

## Psychotic relapse

### Introduction

Studies have been investigating the possibility of identifying early warning signs of an impending psychotic relapse. Early warning signs are thoughts and behaviours that occur immediately prior to a psychotic relapse, which signal to the patient or their family that their condition is deteriorating. Early recognition may offer the potential for early intervention to prevent relapse, such as medication adjustment, psychosocial treatments, social support and stress reduction.

### 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 were given priority 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<sup>1</sup>. 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, 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)<sup>2</sup>. 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 nine systematic reviews that met our inclusion criteria<sup>3-11</sup>.

- Moderate quality evidence suggests the rates of relapse following a first-episode of psychosis are around 28% at one-year post-treatment and up to 54% at 3 years post-treatment.
- 70% of patients and 93% of family members could identify changes in experience or behaviour that preceded a psychotic relapse. Over 50% of patients reported a duration greater than one month between onset of signs and relapse.



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- Moderate to low quality evidence suggests common early warning signs for psychotic relapse include hallucinations, suspiciousness, change in sleep, anxiety, cognitive inefficiency, hostility, somatic symptoms, delusions, thought disorder, inappropriate behaviour and depression.
- Moderate quality evidence suggests the mean relapse rate following discontinuation of antipsychotics is around 38.3% in people with schizophrenia.
- Factors most consistently associated with *lower* risk of relapse include being maintained on a lower antipsychotic dose prior to discontinuation, shorter duration of untreated psychosis, better social functioning, and fewer previous relapses. Older age may also be a protective factor. Factors associated with *higher* risk of relapse include substance use disorders, poor medication adherence, high levels of familial critical comments and expressed emotion, poor premorbid adjustment, and being in a perimenstrual phase.
- Moderate quality evidence suggests a medium to large association between increased mean maximum monthly temperature and increased psychotic relapse rates, measured as psychiatric hospital admissions.
- Moderate quality evidence finds a small effect that children and adolescents with a psychotic disorder were more likely to be readmitted to a psychiatric hospital than children and adolescents with other psychiatric disorders.
- Moderate to low quality evidence suggests early recognition and intervention may be effective adjuncts, but not alternatives to maintenance medication.
- Moderate quality evidence finds no consistent use of adequate measures for defining psychotic relapse in RCTs of interventions for psychosis or schizophrenia.



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Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker AG, McGorry PD, Gleeson JF

### Risk factors for relapse following treatment for first episode psychosis: A systematic review and meta-analysis of longitudinal studies

Schizophrenia Research 2012; 139(1-3): 116-128

[View review abstract online](#)

<p><b>Comparison</b></p>	<p><b>Prevalence and predictors of psychotic relapse in treated first-episode psychosis patients.</b></p>
<p><b>Summary of evidence</b></p>	<p><b>Moderate quality evidence (unclear sample sizes, imprecise or inconsistent, direct) suggests rates of relapse are around 28% at one year post-treatment and up to 54% at 3 years post-treatment. Higher rates of relapse may be associated with substance use disorders, poor medication adherence, high levels of critical family comments, and poor premorbid adjustment.</b></p>
<p><b>Relapse</b></p>	
<p><i>The pooled prevalence of relapse of positive symptoms increased over time (at post-treatment follow-up);</i></p> <p>At 1 year: 12 studies, 28% (range 12-47%); PP = 0.278, 95%CI 0.234 to 0.340, I<sup>2</sup> = 79%, p &lt; 0.01              At 1.5 years: 2 studies, 43% (range 34-50%); PP = 0.431, 95%CI 0.282 to 0.593, I<sup>2</sup> = 86%, p &lt; 0.01              At 2 years: 5 studies, 43% (range 33-54%); PP = 0.427, 95%CI 0.326 to 0.534, I<sup>2</sup> = 66%, p = 0.01              At 3 years: 3 studies, 54% (range 40-63%); PP = 0.542, 95%CI 0.404 to 0.674, I<sup>2</sup> = 83%, p &lt; 0.01</p> <p>Stratifying by recruitment strategy (incidence vs. convenience) removed heterogeneity at 2 and 3 years, with studies recruiting by convenience reporting higher relapse rates.</p> <p>Specialised first-episode psychosis treatment centres also reported lower relapse rates compared to generic community treatment settings.</p> <p style="text-align: center;"><u>Clinical predictors of relapse</u></p> <p><i>Only substance use and poor medication adherence were found to be associated with increased relapse rates; no other clinical variables showed significant associations;</i></p> <p>Substance use disorder: 6 studies, OR = 2.27, 95%CI 1.37 to 3.76, Q = 9.81, p = 0.08, I<sup>2</sup> = 49%              Poor medication adherence: 7 studies, OR = 4.09, 95%CI 2.55 to 6.56, Q = 7.33, p = 0.29, I<sup>2</sup> = 18%              Diagnosis (affective vs. non-affective): 3 studies, OR = 1.43, 95%CI 0.43 to 4.73, Q = 8.67, p = 0.01, I<sup>2</sup> = 77%</p> <p>Positive symptoms: 6 studies, OR = 1.01, 95%CI 0.99 to 1.03, Q = 4.57, p = 0.47, I<sup>2</sup> = 0%              Negative symptoms: 6 studies, OR = 1.03, 95%CI 0.98 to 1.07, Q = 12.64, p = 0.03, I<sup>2</sup> = 60%</p>	



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<p>Affective symptoms: 3 studies, OR = 1.31, 95%CI 0.73 to 2.35, Q = 1.34, <math>p = 0.51</math>, <math>I^2 = 0\%</math>                  Duration of untreated illness: 4 studies, OR = 1.68, 95%CI 0.65 to 4.34, Q = 17.06, <math>p = 0.0007</math>, <math>I^2 = 82\%</math>                  Duration of untreated psychosis: 6 studies, OR = 1.11, 95%CI 0.43 to 2.89, Q = 390802.49, <math>p &lt; 0.0001</math>, <math>I^2 = 100\%</math>                  Poorer insight: 4 studies, OR = 1.46, 95%CI 0.95 to 2.25, Q = 9.38, <math>p = 0.02</math>, <math>I^2 = 68\%</math></p>	
<p style="text-align: center;"><u>Socio-demographic predictors of relapse</u></p> <p><i>Only 'critical family comments' was found to be associated with increased relapse rates; no other demographic variables showed significantly associations;</i></p> <p>Critical comments: 3 studies, OR = 2.35, 95%CI 1.16 to 4.77, Q = 1.55, <math>p = 0.46</math>, <math>I^2 = 0\%</math>                  Gender (male): 7 studies, OR = 1.42, 95%CI 0.96 to 2.10, Q = 7.70, <math>p = 0.26</math>, <math>I^2 = 22\%</math>                  Older age: 7 studies, OR = 1.00, 95%CI 0.97 to 1.02, Q = 5.38, <math>p = 0.50</math>, <math>I^2 = 0\%</math>                  Marital status (never married): 3 studies, OR = 1.34, 95%CI 0.77 to 2.35, Q = 0.35, <math>p = 0.84</math>, <math>I^2 = 0\%</math>                  Lower education: 5 studies, OR = 1.20, 95%CI 0.86 to 1.68, Q = 8.09, <math>p = 0.09</math>, <math>I^2 = 51\%</math>                  Unemployment: 3 studies, OR = 1.59, 95%CI 0.73 to 3.44, Q = 2.82, <math>p = 0.24</math>, <math>I^2 = 29\%</math>                  Overall expressed emotion: 2 studies, OR = 1.08, 95%CI 0.28 to 4.24, Q = 2.15, <math>p = 0.14</math>, <math>I^2 = 53\%</math></p>	
<p style="text-align: center;"><u>Premorbid adjustment predictors of relapse</u></p> <p><i>Poorer adolescent premorbid adjustment was found to be associated with increased relapse rates, but not overall premorbid adjustment;</i></p> <p>Early and late adolescent premorbid adjustment: 2 studies, OR = 1.59, 95%CI 1.03 to 2.46, Q = 0.39, <math>p = 0.53</math>, <math>I^2 = 0\%</math>                  Total premorbid adjustment: 3 studies, OR = 2.57, 95%CI 0.91 to 2.32, Q = 5.55, <math>p = 0.06</math>, <math>I^2 = 64\%</math></p>	
<p><b>Readmission</b></p>	
<p><i>The pooled prevalence of hospital readmission also increased over time (at post-treatment follow-up);</i></p> <p>At 1 year: 6 studies, 26% (range 12-56%); ER = 0.265, 95%CI 0.173 to 0.382, <math>I^2 = 90\%</math>, <math>p &lt; 0.01</math>                  At 1.5 years: 3 studies, 31% (range 24-36%); ER = 0.306, 95%CI 0.175 to 0.478, <math>I^2</math>, <math>p</math> not reported                  At 2 years: 4 studies, 50% (range 41-52%); ER = 0.490, 95%CI 0.340 to 0.642, <math>I^2</math>, <math>p</math> not reported                  At 3 years: 2 studies, 34% (range 12-58%); ER = 0.339, 95%CI 0.169 to 0.564, <math>I^2 = 96\%</math>, <math>p &lt; 0.01</math>                  At 7.5 years: 2 studies, 83% (range 82-83%); ER = 0.826, 95%CI 0.654 to 0.923, <math>I^2</math>, <math>p</math> not reported</p>	
<p><b>Consistency in results<sup>†</sup></b></p>	<p>Inconsistent</p>
<p><b>Precision in results<sup>§</sup></b></p>	<p>Precise for prevalence, imprecise for predictors</p>
<p><b>Directness of results<sup>  </sup></b></p>	<p>Direct</p>



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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

[View review abstract online](#)

<b>Comparison</b>	<b>Outcomes in low and middle income countries (as defined by the World Bank).</b>
<b>Summary of evidence</b>	<b>Moderate to low quality evidence (unclear sample sizes, unable to assess consistency or precision, direct) suggests rates of relapse vary considerably across the developing world.</b>
<b>Relapse</b>	
<p><i>Authors state that there is wide variation across studies in relapse rates (relapse measure is not reported);</i></p> <p>2 Chinese studies reported 6.9 to 8.3% relapse rate over 2-12 years</p> <p>1 Colombian study reported 18.1% ≥1 relapses over 26 years</p> <p>1 Jamaican study reported 13% relapses over 1 year</p> <p>3 Indian studies reported between 23% and 83.6% relapses over 2 to 20 years</p>	
<b>Consistency in results</b>	Unable to assess; no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct

Edgcomb JB, Sorter M, Lorberg B, Zima BT

**Psychiatric Readmission of Children and Adolescents: A Systematic Review and Meta-analysis**

Psychiatric services 2020; 71: 269-79

[View review abstract online](#)

<b>Comparison</b>	<b>Rates of psychiatric readmissions in children and adolescents with a psychotic disorder vs. other psychiatric disorders.</b>
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<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, inconsistent, imprecise, direct) finds a small effect that children and adolescents with a psychotic disorder were more likely to be readmitted than children and adolescents with other psychiatric disorders.</b>
<b>Psychiatric readmissions</b>	
<i>A small effect showed children and adolescents with a psychotic disorder were more likely to be readmitted than children and adolescents with other psychiatric disorders;</i> 10 studies, N = 65,785, OR = 1.87, 95%CI 1.53 to 2.28, I <sup>2</sup> = 77%	
<b>Consistency in results</b>	Inconsistent
<b>Precision in results</b>	Imprecise
<b>Directness of results</b>	Direct

*Gleeson J, Alvarez-Jimenez M, Cotton S, Parker A, Hetrick S*

**A systematic review of relapse measurement in randomized controlled trials of relapse prevention in first-episode psychosis**

**Schizophrenia Research 2010; 119: 79-88**

[View review abstract online](#)

<b>Comparison</b>	<b>Relapse measurement criteria reported in RCTs of clinical interventions for people with psychosis or schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large samples, unable to assess consistency or precision, direct) suggests no consistent use of adequate measures for defining psychotic relapse in RCTs of interventions for psychosis or schizophrenia.</b>
<b>Relapse measurements</b>	
16 RCTs, N = 3,081	
<i>Authors state that readmission to a psychiatric hospital was the most commonly reported definition of psychotic relapse, with 6 of 16 studies using this as relapse criteria. Only 3 studies satisfied all 6 criteria outlined below that authors state comprise an adequate 'operationalisation' of psychotic relapse;</i>	



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<i>Symptom severity criteria;</i>	
5/16 studies utilised a priori criteria for assessing changes in symptom severity, e.g. change scores of $\geq 10$ on the PANSS positive scale, a decrease in GAF score of $\geq 20$ , or a CGI change score $\geq 6$ .	
<i>Duration of change criteria for relapse and remission;</i>	
3/16 studies specified a minimum duration for increased symptom severity of 1 week and 1/16 study specified a minimum of 2 weeks duration for increased symptom severity.	
<i>Observer-rated instruments for relapse;</i>	
5/16 studies included standardised symptom measures (e.g. PANSS, BPRS, CGI) but data from these measures was not used to determine relapse.	
<i>Independent rater, blind to treatment allocation;</i>	
6/16 studies reported that treatment allocation was blinded, 7/16 studies reported both blind allocation to treatment and independent raters.	
<i>Inter-rater reliability checks;</i>	
8/16 studies reported inter-rater checks on measures of symptoms, 1 study detailed a training procedure throughout the course of the study and 1 study required concurrence between raters in order for a relapse to be declared.	
<i>Frequency of follow-up assessments;</i>	
5/16 studies reported 6 monthly to yearly assessments, 4/16 studies reported 3-monthly assessments, 1/16 study reported 5 monthly assessments and 5/16 studies reported fortnightly to 6 week intervals.	
<b>Consistency in results</b>	Unable to assess; no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct

<p>O'Driscoll C, Sener SB, Angmark A, Shaikh M</p> <p><b>Caregiving processes and expressed emotion in psychosis, a cross-cultural, meta-analytic review</b></p> <p>Schizophrenia Research 2019; 208: 8-15</p> <p><a href="#">View review abstract online</a></p>	
<b>Comparison</b>	<b>Expressed emotion in families of people with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large sample, consistent, imprecise, direct) suggests increased familial expressed</b>



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	<b>emotion was related to more relapses in patients.</b>
<b>Relapse</b>	
<p><i>A small to medium-sized effect of more relapses in patients with high familial expressed emotion;</i>            34 studies, N = 1,982, RR = 1.95, 95%CI 1.65 to 2.30, <math>p &lt; 0.05</math>, <math>I^2 = 20\%</math>, <math>p = 0.1</math></p> <p>Relapse indicated by case record or assessed by a clinician showed fewer relapses than other methods of relapse assessment. There were no moderating effects of region, year of publication, study design, or study quality.</p>	
<b>Consistency in results</b>	Consistent
<b>Precision in results</b>	Imprecise
<b>Directness of results</b>	Direct

<p><i>Reilly TJ, Sagnay de la Bastida VC, Joyce DW, Cullen AE, McGuire P</i></p> <p><b>Exacerbation of Psychosis During the Perimenstrual Phase of the Menstrual Cycle: Systematic Review and Meta-analysis</b></p> <p>Schizophrenia Bulletin 2020; 46: 78-90</p> <p><a href="#">View review abstract online</a></p>	
<b>Comparison</b>	<b>Psychosis during the perimenstrual phase in women with schizophrenia or another psychotic disorder.</b>
<b>Summary of evidence</b>	<b>Moderate to high quality evidence (large sample, consistent, appears precise, direct) suggests the psychiatric admission rates are increased during the perimenstrual phase.</b>
<b>Psychiatric admissions</b>	
<p><i>A small effect showed the rate of admissions during the perimenstrual phase increased compared to other times;</i>            11 studies, N = 742, incidence ratio = 1.48, 95%CI 1.31 to 1.67, <math>p &lt; 0.05</math></p> <p>There were no moderating effects of perimenstrual phase, study quality or diagnosis.</p>	
<b>Consistency in results</b>	Authors report data are consistent.
<b>Precision in results</b>	Appears precise.





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<b>Directness of results</b>	Direct
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*Tani H, Suzuki T, Wolfgang Fleischhacker W, Tomita M, Mimura M, Uchida H*  
**Clinical characteristics of patients with schizophrenia who successfully discontinued antipsychotics: A literature review**  
 Journal of Clinical Psychopharmacology 2018; 38: 582-9  
[View review abstract online](#)

<b>Comparison</b>	<b>Rates of relapse in people with schizophrenia who discontinued antipsychotics.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests the relapse rate following discontinuation of antipsychotics is around 38.3%. Factors most consistently associated with lower risk of relapse include being maintained on a lower antipsychotic dose prior to discontinuation, shorter duration of untreated psychosis, better social functioning and fewer previous relapses. Older age may also be a protective factor.</b>

<b>Relapse</b>	
<p>37 studies, N = 4,395, mean relapse rate = 38.3%, 95%CI 16.0% to 60.6%</p> <p><i>Factors associated with a lower risk of relapse were;</i></p> <p>3/3 studies found significant effects of shorter duration of untreated psychosis</p> <p>2/2 studies found significant effects of less severe positive symptoms at baseline</p> <p>6/8 studies found significant effects of being maintained on a lower antipsychotic dose before discontinuation</p> <p>2/3 studies found significant effects of better social functioning</p> <p>2/3 studies found significant effects of fewer previous relapses</p> <p>5/12 studies found significant effects of older age</p> <p>1/12 studies found significant effects of younger age</p> <p>3/7 studies found significant effects of older age at the onset of illness</p> <p>2/8 studies found significant effects of being female sex</p> <p>1/8 study found significant effects of being male</p>	



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<b>Consistency in results</b>	Unable to assess; no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct

*Thompson R, Hornigold R, Page L, Waite T*

**Associations between high ambient temperatures and heat waves with mental health outcomes: a systematic review**

Public Health 2018; 161: 171-91

[View review abstract online](#)

<b>Comparison</b>	<b>Associations between high ambient temperature or heat waves and psychiatric hospital admission rates in people with schizophrenia.</b>
<b>Summary of evidence</b>	<b>Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests a medium to large association between increased mean maximum monthly temperature and increased psychotic relapse rates, measured as psychiatric hospital admissions.</b>
<b>Psychiatric hospital admissions</b>	
<p>One Israeli study (N = 33,614) found increased mean maximum monthly temperature was significantly associated with increased psychiatric admission rates for acute exacerbation of schizophrenia (medium to large effect, <math>r = 0.35</math>, <math>p &lt; 0.001</math>). Another Israeli study (N = 247) found an association between increased psychiatric ward temperature and increased schizophrenia symptom severity (<math>r = 0.54</math>, <math>p &lt; 0.0002</math>).</p> <p>One Australian study (N = 171,614) found no significant increase in admissions for schizophrenia during heat waves (<math>\geq 35^{\circ}\text{C}</math> for <math>\geq 3</math> consecutive days; IRR = 1.034, 95%CI 0.969 to 1.102).</p>	
<b>Consistency in results</b>	Unable to assess; no measure of consistency is reported.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct



van Meijel B, van der Gaag M, Sylvian RK, Grypdonck MHF

**Recognition of early warning signs in patients with schizophrenia: A review of the literature**

International Journal of Mental Health Nursing 2004; 13: 107-116

[View review abstract online](#)

<b>Comparison</b>	<b>Identification and recognition of early warning signs for psychosis in patients with schizophrenia or schizoaffective disorder, and assessment of their predictive value.</b>
<b>Summary of evidence</b>	<p><b>Moderate to low quality evidence (small or unclear sample sizes, inconsistent, unable to assess precision, direct) suggests common early warning signs for psychotic relapse include hallucinations, suspiciousness, change in sleep, anxiety, cognitive inefficiency, hostility, somatic symptoms, delusions, thought disorder, inappropriate behaviour and depression.</b></p> <p><b>Moderate quality evidence (medium or unclear sample sizes, inconsistent, unable to assess precision, direct) suggests 70% of patients and 93% of family members could identify changes which predicted psychotic relapse. Over 50% of cases reported a duration greater than one month between onset of signs and relapse. However, the measureable predictive value of early warning signs was inconsistent.</b></p> <p><b>Moderate to low quality evidence (unclear sample size, inconsistent, unable to assess precision, direct) suggests early recognition and intervention may be effective adjuncts, but not alternatives, to maintenance medication.</b></p>

**Identification of early warning signs**

One prospective study (N = 47) of schizophrenia and schizoaffective patients used weekly appointments to measure signs of impending psychotic relapse. 32 signs were identified. The 10 most common were hallucinations (53%), suspiciousness (43%), change in sleep (43%), anxiety (38%), cognitive inefficiency (26%), anger/hostility (23%), somatic symptoms or delusions (21%), thought disorder (17%), disruptive inappropriate behaviour (17%), and depression (17%). All of the patients manifested at least one of these symptoms. Psychotic signs had higher frequency ratings than non-psychotic signs.

One retrospective study (N not reported) reported non-psychotic warning signs to have significantly higher frequency ratings than psychotic signs, these were reported by both patients and family members.



### **Recognition of early warning signs**

Two retrospective studies (N not reported) suggested between 63 to 86% of patients could name one or more early warning signs.

One retrospective study (N = 225) of schizophrenia patients and their family members, comprising 99 stable patients and 46 acute patients, asked respondents to identify changes in experiences, thoughts and behaviour that preceded the most recent psychotic episode. 70% of the patients and 93% of the family members could name one or more specific changes, of where there was significant agreement between the groups.

The period of time between the first warning signs and the actual relapse was also investigated. This period was reported by patients and family members to be less than one day in only 7 to 11% of cases. 16 to 24% said this period lasted from 1 to 7 days, but 50 to 68% of respondents reported a period of one week to over one month.

5 other studies (N, data not reported) confirm an increase in warning signs is apparent for several weeks prior to psychosis onset.

### **Predictive value of early warning signs**

Five studies (N not reported) investigate whether the identified early warning signs are good predictors of a psychotic relapse, and report depressive feelings to be a consistent predictor.

Four studies (N not reported) consider mild psychotic experiences to have a high predictive value. A Positive Predictive Value (PPV) has been determined in three studies, and ranged between 15 – 43%.

However in these studies, early interventions (both pharmacological and psychosocial) affected the course of symptom development. The most intensive interventions were associated with the lowest PPV.

Eleven studies (N not reported) have investigated the sensitivity and specificity of early warning signs. Sensitivity refers to the proportion of relapsing patients who showed increased early warning signs (true positive rate); specificity refers to the proportion of non-relapsing patients for whom there was no increase in early warning rates (true negative rate).

Across all studies, the sensitivity varies between 8 to 81%, with the majority scoring over 50%. Specificity values range from 60 to 93%. Authors report high heterogeneity, where assessed values are influenced by the selection of sign, frequency of scoring, definition of relapse, and follow up period.

### **Effects of early warning signs on intervention for psychotic relapse**

Twelve studies (N not reported) have investigated the application of early recognition methods with intervention strategies, which generally compare maintenance medication with intermittent medication strategies applied upon the first signs of relapse.



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They reported that the modest benefit of reduced medication side effects experienced by an intermittent strategy was exceeded by the higher risk of relapse (no data reported). Authors concluded that early recognition and intervention in combination with maintenance medication may be the most effective means for preventing relapse.

One controlled study (N not reported) administered psychoeducation about early warning signs, active monitoring of early signs, early intervention upon appearance of signs, support groups for improving coping, and multifamily psychoeducation groups, compared to a control group of treatment as usual (supportive therapy and medication management). Both groups received standard maintenance medication. Over an 18 month follow up, the experimental group had significantly lower rates of relapse, 17% compared to 34% in the control group, and lower readmission rates, 22% compared to 39% in controls.

One controlled study (N not reported) investigated readmission rates in patients treated with the Liberman Module “Symptom Management” strategy, which involves a group education program focusing on early recognition and intervention, compared to controls receiving care as usual. Over a two year follow up, no significant difference was reported between the two groups for readmission rates, but significant difference was reported in the duration of admission where patients in the experimental group stayed 2.6 weeks compared to 20 weeks for controls.

One descriptive correlational study (N = 370) considered early recognition in a mixed sample of psychiatric patients (authors report approximately half were schizophrenia patients). Poor recognition of warning signs was associated with poor treatment outcomes and greater use of services.

<b>Consistency in results</b>	Authors report high heterogeneity in predictive value, specificity and sensitivity values.
<b>Precision in results</b>	Unable to assess; no measure of precision is reported.
<b>Directness of results</b>	Direct

## Explanation of acronyms

BPRS = The Brief Psychiatric Rating Scale, CGI = Clinical Global Impression, CI = confidence interval, GAF = Global Assessment of Functioning,  $I^2$  = measure of heterogeneity across study results, N = number of participants, PANSS = Positive and Negative Syndrome Scale,  $p$  = statistical probability of obtaining that result ( $p < 0.05$  generally regarded as significant), OR = odds ratio, PP = pooled prevalence, PPV = positive predictive value, RR = risk ratio, RCT = randomised controlled trial, 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; 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<sup>12</sup>.

† Different effect measures are reported by different reviews.

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).

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.

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. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect<sup>12</sup>.

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  $< 0.2$ <sup>13</sup>. InOR stands for logarithmic OR where a InOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.



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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 unforeseen 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 be 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<sup>12</sup>;

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

§ 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<sup>14</sup>.

|| 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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