# TECHNICAL COMMENTARY

## Remission and recovery

### Introduction

Remission, as a clinical milestone, has generally had varied definitions. In 2003 the Remission in Schizophrenia Working Group (RSWG) proposed evidence-based and consensus-based criteria for defining remission. Remission has consequently been defined as "a level of core symptoms (positive, negative and disorganised) that does not interfere with an individual's behaviour, and is also below that required for an initial diagnosis of schizophrenia to be made according to the Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV)"[1]. Symptom improvements should last for a minimum of six months in order for remission to be reached[2].

Recovery is less precisely defined than remission. In addition to the symptom improvements required for remission, improvements in social and functional dimensions are required. These domains usually include, but are not restricted to; functional independence, maintaining satisfying relationships, being productive, having a sense of empowerment, and overcoming feelings of internalized stigma[2]. It has been suggested that improvements in either clinical or functional domains need to be seen for at least 2 years[3].

Reducing symptoms sufficiently to achieve remission is the main goal of treatment programs, though this becomes more difficult after successive relapses[4]. Remission is used more often than recovery as an ideal endpoint in many studies of treatment efficacy, as remission is easier to measure.

### 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. Reviews 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. Reviews with pooled data are 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[5]. Reviews with less than 50% of items 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 (RCT) 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, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[6]. The resulting

# Remission and recovery

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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 six reviews that met inclusion criteria[2-4, 7-9].

- Moderate quality evidence finds a mean rate of remission around 36% in both first- and multi-episode schizophrenia. For first-episode psychosis (rather than a narrower schizophrenia diagnosis), the long-term mean rate of remission (by 5.5 years) is around 58%.

- Moderate to low quality evidence suggests rates of remission vary considerably in the developing world, with very long-term remission rates (up to 25 years) ranging from 31% in Colombia to 77% in India.

- Moderate quality evidence suggests rates of recovery in schizophrenia are 13% to 16%, with annual rates around 1.4%. Recovery rates are highest in low or low-medium income countries (36.4%) and lowest in high (13%) or high-medium income countries (12.1%). For first-episode psychosis (rather than a narrower schizophrenia diagnosis), the long-term mean rate of recovery (up to 7.2 years) is around 38%.

- Moderate quality evidence suggests rates of recovery and remission in people with schizophrenia increase over time, from around 13% of patients by 5 years to around 68% of patients by 32 years after first diagnosis.

- Moderate to high quality evidence finds small to medium-sized associations between increased symptom severity and decreased personal recovery. A small association was found between increased functioning and increased personal recovery.

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*AlAqeel B, Margolese HC*

## Remission in Schizophrenia: Critical and Systematic Review

**Harvard Review Psychiatry 2012; 20: 281-297**

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| | |
|---|---|
| **Comparison** | **Remission rates in first-episode schizophrenia vs. multiple-episode schizophrenia and predictors of remission in each group.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, inconsistent, unable to assess precision, direct) suggests rates of remission are similar in first- and multi-episode schizophrenia being around 36%.** |

| **Remission** |
|---|
| *Average remission rate in first-episode schizophrenia was 35.6% and the average remission rate in multi-episode schizophrenia was 37%, with no significant differences between groups (p = 0.79);* |
| First-episode schizophrenia: 12 studies, N = 2,644, WM = 35.6%, 95%CI 27.6% to 43.6% |
| Multiple-episode schizophrenia: 13 studies, N = 6,253, WM = 37.0%, 95% CI 30.2% to 43.8% |
| The most frequent predictors of remission were better premorbid function, lower baseline symptom level, early response, and shorter duration of untreated psychosis. |

| | |
|---|---|
| **Consistency in results[‡]** | Authors report the data are inconsistent, and partly explained by predictors of remission. |
| **Precision in results[§]** | Unable to assess; WMs are not standardised. |
| **Directness of results[‖]** | Direct |

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*Cohen A, Patel V, Thara R, Gureje O*

## Questioning an Axiom: Better Prognosis for Schizophrenia in the Developing World?

**Schizophrenia Bulletin 2008; 34(2): 229-44**

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| | |
|---|---|
| **Comparison** | **Outcomes in low and middle income countries (as defined by the** |

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|---|---|
| | World Bank). |
| **Summary of evidence** | Moderate to low quality evidence (unclear sample sizes, unable to assess consistency or precision, direct) suggests long-term rates of remission vary considerably in the developing world, ranging from 31% in Colombia to 77% in India. |
| **Remission** | |
| *Authors state that there is wide variation across studies in remission rates;* | |
| 5 Indian studies reported between 8.2% and 77% remission rates. | |
| 2 Chinese studies reported between 22.1% to 34.5% remission rates. | |
| 1 Indonesian study reported 23.9% remission rates. | |
| 2 Nigerian studies reported between 45.7% and 81.7% remission rates. | |
| 1 Colombian study reported 31% had no or minimal symptoms over the previous month. | |
| **Consistency in results** | Unable to assess; no measure of consistency is reported. |
| **Precision in results** | Unable to assess; no measure of precision is reported. |
| **Directness of results** | Direct |

*Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, Veijola J, Miettunen J*

## A Systematic Review and Meta-Analysis of Recovery in Schizophrenia

**Schizophrenia Bulletin 2013; 39(6): 1296-1306**

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| | |
|---|---|
| **Comparison** | **Rates of recovery in people with schizophrenia.** |
| **Summary of evidence** | **Moderate quality evidence (large sample, unable to assess consistency, appears precise, direct) suggests overall rates of recovery are around 13% to 16%, with annual rates around 1.4%. Recovery rates are highest in low or low-medium income countries (36.4%) and lowest in high (13%) or high-medium income countries (12.1%). Rates do not vary according to sex, year of study, diagnostic method, chronicity of illness, origin of the sample, duration of follow-up, study quality score, or** |

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| | |
|---|---|
| | **definition of recovery.** |
| **Recovery rates** | |

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<tr><td colspan="2">

*50 samples (N = 8,994) assessed recovery rates in schizophrenia;*

WM = 37.0%, 95% CI 30.2% to 43.8%

Median recovery rate = 13.5%

Mean recovery rate = 16.4%, IQR 8.1% to 20.0%

$I^2$ = 99.8%, $p$ < 0.001

Median annual recovery rate = 1.4% per annum, IQR 0.7% to 2.6%

Subgroup analysis revealed a significantly higher recovery estimate in low or lower to middle-income countries (medians 13.0% in high income countries, 12.1% in upper-middle, and 36.4% in low or lower middle-income countries; $p$ = 0.005).

No significant differences in median recovery rates in subgroup analyses of sex, year of study, diagnostic method, first-episode vs. general intake, origin of the sample, duration of follow-up, study quality score, and definition of recovery.
</td></tr>
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| | |
|---|---|
| **Consistency in results** | Inconsistent |
| **Precision in results** | Appears precise |
| **Directness of results** | Direct |

<br>

| | |
|---|---|
| *Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, Murray RM*<br><br>**Remission and recovery from first-episode psychosis in adults: Systematic review and meta-analysis of long-term outcome studies**<br><br>**British Journal of Psychiatry 2017; 211: 350-8**<br>View review abstract online | |
| **Comparison** | **Long-term rates of remission and recovery in people after a first-episode of psychosis.** |
| **Summary of evidence** | **Moderate quality evidence (large samples, inconsistent, appears precise, direct) suggests the long-term rate of remission following a first-episode of psychosis (by 5.5 years) is around 58%, and the long-term rate of recovery (by 7.2 years) is around 38%.** |

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| Remission and recovery |
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| *The rate of remission is around 58% and recovery around 38% following a first-episode of psychosis;* |
| Remission (mean follow-up 5.5 years): 60 studies, N = 12,301, 58%, 95%CI 53% to 63% |
| Recovery (mean follow-up 7.2 years): 35 studies, N = 9,642, 38%, 95%CI 30% to 46% |
| More recent studies and studies conducted in Africa, Asia or North America reported higher remission rates. Recovery rates were higher in North America, in studies with shorter recovery duration criteria, older studies, and in studies conducted in psychiatric hospitals. |
| There were no effects of age, sex, baseline symptom severity, duration of untreated psychosis, medication status, ethnicity, marital status, length of follow-up, employment status, and the number of study drop-outs. |

| | |
| --- | --- |
| **Consistency in results** | Authors report data are inconsistent. |
| **Precision in results** | Appears precise |
| **Directness of results** | Direct |

*Leucht S, Lasse R*

**The concepts of remission and recovery in schizophrenia**

**Pharmacopsychiatry 2006; 39(5): 161-170**

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| | |
| --- | --- |
| **Comparison** | **Definition and rates of remission and recovery in schizophrenia.** |
| **Summary of evidence** | **Moderate quality evidence (large samples, unable to assess precision or consistency, direct) suggests rates of recovery and remission increase over time, from 13% at 5 years to up to 68% by 32 years after first diagnosis.** |
| **Remission - definition** | |

*6 studies assess definition of remission in first episode or acute psychosis, prior to the development of standardised remission criteria by the Remission in Schizophrenia Working Group;*

3 studies reported remission criteria as a rating of ≤ 3 on the SADS-C+PD (or an absence of hallucinations, delusions, thought disorder and catatonic behaviour), a CGI-S rating of ≤ 3 or mild or less and 1 of these studies suggests also a rating of 'at least much improved' on the CGI-C

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improvement scale – all for 8 consecutive weeks.

1 study defines remission as an absence of hallucinations, delusions, thought disorder or the combination of extreme psychomotor dysfunction + one other IFS symptom for consecutive 3 months.

1 study used a global SAPS positive score ≤2 for 8 consecutive weeks.

1 study suggests a reduction by 50% on BPRS, with scores ≤ 3 on each of the 5 scales (unusual thought content, suspiciousness, hallucinations, conceptual disorganisation, mannerisms and posturing), and a CGI-S rating ≤ 3.

*5 studies assess definition of remission in chronic schizophrenia, prior to the development of standardised remission criteria by the Remission in Schizophrenia Working Group;*

1 study suggests rapid reduction in symptoms with only mild signs of psychotic symptomatology (BPRS≤3 and CGI-S≤2); rapid and substantial response to medication at recommended doses, able to function unsupervised in at least one social or vocational domain.

1 study suggests BPRS total score < 30, < 3 on affective flattening on the SANS, < 2 on alogia (poverty of speech), anhedonia (inability to experience pleasure), avolition (lack of motivation), and attention items on the SANS, > 60 on the GAS, no psychotic symptoms for more than 1 month and no hospitalisation for 3 months, no more than 1 residual symptom and social or vocational functioning.

1 study suggests a score of ≤ 4 on BPRS positive and negative scales for 2 consecutive years.

1 study suggests a mean score of ≤ 2 on PANSS positive, negative and general psychopathology at a single time point.

1 study suggests living independently for at least 2 years, no psychiatric hospitalisation in 5 years, 'normal' psychosocial functioning, taking no medication or ½ of highest daily dose.

## Remission and recovery rates

*6 studies assessed long-term remission and recovery rates in schizophrenia*

*Authors state that continuous treatment with antipsychotics for sustained periods of time is crucial for remission and recovery;*

1 study (N = 289) reported that 49% of patients had a favourable long-term outcome at 37 year follow-up after the first hospitalisation, 27% were determined as recovered, 22% were mildly dysfunctional, 15% were in full-time employment and 37% were in part-time employment.

1 study (N = 502) reported that 22.1% of patients reached complete remission at 6 year follow-up, 43.2% had some residual symptoms (without psychosis), 56% were 'socially recovered' (employed).

1 study (N = 268) reported that 68% of patients were significantly improved or recovered at 32 year follow-up, 45% displayed no psychiatric symptoms, 23% had affective or organic disorder symptoms.

1 study (N = 140) reported that 31% were recovered at 21 to 27 year follow-up (no positive symptoms), 46% were improved (mild symptoms) and 74% were 'fully productive'.

| 1 study (1633) reported that 56% (incidence) to 60% (prevalence) were in remission for previous 2 years, as measured at 25 year follow-up. | |
|---|---|
| 1 study (118) reported that 13.7% of patients were recovered for ≥ 2 years at 5 year follow-up, 47.2% achieved symptom remission, 25.5% had adequate social functioning for ≤ 2 years. | |
| **Consistency in results** | Unable to assess; no measure of consistency is reported. |
| **Precision in results** | Unable to assess; no measure of precision is reported. |
| **Directness of results** | Direct |

*Van Eck RM, Burger TJ, Vellinga A, Schirmbeck F, De Haan L (2018):*

**The Relationship Between Clinical and Personal Recovery in Patients With Schizophrenia Spectrum Disorders: A Systematic Review and Meta-analysis**

**Schizophrenia Bulletin 2018; 44: 631-42**

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| **Comparison** | **Associations between symptom severity and personal recovery in people with schizophrenia.** |
|---|---|
| | **Personal recovery involves patients rating themselves as having recovered from the disorder even if they continue to experience symptoms.** |
| **Summary of evidence** | **Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds small to medium-sized associations between increased symptom severity and decreased personal recovery. A small association was found between increased functioning and increased personal recovery.** |
| **Personal recovery** | |
| *Small to medium-sized associations between increased symptom severity and decreased personal recovery;* | |

Overall symptoms: 20 studies, N = 3,994, $r$ = -0.21, 95%CI -0.27 to -0.14, $p < 0.001$, $I^2$ = 76%

Positive symptoms: 17 studies, N = 3,319, $r$ = -0.20, 95%CI -0.27 to -0.12, $p < 0.001$, $I^2$ = 75%

Negative symptoms: 15 studies, N = 2,442, $r$ = -0.24, 95%CI -0.33 to -0.15, $p < 0.001$, $I^2$ = 77%

Affective symptoms: 12 studies, N = 2,442, $r$ = -0.34, 95%CI -0.44 to -0.24, $p < 0.001$, $I^2$ = 85%

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# Remission and recovery

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|---|---|
| *Small association between increased functioning and increased personal recovery;*<br>8 studies, N = 1,938, *r* = 0.21, 95%CI = -0.09 to 0.32, *p* < 0.001, I² = 84% | |
| **Consistency in results** | Inconsistent |
| **Precision in results** | Precise |
| **Directness of results** | Direct |

## Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Index - Severity, CGI-C = Clinical Global Index - Change, GAS = Global Assessment Scale, I² = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IFS = Interim Follow-up Schedule, IQR = interquartile range, N = number of participants, *p* = statistical probability of obtaining that result (*p* < 0.05 generally regarded as significant), PANSS = Positive and Negative Syndrome Scale for Schizophrenia, RSWG = Remission in Schizophrenia Working Group, SADS-C+PD = Schedule for Affective Disorders and Schizophrenia Change Version, psychotic and disorganised symptoms, *r* = correlation coeffient, SANS = Scale for the Assessment of Negative Symptoms, WM = weighted mean

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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].

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† 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) which 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. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over 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

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 are an 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.

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‡ 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. I² 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. I² can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[10];

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

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§ 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].

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‖ 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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