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 (GAD), 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. A panic attack is a distinct period 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 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. As part of a wider search for all topics included in the library, reviews on comorbid anxiety disorders for schizophrenia were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. We prioritised reviews with pooled data 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 five systematic reviews that met our inclusion criteria[3-7].

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Anxiety disorders

- Moderate quality evidence suggests people with schizophrenia show an increased rate of anxiety disorders compared to the general population.
- The prevalence rate of any anxiety disorder in people with schizophrenia is around 38.3%, and the rate of any anxiety disorder in people at high clinical risk for psychosis is around 15%. Anxiety symptoms were reported in around 29% of people with first-episode psychosis.
- Panic disorder occurs in approximately 9.8% of people with schizophrenia, agoraphobia in ~5.4%, social phobia in ~14.9%, social anxiety disorder in ~21%, specific phobia in ~7.9%, and generalised anxiety disorder in ~10.9%.

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Achim A, Maziade M, Raymond E, Olivier D, Merette C, Roy M

How Prevalent Are Anxiety Disorders in Schizophrenia? A Meta-Analysis and Critical Review on a Significant Association

Schizophrenia Bulletin 2011; 37(4): 811–821

View review abstract online

Comparison	**Prevalence of anxiety disorders in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests the prevalence rate of any anxiety disorder in people with schizophrenia is around 38.3%. Panic disorder occurs in approximately 9.8%, agoraphobia in around 5.4%, social phobia in 14.9%, specific phobia in 7.9%, and generalised anxiety disorder in around 10.9% of people with schizophrenia.**

Prevalence

Any anxiety disorder

16 studies, N = 958, 38.3%, 95%CI 26.3 to 50.4%,X^2 = 146.23, $p < 0.001$

Panic disorders

23 studies, N = 1,393, 9.8%, 95%CI 4.3% to 15.4%, X^2 = 162.79, $p < 0.001$

Prevalence rates were higher in samples with a schizophrenia diagnosis vs. a schizophrenia spectrum diagnosis (16.3% vs. 7.3%, $p < 0.001$), for outpatients vs. inpatients (11.9% vs. 6.3%, $p = 0.007$), in older aged samples ($r = 0.45$, $p = 0.045$), and in non-first-episode vs. first-episode samples (11.8% vs. 3.2%, $p < 0.001$). No significant differences were reported for sampling methods and gender.

Agoraphobia

12 studies, N = 862, 5.4%, 95%CI 0.2% to 10.6%, X^2 = 83.52, $p < 0.001$

Agoraphobia prevalence rates were higher in studies with systematic sampling methods (22.2% vs. 4.3%, $p < 0.001$), in samples with a schizophrenia diagnosis vs. a schizophrenia spectrum diagnosis (7.8% vs. 3.8%, $p = 0.02$), and in non-first-episode vs. first-episode samples (6.0% vs. 0%, $p = 0.038$). No significant differences were reported for outpatients vs. inpatients, gender and age.

Social phobia

16 studies, N = 1,259, 14.9%, 95%CI 8.1% to 21.8%, X^2 = 127.37, $p < 0.001$

Social phobia prevalence rates were higher in studies with systematic sampling methods (38.6% vs. 13.9%, $p < 0.001$), and for outpatients vs. inpatients (22.8% vs. 8.7%, $p < 0.001$). No significant differences were reported for diagnosis, gender, non-first-episode vs. first-episode samples, or for age. *Specific phobia* 11 studies, N = 925, 7.9%, 95%CI 1.9% to 13.8%, $X^2 = 80.78$, $p < 0.001$ Simple phobia prevalence rates were higher in studies with systematic sampling methods (30.4% vs. 6.5%, $p < 0.001$), and for inpatients vs. outpatients (10.5% vs. 5.8%, $p = 0.04$). No significant differences were reported for diagnosis, gender, age, or non-first-episode vs. first-episode samples. *Generalised anxiety disorders* 14 studies, N = 939, 10.9%, 95%CI 2.9% to 18.8%, $X^2 = 142.52$, $p < 0.001$ GAD prevalence rates were higher in studies with systematic sampling methods (26.6% vs. 9.9%, $p < 0.001$), in samples with a schizophrenia diagnosis vs. a schizophrenia spectrum diagnosis (16.7% vs. 7.9%, $p < 0.001$), and in non-first-episode vs. first-episode samples (11.6% vs. 0%, $p = 0.01$). No significant differences were reported for outpatients vs. inpatients, gender and age. Review authors note that rates for panic disorder and social phobia are particularly high in people with schizophrenia when compared to the general population rates.

Consistency in results‡	Inconsistent. Authors state that not all heterogeneity was explained by the moderators reported above.
Precision in results§	Appears imprecise.
Directness of results‖	Direct

Braga RJ, Petrides G, Figueira I

Anxiety disorders in schizophrenia

Comprehensive Psychiatry 2004; 45(6): 460-468

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Comparison	**Prevalence of anxiety disorders and treatment effectiveness for people with schizophrenia and comorbid anxiety disorders.**
Summary of evidence	**Moderate quality evidence (large samples, unable to assess consistency, imprecise, direct) suggests high rates of anxiety disorders in patients with schizophrenia. Low quality evidence (very small samples) is unable to determine any effectiveness of treatments for comorbid anxiety symptoms.**

Prevalence
Panic Disorder: 7 studies, N = 443, prevalence: 3.30 to 43% *Social Phobia:* 5 studies, N = 376, prevalence: 8.2 to 36.3% *Agoraphobia:* 4 studies, N = 356, prevalence: 3.8 to 16.70% *General Anxiety Disorder:* 3 studies, N = 172, prevalence: 2.5 to 17.70% *Specific Phobia:* 3 studies, N = 324, prevalence: 2.5 to 13.60% Note: authors state that the reason for variability across study results is probably related to differences in samples (e.g. chronicity), and/or the use of different diagnostic instruments.
Treatment
Panic symptoms CBT: (1 study, N = 11), 7 improved, 3 got worse, 1 no change Alprazolam: (1 study, N = 7) showed improvements *Panic attacks* Diazepam & alprazolam: (1 case report, N = 3) showed improvements Alprazolam: (1 case study, N = 1) showed improvements Imipramine: (3 case reports, N = 5) showed improvements Switch from haloperidol to risperdal: (1 case study, N = 1) showed improvements *Social phobia symptoms* CBT: (2 studies, N = 50) showed improvements, also improved quality of life Flouxetine: (1 study, N = 12) showed improvements

Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Appears imprecise.
Directness of results	Direct

Fusar-Poli P, Nelson B, Valmaggia L, Yung AR, McGuire PK

Comorbid Depressive and Anxiety Disorders in 509 Individuals With an At-Risk Mental State: Impact on Psychopathology and Transition to Psychosis

Schizophrenia Bulletin 2014; 40(1): 120-131 View review abstract online	
Comparison	**Proportion of people at high clinical risk of psychosis with anxiety disorders.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence of an anxiety disorder in people at high clinical risk for psychosis is around 15%.**
Prevalence	
10 studies, N = 1,683, prevalence of anxiety disorders = 15.3%, 95%CI 8.9% to 25%	
Consistency in results	Authors state that study results were inconsistent.
Precision in results	Appears imprecise.
Directness of results	Direct

McEnery C, Lim MH, Tremain H, Knowles A, Alvarez-Jimenez M

Prevalence rate of social anxiety disorder in individuals with a psychotic disorder: A systematic review and meta-analysis

Schizophrenia Research 2019; 208: 25-33 View review abstract online	
Comparison	**Prevalence of social anxiety disorder in people with a schizophrenia spectrum disorder.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence of social anxiety disorder in people with schizophrenia is around 21%.**
Prevalence	
25 studies, N = 92,522, prevalence of social anxiety disorder = 21%, 95%CI 16% to 26%, I^2 = 97% Outpatient samples recorded higher prevalence rates than inpatient samples (25% vs. 9%). Having comorbid anxiety disorder was associated with increased depression, poorer social function, poorer	

subjective quality of life, greater negative self-evaluation, and greater insight.	
Consistency in results	Inconsistent
Precision in results	Appears imprecise.
Directness of results	Direct

Wilson RS, Yung AR, Morrison AP

Comorbidity rates of depression and anxiety in first episode psychosis: A systematic review and meta-analysis

Schizophrenia Research 2019; Nov: doi: 10.1016/j.schres.2019.11.035

View review abstract online

Comparison	**Prevalence of anxiety in people with first-episode psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, imprecise, direct) suggests the prevalence of anxiety in people with first-episode psychosis is around 29%.**
Prevalence	
7 studies, N = 1,016, prevalence of anxiety = 29%, range 20% to 40%, I^2 = 89%	
Consistency in results	Inconsistent
Precision in results	Appears imprecise.
Directness of results	Direct

Explanation of acronyms

CBT = Cognitive Behavioural Therapy, CI = Confidence Interval, GAD = General Anxiety Disorder, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PD = Panic Disorder, vs. = versus, X^2 = Chi-square statistic

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[8].

† 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[8].

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[9]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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[8];

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

§ 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[10].

‖ 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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