TECHNICAL COMMENTARY

Anxiety disorders

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Introduction

Anxiety disorders are a group of mental disorders characterised by excessive fear or worrying. It is important to recognise comorbid anxiety as it may influence treatment strategies and outcomes.

Anxiety disorders include generalised anxiety disorder, which is characterised by continuous and excessive worrying for six months or more. Specific phobias are characterised by anxiety provoked by a feared object/situation, resulting in avoidance. Social phobia is anxiety provoked by social or performance situations. Agoraphobia is anxiety about situations where escape may be difficult or help might not be available. Panic disorder is characterised by a panic attack, which is a distinct episode where a person experiences sudden apprehension and fearfulness, where they may present with shortness of breath, palpitations, chest pain or choking.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2010 that report results separately for people with a diagnosis of bipolar or related disorders. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Hand searching reference lists of identified reviews was also conducted. When multiple copies of review topics were found, only the most recent and/or comprehensive review was included. Reviews with pooled data were prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews with less than 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven systematic reviews that met our inclusion criteria[3-9].

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Anxiety disorders

- Moderate quality evidence suggests the lifetime prevalence of anxiety disorders in people with bipolar disorder is around 45%, and the current prevalence in people in the euthymic phase is around 35%. These rates are significantly higher than in people without bipolar disorder. The most common anxiety disorders were generalised, social anxiety, specific phobias, and panic disorders.
- Moderate quality evidence suggests the lifetime prevalence of anxiety disorders in children or adolescents with bipolar disorder is also around 45%. The prevalence of generalised anxiety disorder is around 27%, separation anxiety disorder is around 26%, social phobia is around 20%, and panic disorder is around 13%. Children under 12 years of age showed more generalised anxiety and separation anxiety disorders than adolescents aged 13-18 years, while adolescents showed more panic disorder and social phobia than children.
- Moderate quality evidence suggests an early age of onset of bipolar disorder is associated with an increased risk of anxiety disorders.
- Moderate to low quality evidence suggests cognitive behavioural therapy is effective for improving anxiety symptoms in people with bipolar disorder.

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Frias A, Palma C, Farriols N

Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment

Journal of Affective Disorders 2015; 174: 378-89

View review abstract online

Comparison	**Lifetime prevalence of anxiety disorders in children and youth with bipolar disorder (4-18 years).**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, inconsistent, imprecise, direct) suggests the lifetime prevalence of anxiety disorders in children or youth with bipolar disorder is around 54%.**
Anxiety disorders	
Any anxiety disorder: 7 studies, N not reported, prevalence = 54%, range 41% to 80% Rates were higher in prospective studies than in cross-sectional studies, and most studies found higher rates of generalised anxiety disorder and/or separation anxiety disorder than other anxiety disorders.	
Consistency in results‡	Authors report the data are inconsistent.
Precision in results§	Appears imprecise
Directness of results‖	Direct

Joslyn C, Hawes DJ, Hunt C, Mitchell PB

Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review

Bipolar Disorders 2016; 18: 389-403

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Comparison	**Association between an early age of onset of bipolar disorder and comorbid anxiety disorders.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent and**

	imprecise, direct) suggests an early age of onset of bipolar disorder is associated with an increased risk of comorbid anxiety disorders.
Anxiety disorders	
Significant, small effect of increased risk of anxiety disorders in people with an early age of onset of bipolar disorder; 10 studies, N = 4,841, OR = 1.72, 95%CI 1.34 to 2.19, $p < 0.001$, $I^2 = 64\%$	
Consistency in results	Inconsistent
Precision in results	Imprecise
Directness of results	Direct

Pavlova B, Perlis RH, Alda M, Uher R

Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis

The Lancet Psychiatry 2015; 2: 710-7

View review abstract online

Comparison	**Lifetime prevalence of anxiety disorders in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests the lifetime prevalence of anxiety disorders in people with bipolar disorder is around 45%, which is significantly higher than in people without bipolar disorder. The most common anxiety disorders were; generalised, social phobia, and panic disorders.**
Anxiety disorders	
Prevalence: 40 studies, N = 14,914, 45%, 95%CI 40% to 51%, $I^2 = 98\%$ The most common lifetime anxiety disorders were generalised anxiety disorder (20%), social phobia (20%), and panic disorder (19%). *Significant, medium-sized increased risk of anxiety disorders in people with bipolar disorder than in people without bipolar disorder;*	

5 studies, N = 58,190, RR = 3.22, 95%CI 2.41 to 4.29, $p < 0.0001$, $I^2 = 98\%$ *No significant differences in anxiety disorders in people with bipolar I or bipolar II disorders;* 13 studies, N = 6,209, RR = 1.07, 95%CI 0.96 to 1.20, $p = 0.223$, $I^2 = 71\%$	
Consistency in results	Inconsistent
Precision in results	Imprecise for vs. control comparison, precise for bipolar I vs. II comparison.
Directness of results	Direct

Pavlova B, Perlis RH, Mantere O, Sellgren CM, Isometsa E, Mitchell PB, Alda M, Uher R

Prevalence of current anxiety disorders in people with bipolar disorder during euthymia: a meta-analysis

Psychological Medicine 2017; 47: 1107-15

View review abstract online

Comparison	**Prevalence of anxiety disorders in people with bipolar disorder during euthymia.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, imprecise, direct) suggests the current prevalence of anxiety disorders in people with bipolar disorder during euthymia is around 35%, which is significantly higher than in people without bipolar disorder. The most common anxiety disorders were; generalised, social anxiety, and specific phobia disorders.**
Anxiety disorders	
Current prevalence: 10 studies, N = 2,120, 34.7%, 95%CI 23.9% to 45.5%, $I^2 = 96\%$ The most common lifetime anxiety disorders were generalised anxiety disorder (11.6%), social anxiety disorder (9.7%), and specific phobia (9.7%). *Significant, medium to large increased risk of anxiety disorders in people with bipolar disorder during euthymia than in people without bipolar disorder;* 3 studies, N = 17,298, RR = 4.60, 95%CI 2.37 to 8.92, $p < 0.0001$, $I^2 = 94\%$	
Consistency in results	Inconsistent

Precision in results	Imprecise
Directness of results	Direct

Preti A, Vrublevska J, Veroniki AA, Huedo-Medina TB, Kyriazis O, Fountoulakis KN

Prevalence and treatment of panic disorder in bipolar disorder: systematic review and meta-analysis

Evidence-Based Mental Health 2018; 21: 53-60

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Comparison	**Prevalence of panic disorder in people with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, appears imprecise, direct) suggests the prevalence of panic disorder in people with bipolar disorder is around 13-17%, with rates similar to those found in people with schizophrenia or unipolar depression, and similar across bipolar disorder I and II.**

Panic disorder

Point prevalence: 15 studies, N = 3,391, 15.1%, 95%CI 7.9% to 23.9%, I^2 = 96%

Point prevalence without outliers: 14 studies, N = 3,295, 13.0%, 95%CI 7.0% to 20.3%, I^2 = 95%

Lifetime prevalence: 25 studies, N = 8,226, 16.8%, 95%CI 12.2% to 22.0%, I^2 = 96%

Lifetime prevalence without outliers: 24 studies, N = 8,157, 15.5%, 95%CI 11.6% to 19.9%, I^2 = 95%

There were no significant differences in rates of panic disorder between people with bipolar disorder I and bipolar disorder II. There were also no effects of age, gender or diagnostic methods.

Authors report the rates were similar to those found in people with schizophrenia or unipolar depression, but much higher than rates in the general population.

Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Stratford HJ, Cooper MJ, Di Simplicio M, Blackwell SE, Holmes EA

Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review

Clinical Psychology Review 2015; 35: 19-34

View review abstract online

Comparison	**Cognitive behavioural therapy (CBT) or psychoeducation for anxiety symptoms in people with bipolar disorder.**
Summary of evidence	**Moderate to low quality evidence (small samples, appears consistent, unable to assess precision, direct) suggests cognitive behavioural therapy is effective for improving anxiety symptoms in people with bipolar disorder.**

Anxiety symptoms

CBT resulted in reduced anxiety symptoms in the following studies;

1 RCT, N = 62 people with cyclothymia and mixed anxiety diagnoses (10 x 45min fortnightly group or individual CBT vs. clinical management).

1 RCT, N = 42 people with treatment resistant bipolar disorder and anxiety symptoms (20 x 1.5hr weekly group CBT vs. treatment as usual).

1 RCT, N = 41 people in a euthymia bipolar disorder phase with anxiety symptoms (14 x 2hr weekly group CBT for bipolar disorder vs. treatment as usual).

1 controlled study, N = 73 people in a euthymia bipolar disorder phase with anxiety symptoms (20 x 2hr weekly group CBT for bipolar disorder vs. treatment as usual).

1 pilot, N = 10 people in a euthymia bipolar disorder phase with anxiety symptoms (6 x 2h weekly group CBT).

1 pilot, N = 10 people in a euthymia phase of rapid-cycling bipolar disorder with mixed anxiety diagnoses (20 x 50min weekly CBT for bipolar disorder).

1 case series with mixed bipolar disorder diagnoses and generalised anxiety disorder or high levels of worry (12 x 1hr weekly sessions of CBT for generalised anxiety disorder).

1 case study with rapid cycling bipolar disorder and anxiety symptoms (1 weekly session per month for 12 months of CBT for rapid cycling bipolar disorder).

1 case study with cyclothymia and anxiety symptoms (19 weekly session of CBT for bipolar disorder).

Mindfulness-based cognitive therapy resulted in reduced anxiety symptoms in the following studies;

1 RCT, N = 95 people in a euthymia bipolar disorder phase with anxiety symptoms (8 x 2h weekly

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group mindfulness-based cognitive therapy vs. treatment as usual). 1 Pilot, N = 22 people in a euthymia bipolar disorder phase with anxiety symptoms (8 x 2h weekly group mindfulness-based cognitive therapy; small effect). *No significant differences between groups for psychoeducation;* 1 RCT, N = 407 people with newly diagnosed bipolar disorder and anxiety symptoms (8 x 30-40min weekly psychoeducation on bipolar disorder vs. weekly emails). 1 controlled study, N = 35 people with mixed bipolar disorder diagnoses and anxiety symptoms (10-13 x 1.5h weekly psychoeducation group therapy vs. treatment as usual).

Consistency in results	Appears consistent
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Yapici Eser H, Taskiran AS, Ertinmaz B, Mutluer T, Kilic O, Ozcan Morey A, Necef I, Yalcinay M, Ongur D

Anxiety Disorders Comorbidity in Pediatric Bipolar Disorder: A meta-analysis and meta-regression study

Acta Psychiatrica Scandinavica 2020; January 03

View review abstract online

Comparison	**Lifetime prevalence of anxiety disorders in children (<12 years) and youth (13-18 years) with bipolar disorder.**
Summary of evidence	**Moderate quality evidence (large sample size, inconsistent, imprecise, direct) suggests the lifetime prevalence of anxiety disorders in children or adolescents with bipolar disorder is around 45%. The prevalence of generalised anxiety disorder is around 27%, separation anxiety disorder around 26%, social phobia around 20%, obsessive-compulsive disorder around 17%, and panic disorder around 13%. Children under 12 years showed more generalised anxiety and separation anxiety disorders than adolescents 13-18 years, while adolescents showed more panic disorder, obsessive-compulsive disorder and social phobia.**
Anxiety disorders	

Anxiety disorders

All anxiety disorders: 22 studies, N = 2,233, prevalence = 44.7%, 95%CI 37% to 52.7%, I^2 = 91%

Generalised anxiety disorder: 21 studies, N = 2,349, prevalence = 27.4%, 95%CI 21.1% to 34.7%, I^2 = 91%

Separation anxiety disorder: 22 studies, N = 2,351, prevalence = 26.1%, 95%CI 19.9% to 33.5%, I^2 = 91%

Social phobia: 22 studies, N = 2,534, prevalence = 20.1%, 95%CI 15.4% to 25.9%, I^2 = 88%

Panic disorder: 23 studies, N = 2,933, prevalence = 12.7%, 95%CI 9.2% to 17.2%, I^2 = 87%

Subgroup analysis showed childhood-onset studies reported significantly more generalised anxiety and separation anxiety disorders than adolescent-onset studies, while adolescent-onset studies reported significantly more panic disorder and social phobia than childhood-onset studies.

Multiple meta-regression showed increased generalised anxiety and separation anxiety disorders with younger age of onset, male gender, and comorbidity of attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder.

Consistency in results	Inconsistent
Precision in results	Appears imprecise
Directness of results	Direct

Explanation of acronyms

CBT = Cognitive Behavioural Therapy, CI = confidence interval, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, OR = Odds Ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RR = risk ratio, vs. = versus

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Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[10];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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