Psychotic relapse

Introduction
Under regular treatment conditions, relapse rates for psychosis are estimated to be around 40%. This figure increases upon discontinuation of medication to between 60 and 75% after one year. These estimates are influenced by age and stage of disorder as younger and acute patients tend to show higher relapse than older and more chronic patients.

Recent research has 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.

The involvement of several parties in the early recognition process is crucial to its success. It is important that these signs be identifiable by family members or carers as patients may minimise or disguise these symptoms in order to appear healthy or to avoid hospital readmission. The ability of patients to recognise altered experiences may also deteriorate as the symptoms progress and insight diminishes.

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 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. Reviews rated as having 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). The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of the Schizophrenia Research Institute.
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Results

We found one systematic review that met our inclusion criteria¹.

- Moderate quality evidence suggests 70% of patients and 93% of family members could identify changes in experience or behaviour which predicted psychotic relapse. Over 50% of cases reported a duration greater than one month between onset of signs and relapse. However, the measurable predictive value of early warning signs was inconsistent.

- 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 to low quality evidence suggests early recognition and intervention may be effective adjuncts, but not alternatives to maintenance medication.
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


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<th>Comparison</th>
<th>Identification and recognition of early warning signs for psychosis in people with schizophrenia or schizoaffective disorder, and assessment of their predictive value.</th>
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<tr>
<td>Summary of evidence</td>
<td>Moderate to low quality evidence (inconsistent, direct, unable to assess precision, moderate sample size) 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 (inconsistent, direct, unable to assess precision, large sample size) 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 measurable predictive value of early warning signs was inconsistent. Moderate to low quality evidence (inconsistent, direct, unable to assess precision or sample size) suggests early recognition and intervention may be effective adjuncts, but not alternatives to maintenance medication.</td>
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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
Recognition of early warning signs

Two retrospective studies (N not reported) suggested between 63 – 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 – 11% of cases. 16 – 24% said this period lasted from 1 to 7 days, but 50 – 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 – 81%, with the majority scoring over 50%. Specificity values range from 60 – 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.

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.

<table>
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<th>Consistency in results</th>
<th>Results appear inconsistent. Authors report high heterogeneity in predictive value, specificity and sensitivity values</th>
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Explanation of acronyms

CI = Confidence Interval, N = number of participants, p = statistical probability of obtaining that result (p < 0.05 generally regarded as significant), PPV = positive predictive value
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.

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.

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. 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 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:

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

§ 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. 

|| 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.
References


