, & Bertone, 2005). Results showed that SSRIs were effective in reducing psychiatric symptoms as measured by the Patient Health Questionnaire. Researchers did not use a specific adjustment disorder measure. The quality of evidence for an SSRI (various kinds) with some concurrent psychotherapy, with no control, was graded as "very low" (poor quality).

Pivagabine (no control). One open pre–post study trialled 1800 mg of pivagabine (antidepressant and anxiolytic) for 30 days in a sample of Italian patients who had been diagnosed with dysthymic (n = 22) and adjustment (n = 38) disorders (Terranova, Gilotta, & Luca, 1997). Although the authors did not use a specific adjustment disorder measure, results of separate depression and anxiety assessments performed at Days 15 and 30 showed significant improvements in both measures. Authors did not report effect sizes. The quality of evidence for an antidepressant, pivagabine, versus no control was graded as "very low" (poor quality).

Benzodiazepine versus antidepressants versus psychotherapy versus inactive control. One Italian study compared the effectiveness of four types of therapy (three pharmacological therapies and one psychotherapeutic) for patients with an adjustment disorder (De Leo, 1989). Patients (N = 70) were randomly assigned to receive either viloxazine (VLX; an antidepressant; n = 18), S-adenosylmethionine (SAM; a methyl donor with antidepressive properties; n = 17), lormetazepam (LMZ; a benzodiazepine; n = 17), or supportive psychotherapy (n = 18), and a further 15 patients were allocated to a placebo

group. Each group was treated for 4 weeks, after which no significant between-group differences were observed. All groups reported significantly improved depression scores at posttreatment compared to baseline. The quality of evidence for a benzodiazepine (LMZ) versus antidepressants (VLX or SAM) versus psychotherapy versus inactive control was graded as "very low" (poor quality).

Non-benzodiazepine anxiolytic (etifoxine) versus benzodiazepine. In two RCTs, researchers compared a non-benzodiazepine anxiolytic (etifoxine) to a benzodiazepine in the treatment of anxious adjustment disorder symptoms (Nguyen et al., 2006; Stein, 2015). In a study by Stein (2015) of 201 South African patients with adjustment disorder, half of the sample received etifoxine for 28 days and the other half received alprazolam for the same period of time; participants were followed for an additional 7 days after medication was discontinued. Results showed that although alprazolam had a stronger effect on anxiety symptoms after 28 days than did etifoxine, anxiety scores as measured by the HAM-A continued to decrease for the etifoxine group after medication discontinuation whereas they increased for the alprazolam group. There were adverse events reported for 35% of participant who received receiving etifoxine compared to 47.5% of the alprazolam group. The majority of adverse events were gastrointestinal- or central nervous system–related. Four serious adverse events were recorded, although only one was considered to be related to treatment. In a similar study by Nguyen and colleagues (2006) of 191 French patients with adjustment disorder, half the sample received etifoxine and the other half received lorazepam for 28 days; researchers continued to follow participants for 7 days after medication discontinuation. At Day 28, both drugs had an equivalent effect on reducing anxiety symptoms as measured by the HAM-A, but significantly more individuals who received etifoxine were deemed to be "responders" (defined as a 50% or greater decrease in anxiety

scores compared to baseline). Researchers did not report effect nor did they use a specific adjustment disorder measure. The quality of evidence for a non-benzodiazepine anxiolytic (etifoxine) versus a benzodiazepine was graded as "low" (moderate quality).

Combined pharmacotherapy and psychological therapy (no control). Although many studies that examined psychological treatments had some proportion of participants on concurrent pharmacotherapy, only one study was specifically designed to investigate the treatment of adjustment disorder using pharmacotherapy and psychotherapy combined (Ichitovkina, Zlokazova, & Solov'ev, 2014). In a pre–post cohort design, researchers investigated outcomes for 94 Russian military combatants who received treatment for adjustment disorder (60%) or PTSD (40%). The psychotherapy components were a mixture of individual rational therapy and group art therapy, family therapy, and hypnosuggestive therapy. The pharmacotherapy consisted mostly of SSRIs and benzodiazepines. Participants showed significant reductions in psychopathological symptoms posttreatment as measured by the Multidimensional Personality Questionnaire. The quality of evidence for combined pharmacotherapy and psychological therapy with no control was graded as "very low" (poor quality).

Discussion

The aim of this review was to assess the evidence related to psychological and pharmacological interventions for adults with adjustment disorder. The variety of psychological treatment approaches was diverse, ranging from pure self-help bibliotherapy to 18 months of psychodynamic therapy. The greatest limitation of the included studies was the lack of measurement using a measure specific to adjustment disorder. Other key limitations

of the studies included lack of baseline clinician-administered assessment (as opposed to self-report measures), lack of follow-up assessment, small sample sizes, and lack of controlling for antidepressants or other medications. Researchers did not routinely report the presence or absence of adverse events nor did they consistently report effect sizes. Although we included 29 studies in our review, including 12 RCTs, the GRADE rankings for the treatment comparisons reviewed in this study were low to very low, meaning we have little confidence as to whether the observed effects are "true effects" of treatment. This finding is consistent with the poverty of high quality of research in the area of adjustment disorder as a whole and is a call to researchers and funders to recognize the importance of conducting research on this diagnosis. Further research is very likely to have an important impact on our current understanding of efficacious treatments for adjustment disorder (GRADE Working Group, 2004).

Beyond the methodological limitations of the studies, there are a number of other fundamental issues with the current adjustment disorder literature. Specifically, the approach to diagnosing and measuring adjustment disorder was inconsistent across studies. Very few studies investigated whether an individual lost his or her adjustment disorder diagnosis after the intervention and many relied on depression and anxiety symptomatology instead. Some studies did not employ the diagnostic criteria for adjustment disorder according to *DSM* or *ICD* stipulations, in that they classified individuals as having an adjustment disorder with a comorbid disorder (commonly depression). This is inconsistent with both *DSM* and *ICD* diagnostic criteria, which state that the symptoms cannot meet the criteria for another disorder. This error in diagnosing is indicative of the confusion around adjustment disorder diagnostic criteria more generally. It is critical that careful consideration is given to how

intervention researchers diagnose adjustment disorder and that treatment trials include measures of adjustment disorder over time.

A final outstanding and pressing issue is the divergence between the *ICD-11* and *DSM* approaches to diagnosing adjustment disorder. In one study, Bachem and Maercker (2016) used the *ICD-11* criteria to identify adjustment disorder; this criteria is significantly different from all other previous *ICD* iterations and the entire *DSM* system. Specifically, *ICD-11* diagnostic criteria focus on intrusions and avoidance—this is diagnostically similar to subthreshold PTSD. It remains unknown if interventions that target adjustment disorder as defined by *ICD-11* will treat adjustment disorder as defined by *DSM-5*. There is potential that there will be significant divergence in treatment studies according to how researchers define adjustment disorder.

The findings of the current review must also be considered alongside the limitations of this study. The omission of potentially important papers, including those that were unpublished, not written in English, or published prior to 1980 limit the comprehensiveness of the review. The study results were not synthesized using meta-analysis, and the review focused specifically on adults, meaning the relevance of these findings in relation to children and adolescents is unknown. Finally, our inclusion criteria required that studies had identified that they were targeting adjustment disorder. This may mean that studies that targeted stress responses or impairment after a stressor (but did not identify these as adjustment disorder interventions) were not included in the review.

There is little doubt that our understanding of treatments for adjustment disorder will benefit from well-designed treatment trials. There are many guides for conducting a well-designed trial (e.g., Najavits, 2003). We highlighted measurement as one of the main problems in past studies, and recently developed adjustment disorder measures, including the

Structured Clinical Interview of *DSM-5* (SCID-5 for *DSM-5*; First, Williams, Karg, & Spitzer, 2015) and the *ICD–11*-specific Adjustment Disorder–New Module (ADNM; Einsle et al., 2010), will help to ameliorate this problem. There are still many unanswered questions which future research could address: Would adjustment disorder respond to a lower-dose intervention (e.g., five sessions of CBT)? Given that adjustment disorder can be made up of anxious, depressive, or PTSD symptoms, are there common mechanisms that could be targeted to treat adjustment disorder? Does treating adjustment disorder prevent the development of more severe disorders? Regardless, the field will only move forward when the diagnostic vagueness surrounding adjustment disorder is clarified with further research.

The current evidence base for the treatment of adjustment disorder is lacking in sufficiently high-quality research. The recategorization of adjustment disorder as a Trauma- and Stressor-Related Disorder in *DSM-5* may provide the impetus for researchers to take more of an interest in the treatment of the disorder (APA, 2013). The trialling and publishing of high-quality research in the treatment of adjustment disorder has the potential to make a significant difference to community members who struggle to recover after stressful events.

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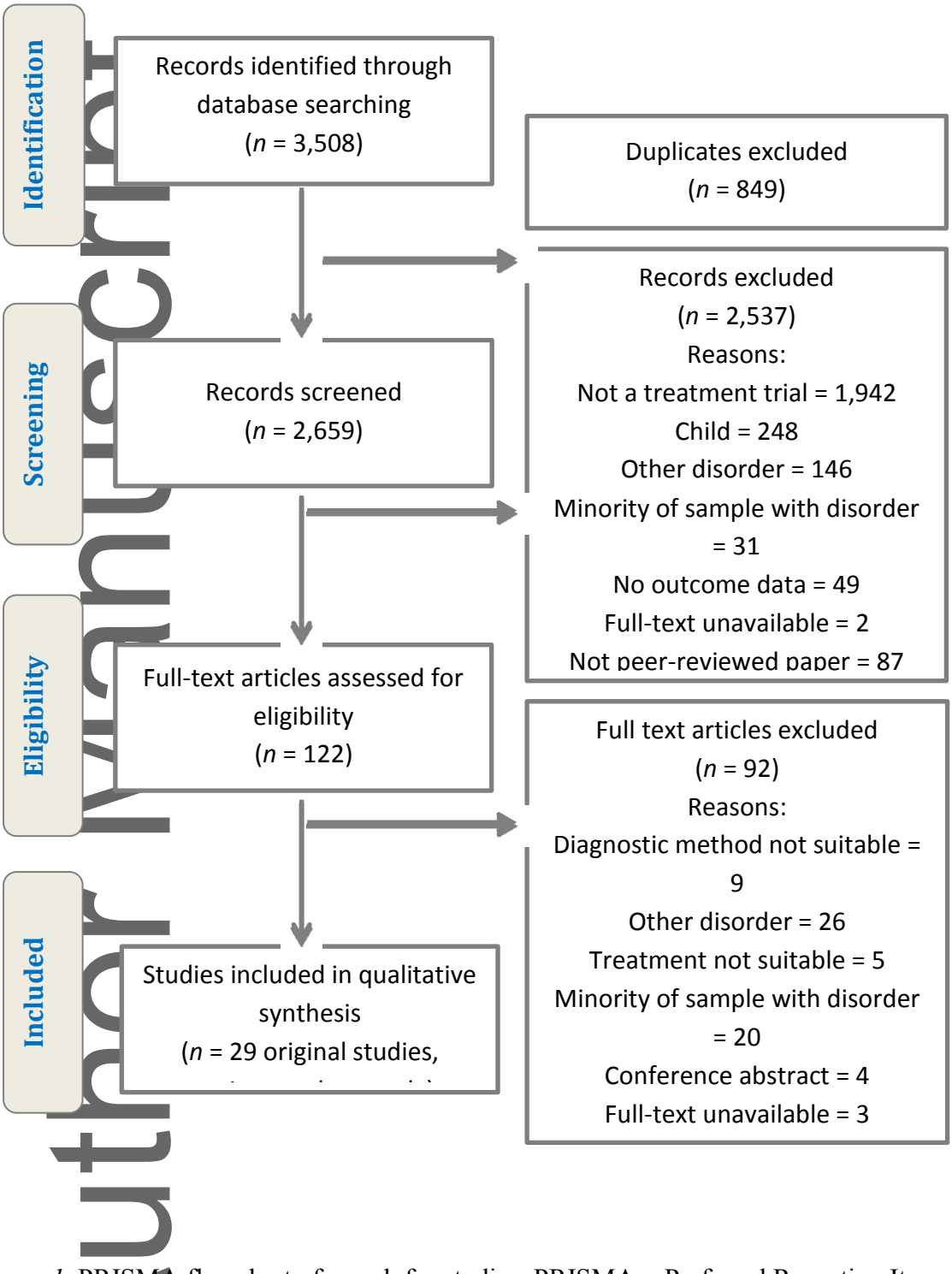

Figure 1. PRISMA flowchart of search for studies. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).