

Evidence Compass



Technical Report

What are effective interventions for adjustment
disorder?

A Rapid Evidence Assessment

October 2016



Australian Government
Department of Veterans' Affairs

Disclaimer

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Table of Contents

Acknowledgements	3
Table of Contents	4
List of Abbreviations	6
Executive Summary	7
Introduction	9
Diagnostic classifications	9
Prevalence	10
Outcomes	11
Risk factors	11
Discrimination of subtypes	12
Summary	13
Method	13
Defining the research question	13
Search strategy	14
Search terms	14
Paper selection	14
Information management	15
Evaluation of the evidence	15
Ranking the evidence	19
Identification	20
Screening	20
Eligibility	20
Included	20
Summary of the evidence	21
Psychotherapy	21
Pharmacotherapy	23
Combined psychological and pharmacotherapy	24
Discussion	24
Implications	26
Future Directions	26
Limitations	27
Conclusion	27
Appendix 1	28

Population Intervention Comparison Outcome (PICO) framework	28
Appendix 2.....	29
Example search strategy	29
Appendix 3.....	30
Quality and bias checklist	30
Appendix 4.....	32
Evidence Profile	32
Appendix 5.....	48
Appendix 6.....	50
References	51

List of Abbreviations

CBT	Cognitive behavioural therapy
CAU	Care as usual
DVA	Department of Veterans' Affairs
DSM	Diagnostic and Statistical Manual
GP	General Practitioner
ICD	International Classification of Diseases
MBCT	Mindfulness-based cognitive therapy
MBSR	Mindfulness-based stress reduction
OP	Occupational physician
PICO	Population Intervention Comparison Outcome
PTSD	Posttraumatic stress disorder
OEF/OIF	Operation Enduring Freedom/Operation Iraqi Freedom
RCT	Randomised Controlled Trial
REA	Rapid Evidence Assessment
SSRI	Selective serotonin reuptake inhibitors
TAU	Treatment as usual
WHO	World Health Organization

Executive Summary

- Adjustment disorder is a psychiatric diagnosis that occurs in response to a stressful or traumatic event. It is diagnosed when an individual responds to a stressful/traumatic event with clinical distress or impairment, and anxiety/depression-like symptoms, but does not meet criteria for another psychiatric disorder (such as major depressive disorder, posttraumatic stress disorder or other psychiatric disorders).
- Adjustment disorder is one of the most common psychiatric disorders yet paradoxically, the least well-understood. The aim of this rapid evidence assessment (REA) was to examine the evidence and efficacy of psychological or pharmacological interventions targeting adjustment disorder in adults.
- Literature searches were conducted to collect studies published from 2000-2016 that investigated the efficacy of interventions for adjustment disorder. Studies were primarily excluded because they did not have a majority sample of individuals with adjustment disorder, or the study did not report on outcomes from a treatment trial relevant to adjustment disorder (e.g., change in adjustment disorder diagnostic status or symptom severity). Studies that met inclusion criteria were assessed for quality of methodology, risk of bias, and quantity of evidence, and the consistency, generalisability and applicability of the findings to the population of interest (e.g., adults with adjustment disorder). These assessments were then collated for each adjustment disorder intervention to determine an overall ranking of level of support for each intervention.
- The ranking categories used in this review were 'Supported' – clear, consistent evidence of beneficial effect; 'Promising' – evidence suggestive of beneficial effect but further research required; 'Unknown' – insufficient evidence of beneficial effect; 'Not supported' – Clear, consistent evidence of no effect or negative/harmful effect.
- Twenty-one studies met the inclusion criteria for review. The majority of studies investigated the efficacy of psychological therapy in adjustment disorder (n = 15), with only 24% (n = 5) of the studies being pharmacotherapy-based, and a single study being a combination of psychological and pharmacotherapy. The range of psychological therapies tested were diverse, with seven studies that were primarily cognitive behavioural in nature, three studies that were primarily psychodynamic, three studies that had a behavioural therapy focus, and two studies that involved relaxation techniques.

- Despite several randomised controlled trials, the overall quality of the studies was moderate to low, with no studies ranked as high quality. As a result, all interventions in the treatment of adjustment disorder were ranked as “Unknown”.
- While the current evidence base for treatment of adjustment disorder is lacking in sufficiently high quality research to support direct recommendations, in the interim, clinicians and providers can rely on indirect evidence from other relevant guidelines. For example, the current recommendations for the treatment of subsyndromal depression are the use of CBT-based treatments, and as such, should be considered a first line choice in the treatment of adjustment disorder.
- Despite adjustment disorder being a part of the Diagnostic and Statistical Manual (DSM) nomenclature since 1968, and being one of the most frequently diagnosed Axis 1 disorders in the aftermath of stress or trauma, there is a stark lack of research investing efficacious treatments for adjustment disorder. This represents an important opportunity for researchers and funders alike, to conduct high quality research testing treatments for adjustment disorder. Ultimately this will make a significant difference to community members who struggle to recover after a stressful event.

Introduction

Adjustment disorder is a psychiatric disorder that captures those people who fail to adjust after experiencing a stressful or traumatic event. Adjustment disorder is often described as a subsyndromal or sub-clinical disorder because it is diagnosed when an individual fails to meet the full diagnostic criteria for other disorders such as depression, anxiety disorders or posttraumatic stress disorder (PTSD). In addition, adjustment disorder is often conceptualised as a transient disorder which occurs in the acute phase after a stressful event, as it is thought to typically resolve itself in a limited period of time (usually six months) after the stressor disappears. However, the symptoms can persist longer if they are occurring in reaction to a chronic or ongoing stressor. Common triggering stressors for adjustment disorder include any major life change such as relationship breakdowns, illness or injury, and employment or financial difficulties. Adjustment disorder can also be diagnosed following exposure to traumatic events when an individual fails to meet full criteria for PTSD. In the military setting, potential stressors include exposure to combat or other potentially traumatic events, and separation from family while on deployment.¹

Diagnostic classifications

Adjustment disorder has existed in some form of psychiatry classifications since 1952, however, the two major psychiatric diagnostic systems used in Australia (Diagnostic and Statistical Manual of Mental Disorders: DSM; and International Classification of Disorders: ICD) have some significant differences in how they define adjustment disorder.

Adjustment disorder was formally introduced into diagnostic lexicon as part of the Diagnostic and Statistical Manual of Mental Disorder 3rd edition (DSM-III) in 1968. The most recent (2014) publication of the Diagnostic and Statistical Manual for Mental Disorders version 5 (DSM-5) saw the re-categorisation of adjustment disorder as a Trauma-and Stressor-Related Disorder in recognition that a stressful event is a necessary (although not sufficient) condition for the development of the disorder. Despite the re-conceptualisation, DSM-5 diagnostic criteria did not change from the previous iterations, as it was argued that so little research had been undertaken on adjustment disorder that any such changes would be based on too limited evidence.² (See Appendix 6 for DSM-5 and ICD-11 diagnostic criteria).

The World Health Organization (WHO) which oversees the development of the ICD first introduced adjustment disorder into ICD-9 in 1978.³ The WHO is in process of updating the adjustment disorder diagnostic criteria in ICD-11, which is expected to be published in 2018. Adjustment disorder will be grouped in the category of disorders specifically associated with stress, alongside PTSD, complex PTSD, and prolonged grief. This maps onto the changes seen in the latest DSM-5. It is anticipated that there will be further significant changes between the current (ICD-10) and future (ICD-11) versions of adjustment disorder criteria. The ICD committee specifically attempted to address the limitations of previous adjustment disorder diagnostic algorithms, and for the first time the proposed ICD-11 diagnosis

represents a substantial redefining and clarification of the adjustment disorder diagnostic criteria. Specifically, the new criteria for adjustment disorder defines it as a stress response disorder defined by intrusions relating to the stressor and a failure to adapt.⁴ This is particularly important because it is the first time that adjustment disorder has had a focus on these aspects of a stress response, which are commonly associated with PTSD. Indeed, research has found that intrusions, ruminations, avoidance and adaptive failure are common processes that appeared to be central to adjustment disorder.⁵ However, this proposed ICD-11 criteria (i.e. intrusions and failure to adapt) marks a significant deviation from the DSM-5 criteria (any one criteria pertaining to distress).

There remains significant ongoing debate about how to best conceptualise adjustment disorder.⁶ The primary concerns with the current classification structure of adjustment disorder, both in the past and in current classification systems, is that it is ill-defined as a specific diagnostic category, and this diagnostic vagueness has made research investigating adjustment disorder exceptionally difficult.⁷ This may account for the remarkable lack of research that has been conducted with adjustment disorder as a central focus.⁴

Prevalence

Despite the concerns with the specificity of the adjustment disorder diagnostic criteria, adjustment disorder is one of the most common diagnoses in clinical settings. In a global sample of psychiatrists, adjustment disorder was ranked as the seventh most frequently diagnosed disorder.⁸ In a large sample of 56 centres across 11 European countries adjustment disorder was found to be the primary clinical diagnosis.⁹ Across primary care and consultation liaison psychiatry settings, prevalence rates for adjustment disorder ranges from 10% to 35%.^{10,11}

Adjustment disorder is also common in certain populations. In cancer patients, where adjustment disorder has been extensively investigated, a meta-analysis found a prevalence of 15%.¹² A recent study of over 800 severe injury survivors found prevalence rates for adjustment disorder were 18% at 3 months and 15% at 12 months post injury which made it the most frequently diagnosed disorder in this population.¹³

High rates of adjustment disorder have also been found in military and veteran populations. A study of returning US soldiers from OEF/OIF operations found a prevalence of 6% for adjustment disorder, which was the third most common psychiatric diagnoses, behind PTSD (12%) and depression (13%).¹⁴ In a review of US OEF/OIF personnel who were psychiatrically evacuated from deployment, 38% were diagnosed with adjustment disorder - more than any other psychiatric disorder.¹⁵

The picture emerging from these studies is that, despite the conjecture around the appropriate conceptualisation of adjustment disorder, it is clearly a frequent diagnosis across a variety of settings and there is some evidence to suggest that it may be more common amongst military populations than civilian.¹

Outcomes

Despite adjustment disorder being one of the most widely diagnosed psychiatric disorders in clinical and primary care settings, it is paradoxically one of the least researched.³ If psychological distress is perceived as occurring on a continuum, then adjustment disorder is often considered to sit between minimal distress and other affective/anxiety disorders such as depression, PTSD, or generalised anxiety disorder.¹³ Yet despite its subthreshold status, this does not mean adjustment disorder is less severe or impactful than other ‘full-blown’ psychiatric disorders. The clinical importance of adjustment disorder can be seen in its relationship with concerning psychopathological behaviours such as self-harm and suicidality. A study of adults with adjustment disorders admitted to hospital found that over 60% had a history of suicidal attempts (compared to 45% of those without adjustment disorders) and suicidal ideation was 93%.¹⁶ In addition, a large population study in Denmark examined the relationship between over 9000 completed suicides and adjustment and found that those diagnosed with adjustment disorder had 12 times the rate of suicide than those without.¹⁷

In addition to a strong link with increased suicidality, adjustment disorder is recognised as a potential prodromal expression of other psychiatric disorders. A recent research study showed that adjustment disorder was associated with high levels of disability and low quality of life in a large sample of injury patients.¹³ Furthermore, this study found adjustment disorder at three months significantly increased risk for developing a more severe psychiatric disorder (excluding adjustment disorder) at 12 months. This finding supports the conceptualisation that adjustment disorder is a gateway disorder to other psychiatric disorders such as depression, PTSD and generalised anxiety disorder. Therefore, adjustment disorder may be a crucial disorder to target interventions towards, in that treatment of adjustment disorder may prevent more serious psychopathology from developing.

In summary, converging evidence supports the view that adjustment disorder is of significant clinical concern, in that it is linked to self-harm and suicidal behaviour. Moreover, it significantly increases disability and reduces quality of life, and it can be an early indicator of risk for developing more severe psychopathology in the future.

Risk factors

While the current ICD-10 states that individual predisposition or vulnerability plays a bigger role in the risk for adjustment disorder than other psychiatric disorders, including PTSD, the evidence supporting this statement has been questioned.¹⁸ There is little research investigating individual predisposition, such as personality factors, in the risk for developing adjustment disorder.

Some emerging research has implicated certain personality traits in adjustment disorder. For example, in a study of Taiwanese military high school students with and without adjustment

disorder, levels of neuroticism and psychoticism were both significantly higher in those with adjustment disorder, although there was no significant difference in levels of extraversion.¹⁹ In a similar sample of Taiwanese military personnel, adjustment disorder was associated with a parenting style characterised by over-protection but less caring, particularly for maternal parenting, compared to those without adjustment disorder.²⁰ The study also found that those with adjustment disorder scored higher in neuroticism and introversion, whereas those without adjustment disorder scored higher in extraversion.

Alexithymia is a personality construct that has been linked to adjustment disorder, defined as a difficulty with identifying, differentiating, verbalising and communicating feelings.²¹

Research has implicated alexithymia in the relationship between parenting style, personality traits, and adjustment disorder. In a sample of Taiwanese military conscripts with adjustment disorder, parental overprotection combined with a low level of care for the child had a perpetuating effect on alexithymia. The authors proposed that parenting influences the development of certain personality traits such as neuroticism and introversion, which then increase the likelihood of developing alexithymia, which in turn leads to adjustment disorder.²¹ A second study found that individuals with adjustment disorder with previous suicide attempts had significantly higher rates of alexithymia than individuals with adjustment disorder without suicidal attempts.²²

Very little research has investigated the neurological/biological underpinnings of adjustment disorder, or how they compare to other psychiatric disorders. A recent study in Korean Army conscripts found that individuals with adjustment disorder had decreased grey matter volume in the right medial frontal gyrus as compared to healthy controls.²³ In contrast, there were no brain regions that were decreased in the healthy controls as compared to patients with adjustment disorder. Reductions in the right medial frontal gyrus have been implicated in emotional dysregulation such as depression and anxiety after stress. Alternatively, such reductions have also been implicated in executive function, which involves higher order cognitive activities such as task planning, attention, and response inhibition that in turn enables goal setting and goal directed activities.²⁴ Diminished grey matter resulting in either emotional dysregulation and/or reduced executive function could explain the symptoms of adjustment disorder.

Discrimination of subtypes

Adjustment disorder has previously been considered in terms of sub-types depending on the symptom profile and predominant presentations. The current DSM-5 retained the subtype approach to adjustment disorder. Under the DSM system, individuals can be given a diagnosis of adjustment disorder with anxiety, depressed mood, or disturbance of conduct, a mixed anxiety/depression subtype, or a mixed disturbance in emotions and conduct. The degree to which these subtypes are discriminatory has received little research attention. A recent study found that individuals with adjustment disorder could be significantly discriminated on symptom severity (low, medium and high), but there was no evidence that

classes were differentiated by subtype symptoms.¹³ Research has also questioned whether different subtypes impact treatment options or outcomes.²⁵ In contrast to DSM approach, ICD-11 is proposing that adjustment disorder is a uni-faceted concept, arguing there is no evidence for the validity or utility of subtypes of adjustment disorder.²⁶

Summary

Adjustment disorder is a psychiatric disorder that captures those people who fail to adjust after experiencing a stressful or traumatic event. Adjustment disorder is associated with high levels of distress and/or impairment and is one of the most common psychiatric disorders yet paradoxically, the least well-understood. The aim of this rapid evidence assessment (REA) was to examine the evidence and efficacy of psychological or pharmacological interventions targeting adjustment disorder in adults.

Method

This review utilised a rapid evidence assessment (REA) methodology to assess the interventions reported in adjustment disorder literature. A REA is a research methodology that uses similar methods to a systematic review, but makes concessions to the breadth and depth of the process, in order to suit a shorter timeframe. The advantage of a REA is that it utilises rigorous methods for locating, appraising and synthesising evidence related to a specific topic. To make a REA rapid, however, the methodology places a number of limitations in the search criteria and in how the evidence is assessed. For example, REAs often limit the selection of studies to a specific time frame (e.g. last 15 years), and limit selection of studies to peer-reviewed published, English studies (i.e. not including unpublished pilot studies, difficult-to-obtain material and/or non-English language studies). Also, while the strength of the evidence is assessed in a rigorous and defensible way, it is not necessarily as exhaustive as a well-constructed systematic review and/or meta-analysis. A major strength however, is that a REA can inform policy and decision makers more efficiently by synthesising and ranking the evidence in a particular area within a relatively short space of time.

Defining the research question

The aim of this REA was to examine the evidence and efficacy of psychological or pharmacological interventions targeting adjustment disorder in adults. The components of this question were defined using terms of the Population Intervention Comparison Outcome (PICO) framework (refer to Appendix 1). Operational definitions were established for key concepts related to the question, and from this, specific inclusion and exclusion criteria were defined for screening studies into this REA. As part of this operational definition, 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 (including self-help) or

pharmacological intervention that targeted symptoms of adjustment disorder. The outcome was defined as any measure of mental health symptoms (e.g., PTSD, depression, anxiety, alcohol and drug abuse, self-harm/suicide) or more general psychological wellbeing (e.g., quality of life, wellbeing, return to work)

Search strategy

To identify the relevant literature, systematic bibliographic searches were performed to find relevant trials from the following databases: EMBASE, MEDLINE, PsycINFO. An example of the search strategy conducted using the EMBASE database appears in the Appendix 2.

In addition, the following databases were searched: Cochrane, Clinical Guidelines Portal (Australia), and the National Guideline Clearinghouse (USA). Although two guidelines were found,^{27,28} both covered highly specific populations (injured workers/occupational settings) and as a result were deemed not sufficiently relevant for inclusion in this REA.

Search terms

Search terms using the Title/s, Abstract/s, MeSH terms and Keywords lists included:

pharmacotherap* 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”

Paper selection

After conducting searches, identified studies were evaluated according to the following inclusion and exclusion criteria:

Included:

1. Internationally and locally published peer-reviewed research studies
2. Research papers published from **1st January 2000 to 20th August 2016**
3. Outcome data reporting on changes in symptoms of adjustment disorder
4. Adjustment disorder was diagnosed using an established measure in 50% or more of the sample
5. If adjustment disorder was diagnosed in less than 50% of the sample, the paper contained sub-analyses of adjustment disorder participants
6. Human adults (i.e. ≥ 18 years of age)
7. English language

Excluded:

1. Non-English papers
2. Papers where a full-text version was not readily available
3. Validation studies
4. Animal studies
5. Grey literature (e.g. media: websites, newspapers, magazines, television, conference abstracts, theses)
6. No quantitative data reported (e.g. protocol only studies)
7. Papers where the study focus was not relevant to adjustment disorder

Information management

A screening process was adopted to code the eligibility of papers acquired through the literature search. Papers were directly imported into the bibliographic tool Endnote X5, and then processed using Excel. All records that were identified through the literature search were screened for relevance against the inclusion criteria. Initial screening for inclusion was performed by one reviewer, and was based on the information contained in the title and abstract. Full text versions of all studies which satisfied this initial screening were obtained.

In screening the full-text paper, the reviewer made the decision on whether the paper should be included or excluded, based on the pre-defined inclusion and exclusion criteria. If the paper met criteria for inclusion, it became subject to data abstraction. At this stage in the information management process, 20% of the articles processed were randomly selected and checked by a second independent reviewer. There was 100% inter-rater agreement between the two reviewers. The following information was extracted from studies that met inclusion criteria: (i) study description, (ii) intervention description, (iii) participant characteristics, (iv) primary outcome domain, (v) main findings, (vi) bias and, (vii) quality assessment.

Evaluation of the evidence

There were five key components that contributed to the overall evaluation of the evidence:²⁹

1. The **strength of the evidence base**, in terms of the quality and risk of bias, quantity of evidence, and level of evidence (study design)
2. The **direction** of the study results in terms of positive, negative or null findings
3. The **consistency** of the study results
4. The **generalisability** of the body of evidence to the target population (i.e. adults/military personnel)
5. The **applicability** of the body of the evidence to the Australian context

The first three components provided a gauge of the internal validity of the study data in support of efficacy for an intervention. The last two components considered the external factors that may influence effectiveness, in terms of the generalisability of study results to the intended target population, and applicability to the Australian context.

Strength of the evidence base

The strength of the evidence base was assessed in terms of the (a) quality and risk of bias, (b) quantity of evidence, and (c) level of evidence.

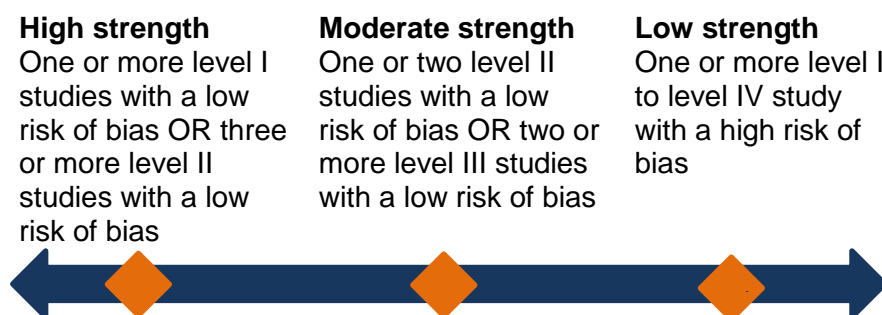
- a) **Quality and risk of bias** reflected how well the studies were conducted, including how participants were selected, allocated to groups, managed and followed-up; and how the study outcomes were defined, measured, analysed and reported. An assessment was conducted for each individual study with regard to the quality and risk of bias criteria utilising a modified version of the Chalmers Checklist for appraising the quality of studies of interventions (see Appendix 3). Three independent raters rated each study according to these criteria, and together a consensus agreement was reached as to an overall rating of 'Good', 'Fair', or 'Poor'.
- b) **Quantity** of evidence reflected the number of studies that were included as the evidence base for each ranking. The quantity assessment also took into account the number of participants in relation to the frequency of the outcomes measured (i.e. the statistical power of the studies). Small underpowered studies that were otherwise sound may have been included in the evidence base if their findings were generally similar- but at least some of the studies cited as evidence must have been large enough to detect the size and direction of any effect.
- c) **Level of evidence** reflected the study design. Details of the study designs included in this REA were assessed against a hierarchy of evidence commonly used in Australia³⁰:
 - Level I: A systematic review of randomised controlled trials (RCTs)
 - Level II: A RCT
 - Level III-1: A pseudo-RCT (i.e. a trial where a pseudo-random method of allocation is utilised, such as alternate allocation).
 - Level III-2: A comparative study with concurrent controls. This can be any one of the following:
 - Non-randomised experimental trial [this includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e.

utilise A vs B and B vs C to determine A vs C with statistical adjustment for B)]

- Cohort study
- Case-control study
- Interrupted time series with a control group
- Level III-3: A comparative study without concurrent controls. This can be any one of the following:
 - Historical control study
 - Two or more single arm study [case series from two studies. This would include indirect comparisons utilise (i.e. A vs B and B vs C to determine A vs C where there is no statistical adjustment for B)]
 - Interrupted time series without a parallel control group.
- Level IV: Case series with either post-test or pre-test/post-test outcomes

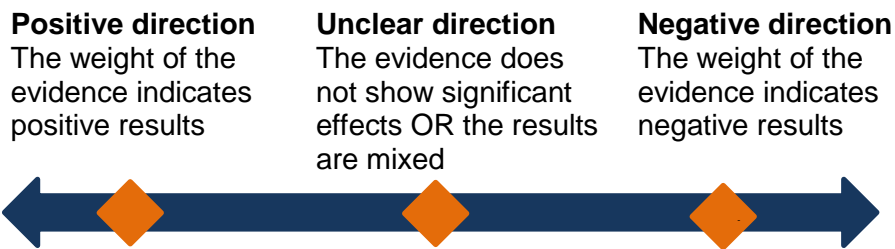
Overall strength

A judgement was made about the strength of the evidence base, taking into account quality and risk of bias, quantity of evidence and level of evidence. Agreement was sought between three independent raters and consensus about the strength of the evidence base was obtained according to the following categories.



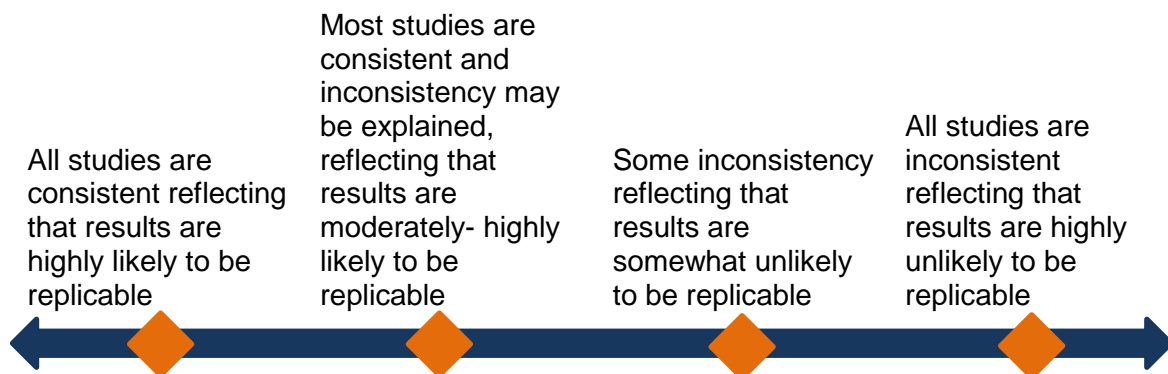
Direction

The direction component of the ranking system makes a judgement as to whether the results are in a positive or negative direction. In cases where there are studies which show findings in different directions, preference is given to the direction of the study findings with the highest level and best quality.



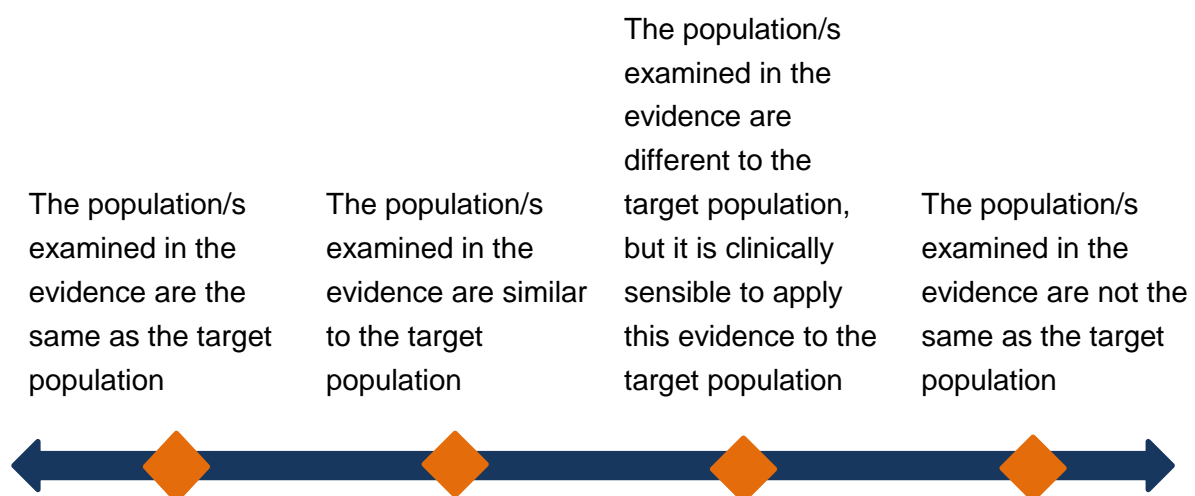
Consistency

The consistency component of the ranking system of the body of the evidence assesses whether the findings are consistent across the included studies (including across a range of study populations and study designs). It was important to determine whether study results are consistent to ensure that the results are likely to be replicable or only likely to occur under certain conditions.



Generalisability

This component covers how well the participants and settings of the included studies could be generalised to the target population. Population issues that might influence this component included gender, age or ethnicity, or level of care (e.g. community or hospital).



Applicability

This component addresses whether the evidence base is relevant to the Australian context, or to specific local settings (such as rural areas or cities). Factors that may reduce the direct application of study findings to the Australian context or specific local settings include organisational factors (e.g. availability of trained staff) and cultural factors (e.g. attitudes to health issues, including those that may affect compliance).

Directly applicable to the Australian context Applicable to the Australian context with few caveats Applicable to the Australian context with some caveats Not applicable to the Australian context



Ranking the evidence

On balance, this next step takes into account the considerations of the strength of the evidence (quantity and risk of bias, quantity of evidence and level of evidence), consistency, generalisability and applicability. The total body of the evidence is then ranked into one of four categories: 'Supported', 'Promising', 'Unknown' and 'Not Supported' (see Figure 1). Agreement on ranking is sought between all three independent raters.

Figure 1: Categories within the intervention ranking system

SUPPORTED	PROMISING	UNKNOWN	NOT SUPPORTED
Clear, consistent evidence of beneficial effect	Evidence suggestive of beneficial effect but further research required	Insufficient evidence of beneficial effect and further research is required	Clear, consistent evidence of no effect or negative / harmful effect

Results

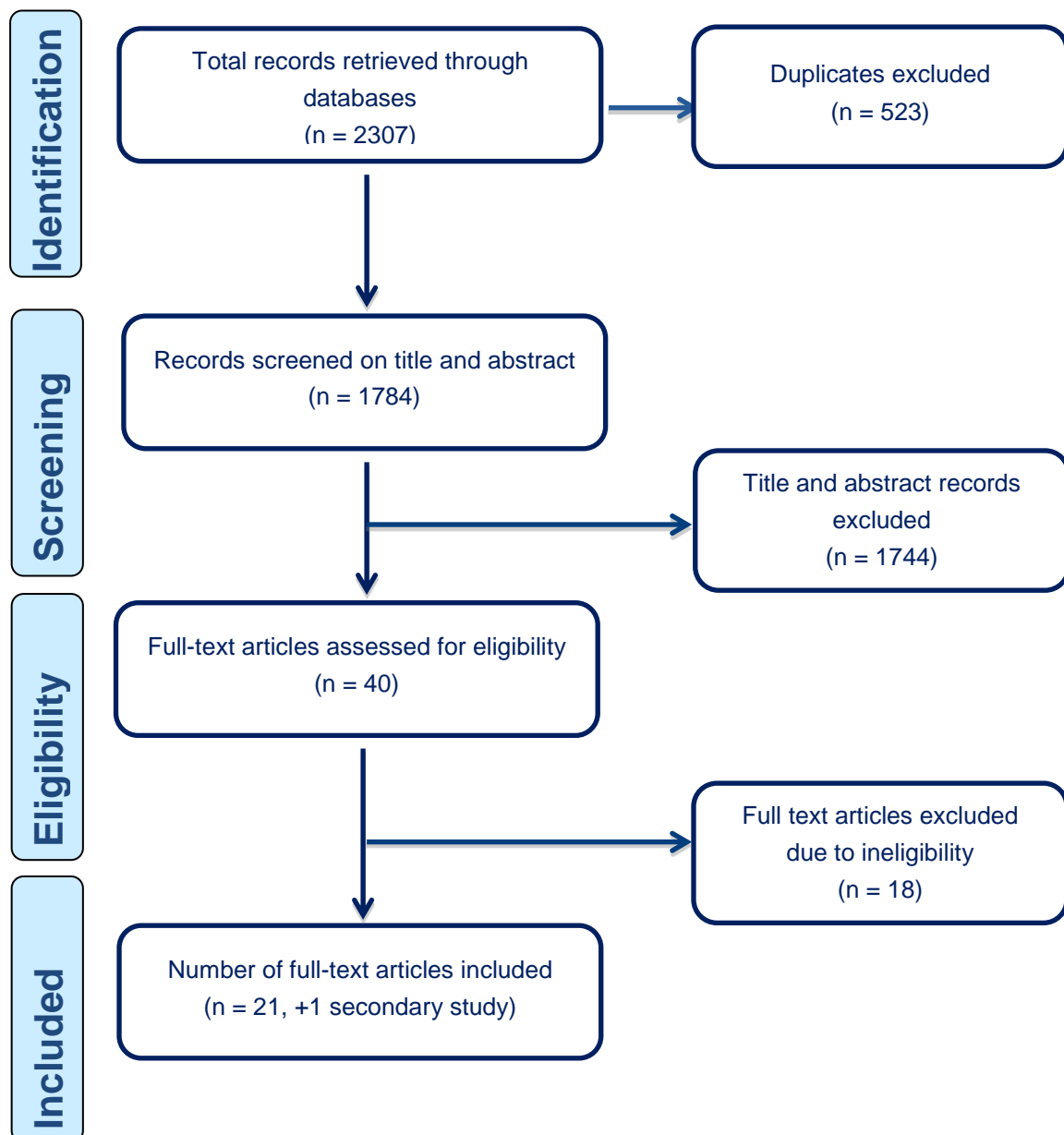
The following section presents the flowchart relating to the number of records identified at each stage of the REA (refer to Figure 2). From all the sources searched, 21 original publications and an additional study based on secondary analyses met the full inclusion criteria and were included in the results of this REA.

The majority of the studies were excluded because the study was not a treatment trial for adjustment disorder (73% of excluded studies) with other reasons being the population focus was children, the study contained no quantitative/qualitative data, the percentage of

adjustment disorder patients was below 50%, or the treatment trial focus was not adjustment disorder.

The 21 original studies originated from a wide range of international locations. Five studies were from the Netherlands, three from the US, two studies each from Japan, France, Switzerland and Italy, and a single study from Taiwan, Israel, Turkey, South Africa and Russia. Over 60% of the studies were published in the last 6 years (2010 to 2016), with the remainder spread across 2000 to 2009.

Figure 2: Flowchart representing the number (n) of records retrieved at each stage of the rapid evidence assessment



Summary of the evidence

The majority of studies investigated the efficacy of psychological therapy in adjustment disorder ($n = 15$), with only 24% ($n = 5$) of the studies being pharmacotherapy-based, and a single study being a combination of psychological and pharmacotherapy.

The range of psychological therapies tested were diverse, with the majority containing cognitive behavioural therapy (CBT) components (47%), followed by three studies that were psychodynamic-related, three studies that were behavioural therapy-based, and two studies that involved relaxation techniques. A summary of the studies is found in the evidence profile presented in Appendix 4 in detail, and in Appendix 5 as a brief overview.

Nine studies (41%) were RCTs, and the remainder were less rigorous designs. The RCTs were of mixed quality, with key limitations including designs that were clustered randomised as opposed to true randomisation (i.e. randomisation occurring at the individual level); short or no follow-up period; high percentages of drop-out and/or completer analyses only. Studies are discussed in detail below with higher quality methodology studies discussed first.

Psychotherapy

Behavioural therapy

Three studies investigated behavioural therapy.³¹⁻³³ One study employed a problem-solving intervention using a clustered RCT.³¹ The sample was 158 Dutch employees on the start of workplace sickness leave for mental health disorders, of which over half were diagnosed with adjustment disorder. The intervention focused on problems that the individual would face with returning to work. Although sickness absence was reduced in the group that received the problem-solving intervention, there was no effect on mental health symptoms. Two studies further investigated behavioural-based therapy in the treatment of adjustment disorder, published by the same authors on different samples.³² Both studies 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. The first study had 47 individuals, of which 12 had adjustment disorder, who were assessed at baseline, at the end of treatment, and six months after baseline.³² A sub-analysis of the adjustment disorder group found that treatment made no impact on their mental health symptoms at any time point. A second follow-up study added an additional three sessions of treatment but the results are inconclusive as the authors reported contradictory findings in various sections of the study.³³

Cognitive behavioural therapy

Seven studies investigated interventions with CBT components in the treatment of adjustment disorder.³⁴⁻⁴⁰ Four of these compared an intervention group to a control group,

with one being an RCT, two studies clustered RCTs, and the fourth study was a quasi-experimental group design.

The RCT compared one month of a self-help (no therapist involvement) bibliotherapy intervention to a control group who were wait-listed to receive the intervention.³⁴ The study included 54 individuals who were victims of a burglary attack and who 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 ICD-11 criteria of 'preoccupations', PTSD symptoms and anxiety symptoms significantly more than controls however, there were no significant differences between groups on depression, stress or other adjustment disorder symptoms.

The two clustered RCTs were randomised at the healthcare provider level, which was GPs in one study and occupational physicians in the other.^{35,36} In a study of 64 rural Italian patients attending their GPs, 30 received GP-only care, while 34 received GP care and psychologist delivered CBT, for a period of six months.³⁵ At baseline, 59% of the sample were diagnosed with adjustment disorder according to DSM-IV. At the end of treatment, both groups improved significantly in depression symptoms, but the group that received the CBT improved significantly more compared to the control group. Only the CBT group improved in quality of life scores. A significant proportion of the sample over all were taking concurrent antidepressant medication.

The second clustered RCT investigated stress inoculation, which is a treatment that includes elements of CBT, and compared outcomes to a group that received usual care.³⁶ The sample was 192 Dutch workers who were on two weeks sick leave because of an adjustment disorder. The two groups were followed for the three months of treatment and 12 months after starting treatment. While return to work rates were significantly higher and sickness leave significantly lower in the group who received CBT, there was no significant change in mental health symptoms in either group as a result of treatment.

The final study investigating CBT in adjustment disorder with a control group compared CBT with a modified work-related CBT in 168 Dutch employees on sick leave due to mental health problems, of which 67% had adjustment disorder.³⁷ Decreases in mental health problems did not significantly differ between groups. Three further studies, including a pre-post study with eight individuals and two case studies of single individuals with adjustment disorder investigated CBT treatment outcomes.³⁸⁻⁴⁰ The lack of control group and for the case studies, the lack of statistical significance testing, significantly limits the interpretation of these studies.

Psychodynamic psychotherapy

Three studies investigated psychodynamic psychotherapy in individuals with adjustment disorder.⁴¹⁻⁴³ One study used an RCT design comparing brief psychodynamic psychotherapy (3 months) with intermediate length (12 months) in 66 Israeli psychiatric outpatients with adjustment disorder.⁴² Both groups were followed-up for nine months after the end of treatment. After three months, both groups had improved significantly in psychiatric symptoms and wellbeing, with the additional nine months of treatment in the intermediate group conferring no additional benefit.

One study used a pre-post design with no control group in a sample of 32 French students with adjustment disorder, with a secondary paper that was published with follow-up analyses of the original sample.^{41,44} The studies reported that there was a significant reduction in general psychiatric symptoms as well as depression symptoms. A final pre-post study sought to treat adjustment disorder in 11 individuals with acquired brain injury.⁴³ Participants received on average 20 sessions over a year, and after treatment there was a significant reduction in depression symptoms, and all participants had lost their adjustment disorder diagnoses.

Relaxation

Two studies investigated relaxation-based interventions in the treatment of adjustment disorder, one study was an RCT and the second was a pre-post design without a control group.^{45,46} The RCT investigated an intervention known as Body-Mind-Spirit, which was a group therapy that combined elements of relaxation, mindfulness, physical exercise, and spiritual recovery that was underpinned by Eastern philosophy, compared to controls.⁴⁵ Seventy participants with adjustment disorder participated and results showed that there was no effect of the intervention on anxiety or depression symptoms, although there was a reduction in the intervention group in suicidal thoughts. A second relaxation-based study investigated the efficacy of mindfulness training on Dutch psychiatric patients, of which 14 were diagnosed with adjustment disorder.⁴⁶ The adjustment disorder patients improved significantly after eight weeks of mindfulness training in both psychiatric symptoms and quality of life. The small sub-sample and lack of control group limit this study's findings.

Pharmacotherapy

Anxiety

Two studies investigated the efficacy of benzodiazepines in the treatment of anxious adjustment disorder symptoms.^{47,48} Both studies used RCTs to compare a non-benzodiazepine anxiolytic (etifoxine) to a benzodiazepine. In a study of 201 South African patients with adjustment disorder, half of the sample received etifoxine and half received alprazolam for 28 days, and were followed for a further seven days after discontinuation.⁴² Results showed that while at 28 days, effect on anxiety symptoms was stronger for

alprazolam, after medication discontinuation, anxiety scores continued to decrease for the etifoxine group whereas they increased for the comparison. In a similar study of 191 French patients with adjustment disorder, half the sample received etifoxine compared to lorazepam for 28 days, and were follow-up for seven days after discontinuation.⁴⁷ At day 28, the drugs had an equivalent effect on reducing anxiety symptoms, but significantly more individuals who received etifoxine were deemed responders (defined as a 50% of greater decrease from baseline anxiety scores).

Depression

Three studies investigated the efficacy of SSRIs in the treatment of depressive adjustment disorder symptoms.⁴⁹⁻⁵¹ One RCT compared two different dosage schedules of an SSRI (paroxetine) in 30 cancer patients, with half of the sample diagnosed with adjustment disorder.⁴⁹ For the first 10 days of treatment, half the group received a gradual dosage schedule compared to the other half who started on full dosage from day one. 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. The lack of follow-up and small sample size are limitations of this study.

A retrospective study reviewed data for 96 individuals receiving various SSRIs, of which 33 individuals had adjustment disorder. Results show that SSRIs were effective in reducing psychiatric symptoms.⁵⁰ A final case study investigated an SSRI in the treatment of adjustment disorder (fluoxetine), and found reductions in depression levels at the end of treatment.⁵¹

Combined psychological and pharmacotherapy

Although many studies 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.⁵² 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. Although the treatment resulted in significant reductions in various psychological symptoms, the study design limits the interpretation.

Discussion

The aim of this review was to assess the evidence related to effective psychological and pharmacological interventions for adults with adjustment disorder. The range of psychological treatment approaches, including the length of the treatments and the treatment dose was diverse, ranging from pure self-help bibliotherapy to 12 months of psychodynamic therapy.

Despite 21 original studies, none of the range of the types of treatments, psychological or pharmacological, were ranked as promising or supported after our evaluation of the evidence. All the treatments reviewed in this report were for adjustment disorder and their efficacy were ranked as unknown, due to the strength of the evidence being low. Despite a large number of RCTs, none were of sufficient quality to upgrade the strength rating to 'moderate.' The key limitations of the studies included lack of follow-up assessment, lack of measurement of adjustment disorder (especially at post treatment or follow-up), lack of baseline clinician-administered assessment (as opposed to self-report measures), small sample sizes and lack of controlling for antidepressants or other medications.

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 their adjustment disorder diagnosis after the intervention, and relied on depression and anxiety symptomatology instead. Some studies did not employ the diagnostic criteria for adjustment disorder according to DSM or ICD stipulations, and classified individuals as having dual diagnoses of depression or other psychiatric disorders in addition to adjustment disorder. According to DSM and ICD, it is not possible to have adjustment disorder in conjunction with 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. It is important to note the DSM-5 versions of two influential structured clinical interviews (Structured Clinical Interview of DSM-5: SCID, and the Mini International Neuropsychiatric Interview 7: MINI-7) now have interviews for adjustment disorder. This means there are gold standard measures of adjustment disorder which will help advance the intervention field.

In addition to the efficacy of treatments for adjustment disorder being unknown, a number of other significant gaps in knowledge remain. For example, all of the studies focused on the treatment of adjustment disorder, as opposed to the prevention of other psychiatric disorders, despite emerging evidence that adjustment disorder is a gateway disorder to full-blown psychiatric disorders.¹³ Whether current treatments can prevent adjustment disorder from developing into a more severe psychiatric disorder has not been investigated.

A final outstanding and pressing issue is the divergence between ICD-11 and the DSM approach to diagnosing adjustment disorder. One study³⁴ used the ICD-11 criteria to identify adjustment disorder, which is significantly different from all other previous ICD iterations and the entire DSM system. Specifically, ICD-11 criteria focuses on intrusions and avoidance as diagnostic criteria, which is diagnostically similar to sub-threshold PTSD. Interventions that focus on proposed ICD-11 criteria and their applicability to DSM-5 adjustment disorder remains unknown and if the proposed ICD-11 criteria is adopted formally in 2018, there will

be significant divergence in treatment studies according to how they define adjustment disorder.

Implications

Although we could find no 'supported' psychological or pharmacological interventions for the treatment of adjustment disorder, we can look to other literature to inform us of treatment options until the adjustment disorder literature catches up. There are a number of guidelines for the treatment of similar disorders, such as depression,⁵³ that may be relevant to appropriate treatment for adjustment disorder. People with a subthreshold or mild depression will often also meet criteria for an adjustment disorder and if this was the case, evidence based treatments for subsyndromal/mild depression could also be relevant for adjustment disorder. For example, depression guidelines detail the approaches that should be taken to subthreshold depression or mild depressive symptoms, which consists of low-intensity psychosocial interventions, such as:

- individual guided self-help based on the principles of CBT
- computerised CBT
- structured group physical activity program.

Alternatively, group CBT may also be offered. Pharmacological treatment is not recommended routinely for subthreshold depressive symptoms or mild depression because the risk-benefit ratio is poor.

For persistent subthreshold depressive symptoms, or depression that fails to respond to low-intensity options, guidelines then recommend an antidepressant or high-intensity psychological interventions. SSRIs are the first line in antidepressants, because they are equally effective as other antidepressants and have favourable risk-benefit ratios. High-intensity psychological interventions include: CBT, interpersonal therapy, behavioural activation and behavioural couple's therapy (where suitable). For those who decline pharmacotherapy or high intensity psychological therapies, guidelines recommend counselling or short term psychodynamic psychotherapy, although these have more uncertain levels of evidence supporting efficacy.

Future Directions

While the literature reporting the efficacy of adjustment disorders treatment is lacking, there is useful research which can help to inform what adjustment disorder treatments could look like. Adjustment disorder may be considered well-suited to a self-help intervention or other low-intensity intervention, as it is considered a subthreshold disorder.³⁴ Self-help interventions can vary in their amount of therapist involvement, from pure self-help (no therapist contact) to guided self-help (minimal therapist contact) and can occur across a

range of mediums including bibliotherapy, computerised, and internet-administered self-help.⁵⁴ Other forms of low intensity interventions should also be considered such a brief face to face interventions with non-expert therapists such as in the UK Improving Access to Psychological Therapies model.

There is a lack of RCTs for pharmacological treatments of adjustment disorder.⁶ Given the depression guidelines for subthreshold depression do not recommend antidepressant medication as first line treatment, it is probably the case that until further pharmacological trials identify the usefulness of medication in the treatment of adjustment disorder, pharmacological medications should not be considered first line treatment for adjustment disorder.

Limitations

The findings from this REA should be considered alongside some limitations. These limitations included: the omission of potentially relevant papers that were published prior to or after the defined search period; the omission of non-English language papers; and reference lists of included papers were not hand-searched to find other relevant studies. Finally, the information presented in this REA is a summary of information presented in available papers. We recommend readers source the original papers if they would like to know more about a particular intervention or study.

Conclusion

While the current evidence base for treatment of adjustment disorder is lacking in sufficiently high quality research to support direct recommendations, in the interim, clinicians and providers can rely on indirect evidence from other relevant guidelines. For example, the current recommendations for the treatment of subsyndromal depression are the use of CBT-based treatments, and as such, should be considered a first line choice in the treatment of adjustment disorder. Adjustment disorder remains a poorly researched and poorly understood disorder. This represents an opportunity for funders and researchers alike to develop high quality research in the treatment of adjustment disorder. This research has the potential to make a significant difference to community members who struggle to recover after a stressful event.

Appendix 1

Population Intervention Comparison Outcome (PICO) framework

This question was formulated within a Population Intervention Comparison Outcome (PICO) framework. Application of a PICO framework helps to structure, contain and set the scope for the research question. Inclusion of intervention and comparison components is dependent on the question asked, and may not be appropriate for all question types.

- **What are the effective interventions for adults with adjustment disorder?**
 - **PICO format: In people who are diagnosed with adjustment disorder, which psychological or pharmacological interventions lead to improved mental health outcomes?**

P Patient, Problem, Population	I Intervention	C Comparison (optional)	O Outcome (<i>“more effective” is not acceptable unless it describes how the intervention is more effective</i>)
<p>Patient – adults who are diagnosed with adjustment disorder as defined by ICD and DSM</p> <p>Problem – adjustment disorder (i.e. a psychological response to stress involving marked distress and significant impairment in functioning)</p> <p>Population- adults</p>	Any psychological or pharmacological treatment which targets adjustment disorder		<p>Improvements in any of the following:</p> <ul style="list-style-type: none"> - mental health symptoms (e.g., PTSD, depression, anxiety, alcohol and drug abuse, self-harm) - psychological wellbeing (e.g., quality of life, disability, wellbeing shame, guilt, self-destructive behaviours, aggression)

Appendix 2

Example search strategy

The following is an example of the search strategy conducted in the EMBASE database:

Step	Search Terms	No of records
S1	pharmacotherap* 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	12678701
S2	Limit 1 to (human and English language and yr="2000-Current")	4708165
S3	Drug therapy/	427344
S4	Behaviour therapy/ or therapy/	1386918
S5	Limit 4 to (human and English language and yr="2000-Current")	300026
S6	"adjustment disorder".mp. or adjustment disorder	4049
S7	Limit 6 to (human and english language and yr="2000-Current")	2129
S8	2 or 3 or 5	5039955
S9	6 and 8	1334

Appendix 3

Quality and bias checklist

Chalmers Checklist for appraising the quality of studies of interventions⁵⁵

Completed		
Yes	No	
		1. Method of treatment assignment
		<ul style="list-style-type: none"> Correct, blinded randomisation method described OR randomised, double-blind method stated AND group similarity documented
		<ul style="list-style-type: none"> Blinding and randomisation stated but method not described OR suspect technique (eg allocation by drawing from an envelope)
		<ul style="list-style-type: none"> Randomisation claimed but not described and investigator not blinded
		<ul style="list-style-type: none"> Randomisation not mentioned
		2. Control of selection bias after treatment assignment
		<ul style="list-style-type: none"> Intention to treat analysis AND full follow-up
		<ul style="list-style-type: none"> Intention to treat analysis AND <25% loss to follow-up
		<ul style="list-style-type: none"> Analysis by treatment received only OR no mention of withdrawals
		<ul style="list-style-type: none"> Analysis by treatment received AND no mention of withdrawals OR more than 25% withdrawals/loss-to-follow-up/post-randomisation exclusions
		3. Blinding
		<ul style="list-style-type: none"> Blinding of outcome assessor AND patient and care giver (where relevant)
		<ul style="list-style-type: none"> Blinding of outcome assessor OR patient and care giver (where relevant)
		<ul style="list-style-type: none"> Blinding not done
		<ul style="list-style-type: none"> Blinding not applicable
		4. Outcome assessment (if blinding was not possible)
		<ul style="list-style-type: none"> All patients had standardised assessment
		<ul style="list-style-type: none"> No standardised assessment OR not mentioned

		5. Additional Notes
		<ul style="list-style-type: none">Any factors that may impact upon study quality or generalisability

Appendix 4

Evidence Profile

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
Behavioural-based								
Arends et al. (2014)	Clustered RCT with 3, 6 and 12 month follow-up	<p>Dutch workers who returned to work after sickness absence due to mental health disorders</p> <p>Intervention: Age: 41.3 Male: 27%</p> <p>Control: Age: 43.3 Male: 38%</p>	<p>Intervention: 73% Control: 50% (ICD-10)</p> <p>Stressor: Not reported</p>	Problem solving intervention (SHARP)	<p>Intervention:</p> <ol style="list-style-type: none"> 1. Create inventory of problems related to return to work 2. Develop solutions and an action plan 3. Evaluate action plan/implemented solutions <p>Control: Care as usual (Guidelines around management of mental health problems in workers)</p>	Occupational therapist delivered 30 minute consultations (2 – 5 sessions) over 3 months	<ul style="list-style-type: none"> - Hospital Anxiety and Depression Scale - Four-Dimensional Symptom Questionnaire - Return to work 	N = 153

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
Both groups improved on mental health functioning at all follow-up time points, with no significant differences between groups in level of improvement. Full return to work occurred 65 days earlier and partial return to work occurred 12 days earlier for the intervention group compared to controls.								
Hosaka et al. (2000)	Single group pre-post with 6 month follow-up	Japanese cancer patients Age: 51.3 (8.8) Male: Unknown	26% (DSM-IV) Stressor: Not reported	Psychiatric intervention	1. Cancer psychoeducation 2. Problem-solving 3. Psychological support 4. Relaxation training 5. Guided imagery (cancer-focused)	Five weekly 90 minute group based sessions	- Profile of Mood States (POMS)	N = 47
There were no significant changes in individuals with adjustment disorder from pre to post treatment or at follow-up.								
Hosaka et al. (2001)	Single group pre-post with 6 month follow-up	Japanese cancer patients Age: 50.2 (6.0) Male: Unknown	26% (DSM-IV) Stressor: Not reported	Psychiatric intervention	1. Cancer psychoeducation 2. Problem-solving 3. Psychological support 4. Relaxation training 5. Guided imagery (cancer-focused)	Five weekly 90 minute group based sessions, followed by 3 further monthly free talk group session	- Profile of Mood States (POMS)	N = 34

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
This study reported contradictory findings.								
Relaxation-based								
Bos et al. (2014)	Pre-post	Dutch psychiatric outpatients Age: 45.5 (10.5) Male 31%	10% adjustment disorder (DSM-IV) Stressor: Not reported	Mindfulness training (MBSR + MBCT)	1. Formal mindfulness exercises (Body scan, sitting meditation, yoga) 2. Group discussion of above experiences 3. Psychoeducation 4. Homework	Group therapy for 8 weekly session of 2.5 hours each	- Short Symptom List (SSL) - World Health Organization Quality of Life (WHOQOL-Bref)	N = 214
The adjustment disorder sub-analyses revealed a significant improvement to SSL and WHOQOL-Bref scores, with moderate to large effect sizes of $d = 0.59$ and 0.87 , respectively.								
Hsiao et al. (2014)	RCT with 5, 8, and 14 month follow-up	Taiwanese psychiatric outpatients Intervention: Age: 44.5	100% adjustment disorder with depression (DSM-IV)	Holistic/Eastern therapy (Body-Mind-Spirit)	Intervention: Treatment as usual (TAU) + Body-Mind-Spirit: 1. Cognitive restructuring	Eight weekly group-based sessions	- Beck Depression Inventory (BDI) - State Trait Anxiety Inventory (STAI)	N = 71

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Male 32% Control: Age: 44.0 Male 27%	Stressor: Not reported		2. Meditation, relaxation and guided imagery 3. Emotion work 4. Physical exercises 5. Spiritual work Control: TAU (medication and psychoeducational advice)		- Suicidal ideation	
Both groups showed significant reductions in the BDI and STAI, with no significant differences between groups. Suicidal ideation decreased significantly for both groups and there was a greater reduction in suicidal ideation in the intervention group.								
Cognitive behavioural therapy based								
Bachem & Maercker (2016)	RCT with 3 month follow-up (for intervention only)	Burglary victims Intervention: Age: 50.4 (15.7) Male 21%	100% adjustment disorder or adjustment disorder symptomatology (ICD-11)	Self-help bibliotherapy	Intervention: Manualised CBT-based self-help including psychoeducation, learning coping strategies, activation	Self-help manual self-administered over 1 month	- Adjustment disorder New Module – 20 (ADNM-20) - Post-traumatic stress symptoms	N = 103

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Control: Age: 41.9 (15.9) Male 0%	Stressor: Burglary		of self and social network, and relaxation Control: Wait-list		- Depression anxiety and stress scale (DASS-21)	
There were significant reductions in both groups in ADN-20 preoccupation scores from pre to post treatment; reductions were significantly greater for the intervention group ($d = .90$). For PTSD symptoms, both groups reduced significantly from pre to post treatment, with significantly greater reductions in the intervention group ($d = .66$). DASS-21 stress and depression scores showed no significant reductions for either group, but the anxiety score showed a significant reduction between pre and post treatment in both intervention and control groups ($d = .71$ and $d = .36$, respectively). At the end of treatment, the number of participants still meeting criteria for adjustment disorder was half as big in the intervention group compared to control.s								
Carta et al.,2012	Clustered RCT	Rural Italian patients attending GPs with no access to psychological care Intervention: Age: 42.2 (19.1)	Intervention: 59% Control: 53% (DSM-IV-TR) Stressor: Not defined	Psychological therapy	Intervention: Manualised cognitive behavioural counselling Control: TAU (not described)	Intervention: TAU delivered by GPs, intervention delivered by psychologists fortnightly over 6 months Control: TAU delivered by GPs	- Beck Depression Inventory (BDI) - World Health Organization Quality of Life (WHOQOL-Bref) - Clinical Global Impression (CGI)	N = 64

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Male 35% Control: Age: 42.8 (18.5) Male 33%						
At the halfway point of treatment, BDI scores had reduced significantly for both intervention and controls. However, at the end of treatment, intervention had significantly lower BDI scores compared to controls. Quality of life also improved significantly in the intervention group compared to controls from the start of treatment to the end. CGI improved significantly in the intervention group but not in controls.								
Hirsh et al. (2009)	Case study	Male with an Implantable Cardioverter Defibrillator Age: mid 50's	100% adjustment disorder with anxiety (DSM-IV) Stressor: Health	Psychological therapy	Cognitive behaviour stress management adapted from manual, including psychoeducation, stress management/relaxation and family therapy.	Five session inpatient and five session outpatient over six weeks, with further follow-up sessions at one and three months	- State Trait Anxiety Inventory (STAI) - Beck Depression Inventory (BDI)	N = 1
Scores on STAI-State reduced from 72 at baseline to 24 at post treatment and STAI-Trait reduced from 62 at baseline to 22 at post treatment. BDI scores reducing from 18 at pre-treatment to 1 at follow-up (14 weeks).								

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
Lagerveld et al. (2012)	Clustered controlled trial with 12 month follow-up	Dutch employees on sick leave due to psychological problems	67% adjustment disorder (DSM-IV) Stressor: Not reported	Psychological therapy	Intervention: Work-focused CBT, which was CBT with a work context, plus an additional module focusing on returning to work Control: Manualised CBT	Intervention: Individual therapist delivered 12 sessions over 6 months Control: Individual therapist delivered 12 sessions over 6 months	- Symptom Checklist (SCL-90) - Depression anxiety and stress scale (DASS-21)	N = 208
While the intervention was more effective on return to work levels, it did not significantly differ from controls in the impact on mental health outcomes. Depression and anxiety levels significantly improved in both groups but there was no significant impact of either intervention or control on stress levels.								
Powell & McCone (2004)	Case study	US military cadet Age: 20 Male	100% adjustment disorder with anxiety (DSM-IV-TR) Stressor: Terrorism	Psychological therapy	CBT with the following components: Cognitive impulse control Challenging irrational beliefs Stress management skills Relaxation training	13 sessions over 12 months	- Outcome Questionnaire 45 (OQ-45)	N = 1

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
The individual participant showed a reduction from 66 on the OQ-45 at the first session to 11 at 12 month follow-up.								
van der Heiden & Melchior (2012)	Pre post with three month follow-up	Dutch GP patients referred to an outpatient treatment centre Age: 43.6 Male 32%	100% adjustment disorder: 50% with depressed mood; 30% with anxiety; 20% other (DSM-IV) Stressor: Not reported	Psychological therapy	Manualised CBT consisting of psychoeducation, self-monitoring of stress, improving lifestyle and coping strategies, modifying negative thoughts	Individual weekly 45 minute sessions	- Symptom Checklist (SCL-90)	N = 10
There were significant reductions in symptomatology as measured by the SCL-90 between pre and post treatment ($d = 1.25$) and from pre-treatment to follow-up ($d = 1.37$).								
van der Klink et al. (2003)	Cluster RCT with 12 month follow-up	Dutch employees from a private company who were on 2 weeks sick leave for an	100% adjustment disorder (DSM-IV) Stressor: Not reported	Psychological therapy	Intervention: Graded activity approach resembling stress inoculation training (a form of CBT)	Four to five consultations over six weeks, 90 minutes in length, delivered by occupational therapists and a	- Symptom Checklist (SCL-90) - Four-Dimensional Symptom	N = 192

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		adjustment disorder			Control: Usual care (empathic counselling, stress and lifestyle advice, and work-related issue discussion)	relapse prevention session	Questionnaire (4DSQ)	
At 3 and 12 months, both groups improved significantly on outcomes with no significant differences between groups.								
Psychodynamic psychotherapy-related								
Ben-Itzhak et al. (2012)	RCT	Israeli outpatients Intervention: Age: 46.7 (10.9) Male: 23% Control: Age: 40.6 (10.2) Male: 19%	100% adjustment disorder: 85% mixed depression and anxiety (DSM-IV) Stressor: interpersonal, occupational, economic, health	Psychological therapy	Intervention: Manualised brief psychodynamic psychotherapy Control: Intermediate psychotherapy	Intervention: Twelve sessions over 12 weeks Control: Approximately 48 sessions for 1 year	- Symptom Checklist (SCL-90)	N = 91

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
Both groups improved significantly in SCL-90 scores from pre-treatment to 3 months with no significant differences between groups. The additional 9 months of therapy in the control group did not add any significant improvement to participants, and at post-treatment for the controls (12 months) compared to the same time point of 9 month follow-up for the intervention group, scores did not significantly differ.								
Hofer et al. (2010)	Pre-post	Outpatients with an acquired brain injury (ABI) Age: 51 (36 – 61) Male 55%	100% adjustment disorder: depressed mood (80%); anxiety (20%) (DSM-IV-TR) Stressor: Health	Psychological therapy	1. Resource activation 2. Problem activation 3. Clarification of meaning 4. Problem mastery	Unlimited psychotherapy sessions which lead to on average 23 sessions over 12 to 18 months	- Beck Depression Inventory (BDI)	N = 11
At the end of treatment, none of the patients retained their adjustment disorder diagnoses. From pre to post therapy, BDI scores reduced significantly ($d = 1.3$).								
Kramer et al. (2010)	Pre-post	French university students Age: 24 (3.86) Male 18%	100% with adjustment disorder with depressed mood (DSM-IV)	Psychological therapy	Manualised short-term psychodynamic psychotherapy	Treatment lasting up to one year of weekly sessions	- Symptom Checklist (SCL-90)	N = 32

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
			Stressor: Not described					
<p>SCL-90 scores decreased significantly at the end of treatment ($d = 1.24$).</p> <p>A second study (Kramer et al., 2015) published from this data set investigated changes in depression scores and found a significant reduction from pre to post treatment ($d = 0.69$)</p>								
Pharmacotherapy – Depressive symptoms								
Amodeo et al. (2011)	RCT	<p>Italian cancer patients with depressive disorders</p> <p>Intervention: Age: 59.9 (11.7) Male: 27%</p> <p>Control: Age: 61.8 (10.5)</p>	<p>50% with adjustment disorder with depressed mood (DSM-IV-TR)</p> <p>Stressor: Health</p>	Pharmacotherapy	<p>Intervention: Slow-up titration of paroxetine (SSRI)</p> <p>Control: Standard-up titration of paroxetine (SSRI)</p>	<p>Intervention: 2.5 m/g day increasing by 2.5m/g each third day until 10m/g was reached day 8. Day 9 dose was increased to 15m/g day and on day 11 the full 20m/g day dose was reached</p> <p>Control: 10m/g day and increased to 20m/g day on day 8</p>	<ul style="list-style-type: none"> - Hospital Anxiety and Depression Scale (HADS) - Montgomery Asberg Depression Rating Scale (MADRS) - Hamilton Anxiety Rating Scale (HAM-A) 	N = 30

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Male: 33%				Both treatments lasted 8 weeks	<ul style="list-style-type: none"> - Clinical Global Impression (CGI) - Quality of life (EORTC QLQ-C30) 	
Both groups reduced significantly in their MADRS, HADS, HAM-A scores, and CGI scores in addition to improving their quality of life scores from pre-treatment to end of treatment. Those who received slow-up titration paroxetine had significantly lower MADRS scores at mid-treatment (4 weeks) and significant lower HADS scores at mid treatment (4 weeks) and end of treatment (8 weeks). There was no significant differences between groups on HAM-A scores or quality of life total scores at the end of treatment. There was no significant differences in CGI improvement between groups. Participants in the intervention arm (slow-up titration paroxetine) reported less side effects than the controls.								
Hameed et al. (2005)	Retrospective cohort followed over 4 months	Primary care patients with depressive disorders receiving antidepressants Age: Unknown Male: 20%	34% adjustment disorder with depressed mood (DSM-IV) Stressor: Not reported	Pharmacotherapy	SSRIs (24% of patients received concurrent psychotherapy)	Naturalistic delivery of antidepressant medication as determined by the depression management team	<ul style="list-style-type: none"> - Number of DSM-IV symptoms - Patient Health Questionnaire (PHQ-9) 	N = 96

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
Response was defined as when any follow-up symptom value was equal to 0. Patients who continued to have 0 symptoms throughout the follow-up period were defined as a sustained response. Overall response to treatment for adjustment disorder participants was 33-100% and sustained response over 4 months was achieved for 33-100% of patients. No specific SSRI was found to be more effective than any other.								
Özten et al. (2015)	Case study	Psychiatric patient Age: 34 years Female	100% adjustment disorder with mixed anxiety-depressive mood Stressor: Interpersonal	Pharmacotherapy	Sertraline (SSRI) started and discontinued due to side effects; Fluoxetine (SSRI) started and maintained + Couples psychotherapy	Sertraline (25 mg/day – 50 mg/day) for a week, then fluoxetine (20mg/day) for 7 weeks	- Hamilton Depression Rating Scale (HDRS) - Hamilton Anxiety Rating Scale (HAS) - Beck Depression Inventory (BDI)	N = 1
Pre-treatment scores were 18 (HDRS); 12 (HAS); and 24 (BDI), after 2 months of treatment scores had dropped to 11, 6, and 9.								
Pharmacotherapy – Anxious symptoms								
Nguyen et al. (2006)	RCT with 1 week follow-up	French outpatients seeing GPs	100% adjustment disorder with	Pharmacotherapy	Intervention: Etifoxine (non-	Intervention: 150 mg/day for 28 days	- Hamilton Anxiety	N = 191

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
	after discontinuation	Intervention: Age: 44.0 (13.4) Male: 38% Control: Age: 42.0 (13.1) Male: 30%	anxiety (DSM-IV) Stressor: 41% family-related; 30% work related; 9% health; 20% other		benzodiazepine anxiolytic) Control: Lorazepam (benzodiazepine)	Control: 2 mg/day for 28 days	Rating Scale (HAM-A) - Clinical Global Impression Scale (CGI) - Sheehan Disability Scale (SDS) - Social Adjustment Scale Self-Report (SAS-SR)	
Etifoxine was found non-inferior (i.e. at least as effective) to the control, but a significantly higher percentage of the treatment group were classified as responders (72%) at the end of treatment compared to controls (56%). Both groups improved in CGI ratings, but etifoxine had a higher proportion of markedly improved individuals. SAS-SR and SDS scores improved comparably between groups with no significant differences.								
Stein (2015)	RCT	South African outpatients Intervention:	100% adjustment disorder with anxiety (DSM-IV)	Pharmacotherapy	Intervention: Etifoxine (non-benzodiazepine anxiolytic)	Intervention: Three capsules per day for 28 days (150mg/day) Control: Three	- Hamilton Anxiety Rating Scale (HAM-A)	N = 201

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Age: 40.0 (11.8) Male: 32% Control: Age: 38.9 (12.8) Male: 30%	Stressor: 39% interpersonal, (38%) work/school; economic (12%); other (11%)		Control: Alprazolam (benzodiazepine)	capsules per day for 28 days (1.5mg/day)	- Self-report for the Assessment of Adjustment Disorders	
Alprazolam improved outcomes on HAM-A significantly more than etifoxine at day 7 but at day 35 (one week after discontinuation), etifoxine demonstrated non-inferiority compared with alprazolam on HAM-A measures. There were no significant differences at day 35 for other measures. There were more adverse events reported in the alprazolam group.								
Combined psychological and pharmacotherapy								
Ichitovkina et al. (2014)	Controlled cohort	Russian combatants recently returned from assignment Intervention: Age: 40.0 (1.4)	60% with adjustment disorder: 27% with depressed mood; 32% with mixed anxiety and depressed mood; 10%	Medical-psychological rehabilitation	Psychological: Art therapy, collective hypnosuggestion, rational therapy, family therapy Pharmacotherapy: Primarily SSRIs and benzodiazepines	Psychiatrist delivered 14 days of inpatient treatment followed by twice-weekly outpatient treatment for five weeks, consisting of	- Adaptivity multi-factorial personality questionnaire (MPQ)	N = 199

Authors & year	Design	Sample	% of sample with adjustment disorder (Diagnostic method), stressor	Intervention type (Name)	Key intervention components	Intervention delivery method, frequency, duration, (delivered to)	Outcomes (Measure(s))	Participants
		Male: Unknown Control: Age: 31.3 (1.5) Male: Unknown	conduct (ICD-10) Stressor: Not defined			individual, group and family therapy		
Symptoms of detachment, intrusive thoughts, feelings of emptiness, fear and anxiety, and irritability as measured by the MPQ were significantly reduced after treatment in the intervention group. It is unknown how these changes compared to controls.								

Appendix 5

<i>Type of Intervention</i>	<i>Included Studies</i>
<i>Supported</i>	
<i>Promising</i>	
<i>Unknown</i>	
<i>Behavioural-based</i>	Arends et al., 2010 Hosaka et al., 2001 Hosaka et al., 2000
<i>CBT-based</i>	Bachem & Maercker, 2016 Carta et al., 2012 Hirsh et al., 2009 Lagerveld et al., 2012 Powell et al., 2004 van der Heiden et al., 2012 van der Klink et al., 2003
<i>Psychodynamic psychotherapy - related</i>	Ben-Itzhak et al., 2012 Hofer et al., 2010 Kramer et al., 2010
<i>Relaxation-based</i>	Bos et al., 2014 Hsiao et al., 2014
<i>Pharmacotherapy - Benzodiazepines</i>	Stein et al., 2015 Nguyen et al., 2006

<i>Pharmacotherapy - SSRIs</i>	Amodeo et al., 2012 Hameed et al., 2005 Ozten et al., 2015
<i>Combined psychological and pharmacotherapy</i>	Ichitovkina et al., 2014

Appendix 6

Criteria	DSM-5 criteria ⁵⁶	ICD-11 proposal ²⁶
A	The development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s)	A maladaptive reaction to a stressful event, to ongoing psychosocial difficulties or to a combination of stressful life situations that usually emerges within a month of the stressor and tends to resolve in 6 months unless the stressor persists for a longer duration. The reaction to the stressor is characterized by symptoms of preoccupation like excessive worry, recurrent and distressing thoughts about the stressor or constant rumination about its implications. There is failure to adapt, i.e., the symptoms interfere with everyday functioning, like difficulties concentrating or sleep disturbance resulting in performance problems. The symptoms can also be associated with loss of interest in work, social life, caring for others, leisure activities resulting in impairment in social or occupational functioning (restriction of social network, conflicts in family, absenteeism and so on). If the definitional requirements are met for another disorder, that disorder should be diagnosed instead of adjustment disorder.
B	These symptoms or behaviours are clinically significant, as evidenced by one or both of the following: <ol style="list-style-type: none"> 1. Marked distress that is out of proportion to the severity or intensity of the stressor, taking into account the external context and the cultural factors that might influence symptoms severity and presentation 2. Significant impairment in social, occupational, or other important areas of functioning 	
C	The stress-related disturbance does not meet the criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder	
D	The symptoms do not represent normal bereavement.	
E	Once the stressor or its consequences have terminated, the symptoms do not persist for more than an additional 6 months.	

References

1. Fielden JS. Review: management of adjustment disorder in the deployed setting. *Military medicine*. 2012;177(9):1022-1027.
2. Strain JJ, Friedman MJ. Considering adjustment disorders as stress response syndromes for DSM-5. *Depression and anxiety*. 2011;28(9):818-823.
3. Casey P, Doherty A. Adjustment disorder: diagnostic and treatment issues. *Psychiatric Times*. 2012;29(1):43-43.
4. Maercker A, Einsle F, Kollner V. Adjustment disorders as stress response syndromes: a new diagnostic concept and its exploration in a medical sample. *Psychopathology*. 2007;40(3):135-146.
5. Einsle F, Köllner V, Dannemann S, Maercker A. Development and validation of a self-report for the assessment of adjustment disorders. *Psychology, health & medicine*. 2010;15(5):584-595.
6. Carta MG, Balestrieri M, Murru A, Hardoy MC. Adjustment disorder: Epidemiology, diagnosis and treatment. *Clinical Practice and Epidemiology in Mental Health*. 26 Jun 2009;5 (no pagination)(15).
7. Glaesmer H, Romppel M, Brahler E, Hinz A, Maercker A. Adjustment disorder as proposed for ICD-11: Dimensionality and symptom differentiation. *Psychiatry Research*. Oct 2015;229(3):940-948.
8. Evans S, Reed G, Roberts M. The International Union of Psychological Science and WHO global survey of psychologists' attitudes towards the classification of mental disorders. Paper presented at: International Congress of Psychology 2012.
9. Huyse FJ, Herzog T, Lobo A, et al. Consultation-Liaison psychiatric service delivery: results from a European study. *General Hospital Psychiatry*. 2001;23(3):124-132.
10. Casey PR, Dillon S, Tyrer PJ. The diagnostic status of patients with conspicuous psychiatric morbidity in primary care. *Psychol Med*. 1984;14(3):673-681.
11. Strain JJ, Smith GC, Hammer JS, et al. Adjustment disorder: a multisite study of its utilization and interventions in the consultation-liaison psychiatry setting. *General Hospital Psychiatry*. 1998;20(3):139-149.

12. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *The lancet oncology*. 2011;12(2):160-174.
13. O'Donnell ML, Alkemade NR, Creamer MC, et al. A longitudinal study of adjustment disorder after trauma exposure. *American Journal of Psychiatry*. In press.
14. Stecker T, Fortney J, Owen R, McGovern MP, Williams S. Co-occurring medical, psychiatric, and alcohol-related disorders among veterans returning from Iraq and Afghanistan. *Psychosomatics*. 2010;51(6):503-507.
15. Rundell JR. Demographics of and diagnoses in Operation Enduring Freedom and Operation Iraqi Freedom personnel who were psychiatrically evacuated from the theater of operations. *General Hospital Psychiatry*. 2006;28(4):352-356.
16. Kryzhanovskaya L, Canterbury R. Suicidal behavior in patients with adjustment disorders. *Crisis: The Journal of Crisis Intervention and Suicide Prevention*. 2001;22(3):125.
17. Gradus JL, Qin P, Lincoln AK, Miller M, Lawler E, Lash TL. The association between adjustment disorder diagnosed at psychiatric treatment facilities and completed suicide. *Clin Epidemiol*. 2010;2:23-28.
18. Casey P, Bailey S. Adjustment disorders: the state of the art. *World Psychiatry*. 2011;10(1):11-18.
19. Lee F-Y, Shu B-C. The premorbid personality in military students with adjustment disorder. *Military Psychology*. 2006;18(1):77.
20. Fei-Yin L, Bih-Ching S. The relationship between life adjustment and parental bonding in military personnel with adjustment disorder in Taiwan. *Military medicine*. 2002;167(8):678-682.
21. Chen P-F, Chen C-S, Chen C-C, Lung F-W. Alexithymia as a Screening Index for Male Conscripts with Adjustment Disorder. *Psychiatric Quarterly*. 2011;82(2):139-150.
22. Na K-S, Oh S-J, Jung H-Y, et al. Alexithymia and low cooperativeness are associated with suicide attempts in male military personnel with adjustment disorder: A case–control study. *Psychiatry Research*. 2013;205(3):220-226.

23. Myung W, Na K-S, Ham B-J, Oh S-J, Ahn H-W, Jung H-Y. Decreased medial frontal gyrus in patients with adjustment disorder. *Journal of affective disorders*. 2016;191:36-40.
24. Royall DR, Lauterbach EC, Cummings JL, et al. Executive control function: a review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *The Journal of neuropsychiatry and clinical neurosciences*. 2002;14(4):377-405.
25. Strain JJ, Diefenbacher A. The adjustment disorders: the conundrums of the diagnoses. *Comprehensive psychiatry*. 2008;49(2):121-130.
26. Maercker A, Brewin CR, Bryant RA, et al. Diagnosis and classification of disorders specifically associated with stress: proposals for ICD-11. *World Psychiatry*. 2013;12(3):198-206.
27. Arends I, Bruinvels DJ, Rebergen DS, et al. Interventions to facilitate return to work in adults with adjustment disorders. *Cochrane Database Syst Rev*. 2012;12(12):12.
28. Van Der Klink JJ, Van Dijk FJ. Dutch practice guidelines for managing adjustment disorders in occupational and primary health care. *Scandinavian journal of work, environment & health*. 2003;478-487.
29. Varker T, Forbes D, Dell L, et al. Rapid evidence assessment: increasing the transparency of an emerging methodology. *Journal of evaluation in clinical practice*. 2015;21(6):1199-1204.
30. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Medical Research Methodology*. 2009;9(34).
31. Arends I, van der Klink JJ, Bultmann U. Prevention of recurrent sickness absence among employees with common mental disorders: design of a cluster-randomised controlled trial with cost-benefit and effectiveness evaluation. *BMC public health*. 2010;10:132.
32. Hosaka T, Sugiyama Y, Tokuda Y, Okuyama T. Persistent effects of a structured psychiatric intervention on breast cancer patients' emotions. *Psychiatry & Clinical Neurosciences*. 2000;54(5):559-563.
33. Hosaka T, Sugiyama Y, Hirai K, Okuyama T, Sugawara Y, Nakamura Y. Effects of a modified group intervention with early-stage breast cancer patients. *General Hospital Psychiatry*. 2001;23(3):145-151.

34. Bachem R, Maercker A. Self-help interventions for adjustment disorder problems: a randomized waiting-list controlled study in a sample of burglary victims. *Cognitive behaviour therapy*. 2016;45(5):397-413.
35. Carta M, Petretto D, Adamo S, et al. Counseling in primary care improves depression and quality of life. *Clinical Practice and Epidemiology in Mental Health*. Nov 2012;8:152-157.
36. Van Der Klink JJL, Blonk RWB, Schene AH, Van Dijk FJH. Reducing long term sickness absence by an activating intervention in adjustment disorders: A cluster randomised controlled design. *Occupational and Environmental Medicine*. 01 Jun 2003;60(6):429-437.
37. Lagerveld SE, Blonk RW, Brenninkmeijer V, Wijngaards-de Meij L, Schaufeli WB. Work-focused treatment of common mental disorders and return to work: A comparative outcome study. *Journal of Occupational Health Psychology*. Apr 2012;17(2):220-234.
38. van der Heiden C, Melchior K. Cognitive-behavioral therapy for adjustment disorder: A preliminary study. *the Behavior Therapist*. Mar 2012;35(3):57-60.
39. Powell S, McCone D. Treatment of adjustment disorder with anxiety: A September 11, 2001, case study with a 1-year follow-up. *Cognitive and Behavioral Practice*. 2004;11(3):331-336.
40. Hirsh AT, Sears SF, Jr., Conti JB. Cognitive and behavioral treatments for anxiety and depression in a patient with an implantable cardioverter defibrillator (ICD): a case report and clinical discussion. *Journal of Clinical Psychology in Medical Settings*. 2009;16(3):270-279.
41. Kramer U, Despland JN, Michel L, Drapeau M, De Roten Y. Change in defense mechanisms and coping over the course of short-term dynamic psychotherapy for adjustment disorder. *Journal of Clinical Psychology*. December 2010;66(12):1232-1241.
42. Ben-Itzhak S, Bluvstein I, Schreiber S, et al. The effectiveness of brief versus intermediate duration psychodynamic psychotherapy in the treatment of adjustment disorder. *Journal of Contemporary Psychotherapy*. Dec 2012;42(4):249-256.
43. Hofer H, Holtforth MG, Frischknecht E, Znoj HJ. Fostering adjustment to acquired brain injury by psychotherapeutic interventions: A preliminary study. *Applied Neuropsychology*. January 2010;17(1):18-26.

44. Kramer U, Pascual-Leone A, Despland J-N, de Roten Y. One minute of grief: emotional processing in short-term dynamic psychotherapy for adjustment disorder. *Journal of Consulting & Clinical Psychology*. 2015;83(1):187-198.
45. Hsiao F-H, Lai Y-M, Chen Y-T, et al. Efficacy of psychotherapy on diurnal cortisol patterns and suicidal ideation in adjustment disorder with depressed mood. *General Hospital Psychiatry*. 2014;36(2):214-219.
46. Bos EH, Merea R, van den Brink E, Sanderman R, Bartels-Velthuis AA. Mindfulness training in a heterogeneous psychiatric sample: outcome evaluation and comparison of different diagnostic groups. *Journal of Clinical Psychology*. 2014;70(1):60-71.
47. Nguyen N, Fakra E, Pradel V, et al. Efficacy of etifoxine compared to Lorazepam monotherapy in the treatment of patients with adjustment disorders with anxiety: A double-blind controlled study in general practice. *Human Psychopharmacology: Clinical and Experimental*. Apr 2006;21(3):139-149.
48. Stein DJ. Etifoxine versus alprazolam for the treatment of adjustment disorder with anxiety: a randomized controlled trial. *Advances in Therapy*. 2015;32(1):57-68.
49. Amodeo L, Castelli L, Leombruni P, Cipriani D, Biancofiore A, Torta R. Slow versus standard up-titration of paroxetine for the treatment of depression in cancer patients: A pilot study. *Supportive Care in Cancer*. February 2012;20(2):375-384.
50. Hameed U, Schwartz TL, Malhotra K, West RL, Bertone F. Antidepressant treatment in the primary care office: outcomes for adjustment disorder versus major depression. *Annals of Clinical Psychiatry*. 2005;17(2):77-81.
51. Özten E, Hizli Sayar G, Göğçeğöz Gül I, Ceylan ME. Sertraline induced galactorrhea. *Noropsikiyatri Arsivi*. 2015;52(2):202-203.
52. Ichitovkina EG, Zlokazova MV, Solov'ev AG. Efficacy of medical-psychological rehabilitation of combatants. *Neuroscience and Behavioral Physiology*. 2014;44(8):933-938.
53. NICE. *Depression in adults: recognition and management*. 2009.
54. Gellatly J, Bower P, Hennessy S, Richards D, Gilbody S, Lovell K. What makes self-help interventions effective in the management of depressive symptoms? Meta-analysis and meta-regression. *Psychological medicine*. 2007;37(09):1217-1228.

- 55. NHRMC. How to review the evidence: systematic identification and review of the scientific literature. Canberra: Biotext; 1999.
- 56. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-5®)*. American Psychiatric Pub; 2013.