Assessing early signs of relapse in psychosis: Review and future directions

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HIGHLIGHTS

- Conventional early signs of relapse have modest predictive validity.
- Targeted medication is not an effective alternative to maintenance medication.
- The addition of early signs interventions to usual care may reduce relapse.
- Basic symptoms may predict relapse; further empirical research is needed.

ARTICLE INFO

ABSTRACT

Relapse of psychosis is common and has profound adverse consequences. Early signs interventions assume that timely prediction of relapse allows preventative action to reduce the chance of full relapse. The utility of early signs in this context is critically reviewed.

Cohort studies suggest that early signs (e.g. anxiety, insomnia) appear in the few weeks before relapse and have modest predictive validity (sensitivity 10%–80%, median 61%; specificity 38%–100%, median 81%), indicating that accuracy of relapse prediction needs improvement. Trials using early signs to target interventions show that targeted antipsychotic medication is less effective than adequately dosed maintenance medication but relapse rates are lower than when intervention is delayed until relapse. The relative value of more complex interventions including psycho-education and relapse prevention strategies is not yet clearly established because there are few trials, some with important design limitations.

Basic symptoms are subtle, subjective, qualitative changes in experience claimed to precede psychosis. One retrospective cohort study and studies of "at risk mental states'" transition to psychosis indicate some predictive validity. We suggest that basic symptoms are potentially valuable additions to the range of early signs and deserve further investigation in the effort to enhance the predictive validity of the early signs syndrome.

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Contents

1. Introduction

In those diagnosed with schizophrenia or a related psychosis, 'relapse' is usually operationally defined in terms of a recurrence of positive psychotic symptoms (Bebbington et al., 2006; Burns, Fiander, & Audini, 2000; Falloon, Marshall, Boyd, Razani, & Wood-Siverio, 1983; Lader, 1995). Around 80% of those treated for a first episode of psychosis relapse within five years, with cumulative relapse rates of 78% and 86% for second and third relapses during this period (Robinson et al., 1999). Relapses can be devastating for the individual (Maclean, 2008) and are associated with a deteriorating course of illness, such as increased levels of psychotic symptoms remaining after each acute episode (residual symptoms) (Wiersma, Nienhuis, Slooff, & Giel, 1998). Furthermore, individuals experiencing a relapse of acute psychosis frequently require admission to hospital, the principal source of schizophrenia's annual direct cost to the UK National Health Service of over £3.9 billion (over $6 billion) (Almond, Knapp, Francois, Toumi, & Traolach, 2004; Mangalore & Knapp, 2007; The Schizophrenia Commission, 2012).

Given the prevalence and considerable negative consequences of relapse, it is clear that relapse prevention strategies for those with psychosis are a priority. Early signs based relapse prevention interventions work on the premise that timely prediction of relapses will allow preventative action to be taken, minimizing the chance of full relapse occurring (Birchwood, Spencer, & McGovern, 2000). The patient is assisted in identifying and monitoring early signs of relapse, and in developing concrete action plans for dealing with them. Early signs commonly reported to emerge in the weeks before a relapse include: anxiety, dysphoria, insomnia, poor concentration and attenuated psychotic symptoms (Birchwood et al., 1989). A variety of techniques may be included in the preventative action plan, such as short term increases in medication, intensive psychological support or a combination of relapse prevention techniques.

The overall aim of this review is to evaluate the assessment and utility of early signs of relapse in the context of relapse prevention and to suggest ways that this may be improved. In the first section of the review, the difficulties of defining relapse will be briefly discussed. In the second section, the current paradigm for assessing relapse risk using early signs will be outlined. This will include an examination of the validity of early signs as predictors of relapse and a discussion of the limitations of the current approach. The third section will focus on the clinical application of early signs by examining studies that evaluate relapse prevention interventions

with a substantial early signs component (at least half of the intervention content).

Since checklists of conventional early signs are only modestly predictive of relapse, we propose that early signs based interventions could be directly improved by more accurate assessment of relapse risk. In this regard, the 'basic symptom' concept will be introduced in the fifth section of the review. Basic symptoms are subtle, subclinical, qualitative disturbances in one's experience of oneself and the world. It has been suggested that including basic symptoms as additional predictors of relapse may improve the current paradigm of assessing relapse risk, increasing the effectiveness of early signs interventions. Evidence from the literature in support of this suggestion will be reviewed. Since there is little empirical work, to date, directly examining basic symptoms as indicators of relapse risk, other aspects of the basic symptom literature will also be referred to. This will include studies evaluating the specificity of basic symptoms to psychosis and evidence from groups purportedly at high risk of a first episode of psychosis. Finally, future research directions will be recommended.

2. Definitions of relapse

It is worth beginning by discussing how relapse may be defined. Relapse is a relative term with no clear consensus about a definition (Lader, 1995). The 26 papers discussed in this review use no less than 15 definitions, with still more present in the wider psychosis literature. Nevertheless, previous reviews (Falloon et al., 1983; Lader, 1995) and a Delphi study (Burns et al., 2000) have highlighted three key criteria which tend to be used, either individually or in combination, when defining relapse: change in psychopathology; decline in social functioning; change in management (e.g. hospital admission).

In Burns et al. (2000) Delphi study, a panel of experts agreed that a change in psychopathology (e.g. an increase in positive psychotic symptoms) was at the core of all definitions of relapse of psychosis. Management change and decrease in social functioning were viewed as more secondary (Burns et al., 2000) and the difficulties of comparing these across services and individuals have been noted (Falloon et al., 1983). For example, certain aspects of declining social functioning (e.g. violence) may be more noticeable, but not necessarily more indicative of relapse, than others (e.g. self-neglect). Similarly, a change in management such as hospital admission is more likely for individuals presenting as violent or aggressive than for those who

might be considered equally 'unwell' but who are displaying fewer overt signs of relapse.

A further consideration when defining relapse of psychosis is that to be eligible for relapse, individuals must first have achieved some degree of stability or even 'remission' from their previous episode of acute psychosis (e.g. see Andreasen et al., 2005). In reality not all individuals will experience a complete absence of symptoms between acute episodes. Some studies (e.g. Brown, Birley, & Wing, 1972; Leff, Kuipers, Berkowitz, Eberlein-Vries, & Sturgeon, 1982) have formalized this within their definition of relapse by including two categories: type I relapse, where psychotic symptoms have re-appeared in someone who has experienced a complete absence of positive symptoms since their previous episode; type II relapse which involves an exacerbation of psychotic symptoms which had stabilized at a steady level since the last acute episode (Johnstone, 1992). However, only one of the studies in the current review (Jørgensen, 1998) distinguished between type I and type II relapses. Whilst some studies recommended that participants were 'clinically stable' before entering the study, few gave an operational definition of this criterion.

The specific relapse definitions used by studies included in the current review are covered in detail in Sections 4.3.2 and 4.4.3. The characteristics and quality of these definitions are discussed. This is a key methodological consideration since a wide range of different definitions have been used, which adds to the difficulty of comparing outcomes across studies.

3. Assessing early signs of relapse

3.1. Background

Retrospective reports from service users with psychosis and their relatives suggest that the majority of service users experience changes in their thoughts, feelings or behaviors in the 2–3 weeks before a relapse of psychosis (Birchwood et al., 1989; Herz & Melville, 1980). These early signs of relapse include experiences such as anxiety, dysphoria, insomnia, poor concentration and attenuated psychotic symptoms (Birchwood et al., 1989). The evidence from these retrospective studies has formed the basis for two lines of subsequent research. Firstly, as outlined below, a number of prospective studies have evaluated the validity of early signs as predictors of relapse. Secondly, reviewed in Section 4, the effectiveness of early signs based relapse prevention interventions has been investigated.

It is worth emphasizing that this review focuses on measures and interventions concerned with predicting the *timing* of relapse in the short term. Thus, although certain prognostic measures (e.g. poor pre-morbid work and social adjustment, gradual onset of psychosis, emotional blunting) give some guide to long term outcomes (Harrow & Jobe, 2007; Stephens, 1978; Stephens, Richard, & McHugh, 1997; Vaillant, 1978), these are beyond the scope of the current review.

3.2. Prospective studies

3.2.1. Sensitivity and specificity

Eleven prospective studies investigating the utility of a range of early signs as predictors of relapse are summarized in Table 1 and reviewed below. To be included in the review, studies had to use a prospective, repeated measures design to assess early signs and relapse in participants with non-affective psychosis. Analyses must have examined the validity of early signs as predictors of relapse, and sensitivity and specificity figures must have been reported or be calculable from the reported data. In this context, sensitivity refers to the ability of the early signs measure to positively identify relapses without missing any, whereas specificity refers its ability to identify non-relapse cases without missing any (Tait, McNay, Gumley, & O'Grady, 2002). For both sensitivity and specificity, higher values indicate more accurate prediction of relapse.

In the reviewed studies, sensitivity (proportion of relapses correctly predicted) ranged from 10% to 80% (median 61%) and specificity (proportion of non-relapses correctly identified) ranged from 38% to 100% (median 81%) (see Table 1). Thus, on the whole early signs appear to be modestly predictive of relapse. However, there was considerable variability between the studies in their estimates of sensitivity and specificity and only two of the reviewed studies (Gaebel & Riesbeck, 2007; Gaebel et al., 1993; Marder et al., 1991) formally tested whether the early signs assessment predicted relapse better than chance. It is also worth noting that in some cases the threshold of early signs (Birchwood et al., 1989) or the exact symptoms included in the analysis (Subotnik & Neuchterlein, 1988) were defined post hoc.

Several methodological factors may have contributed to the variability in the results. In three of the studies, estimates of sensitivity and specificity may have been confounded by the fact that some (Tait et al., 2002) or all participants (Hirsch & Jolley, 1989) received additional medication when early signs were detected. It is likely that in some cases targeted medication successfully aborted a relapse, resulting in 'false false positives' and lowering sensitivity and specificity estimates. There was also considerable variability between the eleven studies in the frequency of early signs monitoring and in how early signs were defined and assessed. These factors are worth considering in detail in order to determine how relapse risk has been most accurately assessed using early signs to date, and how this might be improved.

3.2.2. Frequency of early signs assessment

The predictive value of early signs depends both on the frequency with which they are assessed in the studies and the typical delay from onset of early signs to onset of relapse (lead time). In the reviewed studies, the frequency of early signs monitoring ranged from weekly (Marder et al., 1991; Marder et al., 1994) or fortnightly (Birchwood et al., 1989; Jørgensen, 1998; Subotnik & Neuchterlein, 1988; Tait et al., 2002) to monthly (Gaebel & Riesbeck, 2007; Gaebel et al., 1993; Gleeson, Rawlings, Jackson, & McGorry, 2005; Hirsch & Jolley, 1989; Malla & Norman, 1994; Tarrier, Barrowclough, & Bamrah, 1991), with one study varying the assessment interval (Hirsch & Jolley, 1989). Since early signs only tend to emerge in the 2–3 weeks before a relapse (Birchwood et al., 1989; Herz & Melville, 1980), monthly assessment is unlikely to be frequent enough to predict the majority of relapses; in fact between a quarter and half of early signs episodes are likely to be detected too late. Birchwood et al. (2000) have recommended that early signs monitoring is carried out at least fortnightly. This appears to be borne out in the studies reviewed; those with the most infrequent early signs monitoring tended to demonstrate lower sensitivity (see Table 1).

3.2.3. Definition and assessment of early signs

Some studies included only non-psychotic (Gaebel et al., 1993; Hirsch & Jolley, 1989; Malla & Norman, 1994; Marder et al., 1994) or only attenuated psychotic symptoms (Subotnik & Neuchterlein, 1988) as early signs, but the majority included a combination of these (Birchwood et al., 1989; Gleeson et al., 2005; Jørgensen, 1998; Tait et al., 2002; Tarrier et al., 1991). The sensitivity and specificity figures for the three types of assessment (non-psychotic indicators; psychotic symptoms; combined non-psychotic and psychotic symptoms) are given in Table 1. These are also represented graphically in Fig. 1, which plots sensitivity versus 1-specificity (true versus false positives) in the manner of a Receiver Operating Characteristic (ROC) curve. The diagonal line delineates the points at which predictors perform no better than chance: the further from it, the greater the predictive power.

The lowest sensitivity estimate (10%) was found when only non-psychotic symptoms were used as early signs (Gaebel et al., 1993), and their ROC analysis indicated that this assessment did not predict relapse above chance. Although the pattern is not clear cut, other measures that included only non-psychotic symptoms tended to also

Table 1
Prospective studies examining the sensitivity and specificity of early signs as predictors of psychosis relapse.

Study	N	Number of relapses	Early signs assessment			Sensitivity	Specificity
			Frequency	Symptom type	Assessment details		
Subotnik and Neuchterlein (1988)	50	17	Fortnightly	Psychotic	BPRS hostile-suspicious & thought disturbance (compared to controls)	59	88
				Psychotic	BPRS thought disturbance subscale (compared to non-relapsing self)	71	88
Birchwood et al. (1989)	19	8	Fortnightly	Combination	Any increase in early signs (ESS rated by service user and relative)	50	100
				Combination	Increase to a score of ≥30 (ESS rated by service user and relative)	63	82
Hirsch and Jolley (1989)	54	11	Monthly; weekly if unstable	Non-psychotic	'Dysphoric episode' — the emergence of neurotic or dysphoric symptoms causing noticeable distress; defined clinically	73	45
Marder et al. (1991)	50	–	Weekly	Non-psychotic	BPRS anxiety-depression subscale	50[a]	75[a]
				Non-psychotic	Individualized Prodromal Scale	58[a]	60[a]
				Combination	Early Signs Questionnaire	–[b]	–[b]
Tarrier et al. (1991)	22	12	Monthly	Non-psychotic	Depression (PAS)	50	81
				Combination	Depression and hallucinations (PAS)	63	88
Gaebel et al. (1993)	115	72	Monthly	Non-psychotic	6 prodromal symptoms: trouble sleeping; trouble concentrating; restlessness; tension; loss of interest; depression (crisis group only)	10[b]	93[b]
Gaebel and Riesbeck (2007)	339	227	Monthly	Combination	Individual symptoms from ESQ	<40[c]	69–95[c]
				Combination	Combined score for adapted ESQ items	72[a]	38[a]
Malla and Norman (1994)	55	–	Monthly	Non-psychotic	Increase in composite score including: depression (BDI), anxiety (SEQ), somatic concern (GHQ-28), feeling stressed (PSS), low general functioning and social withdrawal (SANS asociality subscale)	<50	>90
Marder et al. (1994)	63	54	Weekly	Non-psychotic	Individualized Prodromal Scale: trouble sleeping; trouble concentrating; withdrawn; irritable; thoughts you can't get rid of; using drugs or drinking more	37	–
Jørgensen (1998)	60	27	Fortnightly	Combination	Change score of ≥10 (ESS, Danish translation)	74	79
				Non-psychotic	PANSS general scale change ≥10	26	85
				Combination	Combined ESS and PANSS general subscale	81	79
Tait et al. (2002)	20	4	Fortnightly	Combination	Individualized early signs system including early signs, cognitions & behaviors (e.g. non-return of questionnaire)	75	44
Gleeson et al. (2005)	35	–	Monthly	Combination	Defined a priori: score of ≥30 (ESS)	80	47
				Combination	Defined post hoc: score of ≥50 (ESS)	80	73

Notes: where sensitivity and specificity figures were not reported, these were calculated from the available data where possible; BPRS = Brief Psychiatric Rating Scale; ESS = Early Signs Scale; PAS = problem appraisal scale; ESQ = Early Signs Questionnaire; BDI = Beck Depression Inventory; SEQ = Self-Evaluation Questionnaire; GHQ-28 = General Health Questionnaire; PSS = Perceived Stress Scale; SANS = Scale for Assessment of Negative Symptoms; PANSS = Positive and Negative Syndrome Scale.
[a] ROC analysis significant.
[b] ROC analysis not significant.
[c] ROC analysis significant for 6 items.

demonstrate fairly low sensitivity compared to those using attenuated psychotic symptoms only or a combination of symptoms (see Fig. 1).

Assessments specifically designed to assess early signs (e.g. Early Signs Scale, ESS; Early Signs Questionnaire, ESQ; Individualized Early Signs System) tended to be more sensitive indicators of relapse risk
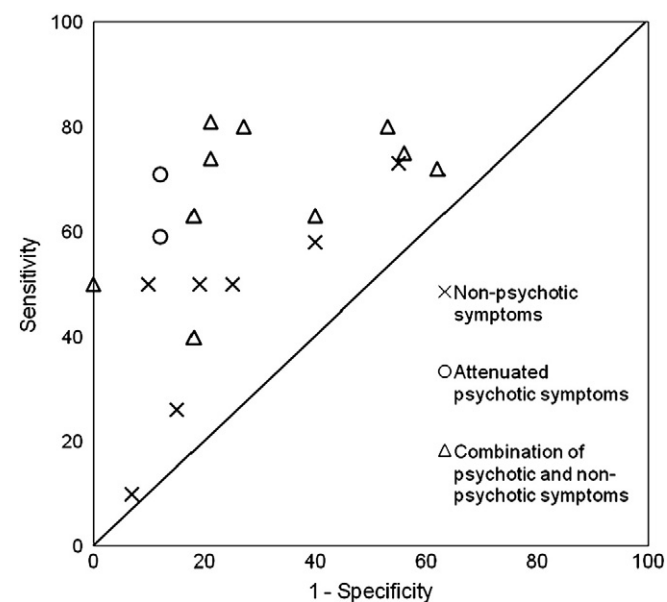

Fig. 1. Comparison of accuracy of three types of assessment (non-psychotic symptoms; attenuated psychotic symptoms; combined psychotic and non-psychotic symptoms) as predictors of relapse. Exact sensitivity and specificity figures are provided in Table 1.

(Birchwood et al., 1989; Gleeson et al., 2005; Jørgensen, 1998; Tait et al., 2002) than the assessments of general psychopathology (Brief Psychiatric Rating Scale, depression subscale; Problem Appraisal Scale; Positive and Negative Syndrome Scale, general subscale) used in other studies (Jørgensen, 1998; Malla & Norman, 1994; Marder et al., 1991; Tarrier et al., 1991). This said, it should be acknowledged that one study found that the Early Signs Questionnaire to be no better than chance in predicting relapse (Marder et al., 1991). Furthermore, in some cases (Gleeson et al., 2005; Tait et al., 2002) early signs scales were also associated with lower specificity. This can be explained as follows. Since assessments such as the ESS or ESQ include a greater variety of possible early signs, including both psychotic and non-psychotic symptoms, there is more chance of detecting true positives (early signs followed by relapse) but also more chance that subtle fluctuations in mental state will be picked up (false positives). This leads to higher sensitivity (true positives / [true positives + false negatives]) but lower specificity (true negatives / [true negatives + false positives]).

The trade-off between the sensitivity of an assessment and its specificity is a common difficulty (Bewick, Cheek, & Ball, 2004). In order to achieve a better balance of sensitivity and specificity, the authors of the ESS experimented with using different thresholds for defining an early signs episode. As indicated in Table 1, they achieved reasonable specificity and better sensitivity by raising the threshold ESS score to ≥30 in post hoc analyses (Birchwood et al., 1989). This was replicated in two further studies that used this threshold a priori (Gleeson et al., 2005; Jørgensen, 1998). Post hoc analyses in the most recent of these studies suggested that predictive power might be further improved by increasing the threshold to ≥50 (Gleeson et al., 2005), but this is yet to be replicated in another sample.

As an alternative to the trial and error approach described above, two of the reviewed studies used ROC analysis to define a threshold

with the optimum balance of sensitivity against specificity (Gaebel & Riesbeck, 2007; Gaebel et al., 1993; Marder et al., 1991). This approach also allowed them to formally test whether the assessments performed better than chance across a range of sensitivities and specificities. Given these advantages, it is surprising that ROC analysis has not been more widely employed to date in studies evaluating the accuracy of early signs as predictors of relapse. We suggest that future studies in this field should consider using this method of analysis.

3.3. Conclusions regarding early signs assessment

Retrospective and prospective studies suggest that early signs appear in the few weeks before relapse, and that these have modest predictive validity. Thus, although the use of early signs to assess relapse risk appears to be a potentially useful paradigm, the accuracy of early signs assessment could be improved further. This is of key clinical importance, since improved assessment of relapse risk is likely to directly improve the effectiveness of early signs based relapse prevention interventions.

In the studies reviewed above, two methodological factors were associated with more sensitive assessment of relapse risk: firstly, frequent assessment of early signs (e.g. at least fortnightly); secondly, inclusion of a wide variety of possible early signs in monitoring assessments. Thus, the sensitivity of early signs assessments may be further improved by the addition of other hypothesized predictors of relapse. With this in mind, in Section 5 of this review, the suggestion that 'basic symptoms' may be used to predict relapse will be discussed in detail. Firstly, in the next section, studies evaluating early signs interventions will be critically evaluated.

4. Early signs interventions for relapse prevention: systematic review

4.1. Systematic review methods

In this section, studies evaluating early signs interventions will be reviewed systematically. To be included, studies must have compared an intervention with substantial early signs content (at least half of the intervention components could be categorized as early signs focused) to one or more other treatments, in samples meeting diagnostic criteria for schizophrenia or a related psychotic disorder. Additionally, details of the study must have been published in English, with relapse and/or hospitalization included as outcomes and participants followed up for at least 6 months.

A computer database search of *PsychINFO*, *Embase*, *Medline*, *Cochrane Central Register of Controlled Trials* and *Cochrane Database of Systematic Reviews* was conducted using the following search terms and logic[1]: (intervention$ OR treatment$ OR therap$) AND (early sign$ OR prodrom$ OR targeted OR self$management OR warning sign$ OR intermittent) AND (schizophreni$ OR psycho$) AND (relapse$ OR $admi$ OR $hospital$ OR decompensation$). Once replications were removed, this resulted in 770 hits, 722 of which could be excluded on the basis of information contained in the title and abstract and a further 19 of which were excluded on the basis of the full text article. This resulted in 15 eligible studies being identified, with 14 secondary papers reporting on the same studies. The reference lists of these and of earlier reviews of early signs interventions (Birchwood & Spencer, 2001; van Meijel, van der Gaag, Kahn, & Grypdonck, 2004) were examined, yielding a further two eligible studies, giving a total of 17 studies eligible for inclusion in the systematic review.

Early signs interventions involve identifying and monitoring an individual's early signs of relapse and putting in place preventative plans to be acted upon when early signs are detected. For the purposes of this review, studies evaluating early signs interventions will be grouped according to the content of the preventative action plans. Thus, the intervention studies will be examined as follows: firstly early signs interventions involving targeted psychological input (n = 1); secondly, relapse prevention packages which combine early signs monitoring with several relapse prevention techniques (n = 4); thirdly interventions involving short term medication changes that are contingent on the emergence of early signs (targeted medication; n = 12).

4.2. Targeted psychological interventions

Only one study was identified that evaluated an early signs intervention in which targeted psychological therapy formed the main component of clients' preventative action plans (Gumley et al., 2003). In this open randomized controlled trial, 'relapse prone' participants with a diagnosis of schizophrenia or a related disorder were allocated to a targeted cognitive behavioral therapy (CBT) early signs intervention (n = 72) or usual treatment (n = 72). During an initial engagement and formulation phase, those in the early signs treatment arm worked with a clinical psychologist to identify their personal early signs of relapse as well as key beliefs that may accelerate the relapse process. Early signs monitoring was then aided by an idiosyncratic early signs monitoring questionnaire (Tait et al., 2002), which the participant completed by post on a fortnightly basis. If the participant reported an increase in their early signs during the 1 year follow up phase, an intensive course (2–3 sessions per week) of relapse prevention focused CBT was delivered until early signs had returned to baseline levels.

Both the initial formulation and the targeted therapy were based on the authors' Interacting Cognitive Subsystems (ICS) model of psychosis relapse (Gumley & Power, 2000; Gumley, White, & Power, 1999). Following Birchwood (Birchwood, 1995), the ICS model conceptualizes dysphoric early signs (e.g. anxiety, depression, insomnia) as responses to internal or external events that resemble the early stages of previous episodes. Once relapse is initiated in this way, the ICS model proposes that the interlock between higher order implicational meaning (e.g. self as failure; others as critical; relapse as uncontrollable) and moment-by-moment propositional meaning (e.g. if I avoid then I'll feel better; if I had a job then people would like me) produces strong affective responses which accelerate relapse. Thus, during the targeted CBT phase of the intervention, the service user and therapist work together to address key beliefs and assumptions that are thought to be accelerating relapse. Relevant cognitive, behavioral and physiological consequences are also addressed as appropriate.

In terms of treatment outcomes in the randomized controlled trial, significantly fewer people relapsed in the early signs intervention (18%) than in usual treatment (35%) during the 1 year follow up period. Hospital admissions were also less likely in the early signs intervention group (15%) than usual treatment (26%), although this was only significant when baseline variables were controlled for. Those in the intervention group made significant improvements in terms of positive, negative and general symptoms and functioning compared to the control group.

The study provides preliminary evidence that early signs interventions using targeted CBT may have positive impacts on outcomes in relapse prone individuals. However, the study had a major methodological weakness in that those assessing relapse were not blind to treatment allocation. Furthermore, unless clinicians judged that a relapse might be occurring, assessments were carried out at wide intervals (12, 26 and 52 weeks), meaning that some relapses may not have been detected. Until the result is replicated in studies with regular, masked assessment of relapse it is difficult to draw any firm conclusions.

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[1] '$' is the truncation symbol which allows substitution of any string of zero or more characters into the search term.

Although methodologically weak, this study is notable in two respects. Firstly, it is interesting to note the positive effect of targeted CBT in this study (Gumley et al., 2003), given the lack of relapse prevention benefits found in other CBT intervention studies. Meta-analyses indicate that non-targeted CBT does not appear to reduce relapse rates in those with psychosis (Lynch, Laws, & McKenna, 2010; Pilling et al., 2002), although a planned further analysis (Dunn et al., 2012) of a recent randomized controlled trial (Garety et al., 2008) did show a treatment effect in a subgroup of participants receiving 'full' CBT compared to a suitably generated control group. Secondly, as already highlighted, this is the only study to date to evaluate an early signs intervention in which the main component of preventative action plans was a complex psychological intervention, in this case CBT. The psychological model on which the intervention is based is particularly interesting since early signs are regarded as potentially having a causal role in the relapse process rather than just being inert indicators that relapse is occurring. Although further empirical work is needed to test this hypothesis, it ought to be borne in mind by those designing early signs interventions. If early signs are more than just inert relapse indictors, activities such as early signs monitoring may actually be unhelpful in some cases since they encourage service users to be hyper-vigilant to small changes in their mental state.

The targeted CBT approach required intensive therapy from highly trained therapists, which may make its application to the majority of clients in routine settings unlikely. Other interventions have used a number of lower-level psychosocial components such as stress management techniques, crisis problem solving and increased supportive visits. These multi-component early signs interventions are likely to be more widely available since they can be delivered by less specialized clinicians. The effectiveness of such interventions in decreasing relapse is therefore of interest; studies evaluating this are reviewed in the next section.

4.3. Multi-component early signs interventions

The use of multi-component interventions, delivered by a range of mental health workers, is already fairly widespread in clinical practice. It is surprising, therefore, that only four studies evaluating such interventions were identified in literature searches and eligible for the review. The design and outcomes of these studies are summarized in Tables 2 and 3.

All four studies compared an early signs intervention, delivered in the context of psycho-education, to usual treatment (Herz et al., 2000; Lee et al., 2010; Stenberg, Jaaskelainen, & Royks, 1998; van Meijel, Kruitwagen, van der Gaag, Kahn, & Grypdonck, 2006). In each case, participants in the active treatment condition were taught to identify and monitor early signs and to manage these with a preventative action plan. These action plans contained a number of preventative strategies, including crisis problem solving, increased supportive therapy visits, stress management, help seeking and short term medication increases. Some interventions contained other psycho-educational content in addition to early signs aspects of the treatment, for example: background information regarding psychosis (van Meijel et al., 2006); advice on coping with persistent symptoms and avoiding alcohol and street drugs (Stenberg et al., 1998); information about depot medication and the benefits of medication adherence (Lee et al., 2010).

In three studies, a relative or other social contact was involved where possible (Herz et al., 2000; Lee et al., 2010; van Meijel et al., 2006). The intervention was delivered individually in two cases (Lee et al., 2010; van Meijel et al., 2006) and via patient and multi-family groups in one case (Herz et al., 2000). Service user intervention sessions ranged from weekly (Herz et al., 2000) to fortnightly (Lee et al., 2010), with family sessions held fortnightly (Herz et al., 2000; Lee et al., 2010). Stenberg et al. (1998) gave no information whether the intervention was delivered in an individual or group context,

the frequency of sessions or whether the participant's family was involved.

4.3.1. Outcomes

4.3.1.1. Relapse. Relapse was assessed in three of the studies (Herz et al., 2000; Lee et al., 2010; van Meijel et al., 2006) (see Table 3). Two of these demonstrated a significant advantage of the early signs intervention over usual treatment in terms of the proportion of patients relapsing (Herz et al., 2000; Lee et al., 2010). In the remaining study (van Meijel et al., 2006) the percentage of patients relapsing in the usual treatment group was roughly double that in the early signs group but the difference was not statistically significant. The study had assumed that 15% and 40% would relapse in early signs and usual treatment groups respectively. Given that the actual relapse rates were lower than this, it is likely that the study was underpowered.

It is worth noting that the difference in relapse between the treatment groups in Lee et al.'s (2010) study was only marginally significant (p = 0.06) when medication adherence was controlled for. This highlights the difficulty, encountered in many early signs intervention studies, of isolating the specific effect of the early signs intervention. The additional psycho-educational content of Lee et al.'s (2010) intervention included information on the benefits of medication adherence. It is possible that this was more of an 'active ingredient' in the intervention than early signs components. Alternatively, it could be argued that taking part in an early signs intervention may have increased adherence by increasing alliance with clinical staff (van Meijel, van der Gaag, Kahn, & Grypdonck, 2002a, 2002b).

4.3.1.2. Hospital admission. Only two studies assessed hospital admission. Herz et al. (2000) demonstrated a significantly lower 18 month hospitalization rate in the early signs group than usual treatment. Stenberg et al. (1998) found no difference in the number of hospitalizations per person but they did find a difference in the proportion of time spent in hospital, with the mean duration being 17.5 weeks longer for usual treatment than in the early signs intervention group. However, the results of the latter study are of questionable validity due to its extensive methodological weaknesses. These are discussed in detail below.

4.3.2. Methodological considerations

As mentioned, Stenberg et al.'s (1998) study had a number of methodological weaknesses. Details of early signs monitoring and dropout rates were not provided and, although all participants met DSM-III (Diagnostic and Statistical Manual of Mental Disorders, Third Edition) criteria for schizophrenia, other inclusion or exclusion criteria were not reported. Participants were not randomly allocated to treatment groups; instead a matched control group was used. Although the length of follow up was matched between treatment groups it was not the same for all participants, varying between 1 and 2 years. Finally only hospitalization outcomes were reported, rather than relapse per se, and those assessing outcomes were not blind to treatment allocation. Given these methodological problems, little weight can be attached to the results. The remaining three studies were more robust. Methodological details regarding early signs monitoring, relapse assessment and potential sampling and dropout biases are discussed below.

4.3.2.1. Early signs monitoring. As discussed earlier (Section 3), methods of identifying and monitoring early signs are likely to determine the accuracy of relapse prediction and the effectiveness of early signs interventions in preventing relapse. It is therefore worth outlining the different definitions of early signs, and the methods for monitoring these, that were used in the remaining three studies (Herz et al., 2000; Lee et al., 2010; van Meijel et al., 2006). In two cases the Early Signs Questionnaire was used (Herz et al., 2000; Lee et al., 2010) and

Table 2
Design and methods of studies comparing multi-component early signs interventions to usual treatment.

Study	Treatment groups	Length of follow up	Design	Early warning signs definition and monitoring	Relapse definition and assessment	Diagnostic inclusion criteria	Notable exclusion criteria	Dropout rate
Stenberg et al. (1998)	Early signs intervention (n = 29) Treatment as usual (n = 18)	1–2 years	Open, non-randomized study	Not reported	Relapse not defined; hospital admission used instead	Schizophrenia (DSM-III)	Not reported	Not reported
Herz et al. (2000)	Early signs intervention (n = 41) Treatment as usual (n = 41)	1.5 years	Single blind RCT	Defined using the Early Signs Questionnaire, including dysphoric and attenuated psychotic symptoms; weekly monitoring with help from clinician, family or others	PANSS positive item ≥5 and GAS ≤ 30; assessed by the researcher when the clinician reported that patient had early signs	Schizophrenia or schizoaffective (DSM-III); relapse prone (≥1 admission in past 3 years or ≥2 during lifetime)	Severe substance dependence requiring detoxification or hospital admission	ESI = 12% TAU = 15%
van Meijel et al. (2006)	Early signs intervention (n = 51) Treatment as usual (n = 44)	1 year	Open RCT	Early signs systematically inventoried and rated on 3 point scale (normal, light-moderate, severe); weekly monitoring with help from nurse and family	Psychotic symptom increase (nurse and psychiatrist consensus) and CGI score ≥6, lasting at least 7 days	Schizophrenia or a related psychotic disorder (DSM-IV); stable (all PANSS positive items ≤4)	Substance abuse with serious communication problems	ESI = 22% TAU = 5%
Lee et al. (2010)	Early signs intervention (n = 24) Treatment as usual (n = 33)	2 years	Single blind, non-randomized study	Defined using the Early Signs Questionnaire; monitored fortnightly by the psychiatrist based on the service user's self report on the Early Signs Questionnaire	PANSS positive item ≥5 and GAF ≤ 30, assessed every 3 months and when early signs detected. Alternatively, if the service user dropped out of the study, family report used	Schizophrenia or schizoaffective (DSM-IV); stable for past 4 weeks	Severe substance dependence requiring detoxification or hospital admission	Excluded post hoc: ESI = 13%TAU = 24%

Notes: RCT = randomized controlled trial; PANSS = Positive and Negative Syndrome Scale; GAS = Global Assessment Scale; CGI = Clinical Global Impression; GAF = Global Assessment of Functioning; DSM = diagnostic and statistical manual of mental disorders; ESI = early signs intervention; TAU = treatment as usual.

in one case service users' personal early signs were systematically inventoried and rated on a three point scale (normal, light-moderate or severe) in terms of their severity (van Meijel et al., 2006). Early signs monitoring appears to have been appropriately systematic in all three studies, with a range of potential early signs considered, including both non-psychotic and psychotic symptoms.

For an early signs intervention to be effective, it is important that monitoring is frequent enough that any emerging signs are spotted sufficiently early for preventative action to be taken. In the studies in question, monitoring was either carried out weekly with the assistance of the therapist and a relative or friend (Herz et al., 2000; van Meijel et al., 2006), or fortnightly on the basis of the participant's self-report (Lee et al., 2010). This is in line with Birchwood et al.'s (2000) suggestion that monitoring should be at least fortnightly.

4.3.2.2. Relapse assessment. It is important that randomized controlled trials evaluating relapse prevention interventions provide a clear operational definition of relapse. Since previous reviews have noted that relapse is often poorly defined in randomized controlled trials (Bebbington et al., 2006; Falloon et al., 1983; Nuechterlein et al., 2006), Gleeson, Alvarez-Jimenez, Cotton, Parker, and Hetrick (2010) drew together six key recommendations with regard to its measurement: relapse assessment should be carried out at least monthly, by trained assessors who are blind to treatment condition; an objective rating instrument should be used, and both severity and duration thresholds should be specified a priori; inter-rater reliability should be reported. In order to evaluate their methodological quality, the three studies in question will be evaluated against these criteria.

In all three studies (Herz et al., 2000; Lee et al., 2010; van Meijel et al., 2006), severity criteria were specified a priori, objective rating instruments were used to assess relapse and the assessor was either blind to the treatment status of the participant (Herz et al., 2000; Lee et al., 2010) or their rating was checked by a blind assessor (van Meijel et al., 2006). On the other hand, only one study defined the duration of a relapse (van Meijel et al., 2006), only one assessed inter-rater reliability (Lee et al., 2010) and in all three studies the relapse severity criteria allow subjective judgment to be used in some or all cases.

Regarding the latter point, one study (Lee et al., 2010) assessed relapse status based on a family member's report for participants who had dropped out of assessments. The other studies relied on a clinician's judgment that psychotic symptoms had increased (van Meijel et al., 2006) or that early signs had emerged (Herz et al., 2000) in order to initiate assessments of relapse. The latter in particular may differentially bias the number of relapses reported in the two groups, since early signs are presumably more likely to be detected in the early signs intervention group than usual treatment. If so, relapses are less likely to be detected in the usual treatment group, which may bias the results in favor of this group.

4.3.2.3. Sampling and dropout. Participants in all three studies (Herz et al., 2000; Lee et al., 2010; van Meijel et al., 2006) met DSM-III or DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for schizophrenia, schizoaffective or a related psychotic disorder. Additionally, two studies specified that individuals must be 'clinically stable' (Lee et al., 2010; van Meijel et al., 2006), although this criterion was only adequately defined in one case (van Meijel et al., 2006), and Herz et al. (2000) specified that individuals should be relapse prone. All three studies excluded some potential participants on the basis of their substance use, a common exclusion criterion in clinical trials but nevertheless one which reduces external validity.

Dropout from treatment was not systematically higher in one particular trial arm. However, eleven participants were removed from Lee et al.'s (2010) study post hoc due to not visiting the hospital regularly in the first three months of treatment (3 from active treatment; 8 from usual care). This may have biased the results in favor of usual

Table 3
Relapse and admission outcomes in studies comparing multi-component early signs interventions to treatment as usual.

Study	Proportion relapsing		Proportion admitted		Comparison of early signs intervention and treatment as usual					
	Early signs intervention	Treatment as usual	Early signs intervention	Treatment as usual	Early signs intervention	Treatment as usual	Proportion relapsing	Proportion admitted	Number of admissions per person	Total time spent in hospital
Stenberg et al. (1998)	–	–	–	–	–	–	–	–	n.s.	**ESI < TAU**
Herz et al. (2000)	7/41 (17%)	14/41 (34%)	9/41 (22%)	16/41 (39%)	**ESI < TAU**	**ESI < TAU**	–	–	–	–
van Meijel et al. (2006)	5/38 (13%)	11/42 (26%)	–	–	n.s.	–	–	–	–	–
Lee et al. (2010)	5/21 (24%)	12/25 (48%)	–	–	**ESI < TAU**[a]	–	–	–	–	–

Notes: results are for the full study follow-up period (as detailed in Table 2); statistically significant results (p < 0.05) are indicated in bold type; n.s. = not statistically significant at p = 0.05; ESI = Early Signs Intervention; TAU = Treatment as usual; n.s. = not significant at p = 0.05.
[a] Marginal effect (p = 0.06) when medication adherence co-varied.

care since more non-compliant participants were removed from this group. It is also worth noting that, unlike in the other two studies (Herz et al., 2000; van Meijel et al., 2006), Lee et al. (2010) did not assign participants randomly between the two treatment conditions, a weakness that may introduce considerable bias.

4.3.3. Conclusions regarding multi-component early signs interventions

The limited data from the four reviewed studies suggests that multi-component early signs interventions may be effective in improving relapse and hospitalization outcomes in those with psychosis. However, it was difficult to isolate the specific effect of the early signs components from other components of the intervention. Furthermore, one of the studies (Stenberg et al., 1998) was methodologically poor and, although more robust, the other studies were not without limitations. Nevertheless, most of the limitations of the latter studies are likely to have biased the results in favor of treatment as usual (TAU) rather than the intervention. Thus the positive findings regarding the effectiveness of multi-component early signs interventions on relapse outcomes may still be valid, although methodologically robust trials with larger samples are required before definitive conclusions may be drawn.

4.4. Targeted medication

In the early signs intervention studies reviewed above, clients' preventative action plans included short term medication increases as well as other preventative strategies. The following section concerns early signs interventions with preventative action plans consisting of medication changes *only*, without other components. In a targeted medication intervention participants are monitored for early signs of relapse and medication is given contingent on the emergence of early signs. Studies reviewed below evaluate the targeted medication strategy both as an addition to maintenance medication and as an alternative to maintenance medication. In the latter case (intermittent targeted medication), maintenance medication is reduced to zero during the pre-intervention phase and early warning signs monitoring takes place on the background of no medication.

4.4.1. Identified studies

4.4.1.1. Maintenance plus targeted medication (1 study). Searches of the literature identified only one study which evaluated the effectiveness of targeted medication as an *addition* to usual maintenance medication (Marder et al., 1994). All participants (n = 80) in this double blind randomized controlled trial were maintained on a low dose depot medication and monitored weekly with regards to their three most common early warning signs. If early signs emerged, the participant was randomly allocated to receive either a targeted oral antipsychotic (n = 17) or targeted placebo (n = 19). There was no significant advantage of the active targeted medication over placebo at two year follow up in terms of time to a 'symptom exacerbation' (mild relapse).

When data from the second year were examined separately, participants taking the active drug survived significantly longer without a symptom exacerbation than those taking placebo. However, the latter finding only emerged in exploratory post hoc analysis so cannot be given weight without subsequent replication. It is also worth emphasizing that a low dose of maintenance medication was used as the comparison treatment, and other studies have demonstrated this to be inferior to moderate doses in terms of relapse outcomes (Schooler et al., 1997). The addition of targeted medication to moderate doses of maintenance medication may have even less of an effect than its addition to low dose medication did in Marder et al.'s (1994) study. On the other hand, their study was small, with less than twenty people in each trial arm. In a larger replication, a beneficial effect of targeted medication might be demonstrated for the whole follow up period rather than just in the second year.

4.4.1.2. Intermittent targeted medication (11 studies). Meta-analysis has demonstrated the superiority of ongoing maintenance antipsychotic medication over placebo in the prevention of relapse (Johnstone, Crow, Frith, Carney, & Price, 1978; Leucht et al., 2003; NICE, 2009). However, the side effects of both first and second generation antipsychotics are prevalent and often burdensome (Leucht et al., 2009). This has prompted a search for alternative medication strategies that prevent relapse as effectively as maintenance medication but involve less exposure to antipsychotics, reducing the total side effect burden.

One proposed alternative, intermittent targeted medication, involves service users' antipsychotic medication being withdrawn and then targeted medication being used if ongoing monitoring reveals early signs of relapse. Intermittent targeted medication strategies have been compared to maintenance medication in eleven randomized controlled trials of varying size and methodological quality (Carpenter & Heinrichs, 1983; Carpenter, Heinrichs, & Hanlon, 1987; Carpenter et al., 1990; Gaebel et al., 2011; Herz et al., 1991; Jolley, Hirsch, Morrison, McRink, & Wilson, 1990; Pietzcker et al., 1993; Ruskin, Bland, & Feldman, 1994; Schooler et al., 1997; Wiedemann et al., 2001; Wunderink et al., 2007). Tables 4–6 provide details of the methods (Tables 4 and 5) and main outcomes (Table 6) of these studies, which are reviewed in detail below.

Although all eleven studies in Tables 4–6 essentially test whether intermittent targeted medication is a viable alternative to continuous maintenance medication, there is some variety in the treatments being compared. The studies can be grouped as follows in terms of treatment comparisons:

a) Maintenance + targeted medication vs. intermittent targeted medication + individual and family psychosocial support (Carpenter & Heinrichs, 1983; Carpenter et al., 1987)
b) Maintenance + targeted medication vs. intermittent targeted medication alone (Carpenter et al., 1990; Gaebel et al., 2011; Herz et al., 1991; Jolley et al., 1990; Ruskin et al., 1994; Schooler et al., 1997)
c) Maintenance treatment alone vs. intermittent targeted medication alone (Pietzcker et al., 1993; Wiedemann et al., 2001; Wunderink et al., 2007).

Since treatment effects do not appear to vary systematically with respect to the exact treatment comparison (a, b, or c above), the eleven studies will be discussed together. In terms of type and dosage of medication, the majority of studies left this at the clinician's discretion (Carpenter & Heinrichs, 1983; Carpenter et al., 1990; Gaebel et al., 2011; Pietzcker et al., 1993; Wiedemann et al., 2001), with loose guidance given in some cases (Carpenter et al., 1987; Herz et al., 1991; Wunderink et al., 2007) and three studies specifying the particular medication to be prescribed (Jolley et al., 1990; Ruskin et al., 1994; Schooler et al., 1997). Again, this did not appear to vary systematically with outcome.

4.4.2. Outcomes: relapse, hospital admission, medication side effects and first episode subgroup analysis

4.4.2.1. Relapse. In all but one (Herz et al., 1991) study in which relapse was assessed, the proportion of patients relapsing during the full follow-up period was significantly lower for those prescribed a moderate dose of maintenance medication (with or without targeted medication) than for those receiving only targeted medication (Table 6). It is likely that Herz and colleagues' study was simply underpowered to detect a difference between groups, given the relatively small sample size and the fact that the proportion of patients relapsing was numerically lower in the maintenance treatment than intermittent targeted treatment. Furthermore, as with the other reviewed studies, Herz and colleagues did find that *time to relapse* was significantly longer in maintenance than the intermittent targeted medication condition (Herz et al., 1991).

As well as comparing maintenance medication (n = 122) to intermittent targeted medication (n = 127), one of the reviewed studies (Pietzcker et al., 1993) compared these strategies to intermittent crisis medication (n = 115), in which medication is given only when an individual has begun to relapse. There were significant differences between the three groups in terms of the proportion of participants relapsing in two years (23%, 49% and 63% respectively) and time to relapse. Thus, although not as effective as maintenance medication, intermittent targeted medication appears to perform better than intermittent crisis medication in terms of relapse outcomes.

4.4.2.2. Hospital admission. In terms of the effect of treatment on admission to hospital, the results were more varied across the studies (Table 6). In five of the studies there was no significant treatment effect when comparing patients treated with maintenance medication (with or without targeted medication) to those treated with intermittent targeted medication (with or without psychosocial intervention) (Carpenter & Heinrichs, 1983; Carpenter et al., 1987; Herz et al., 1991; Ruskin et al., 1994; Wunderink et al., 2007). The other four studies showed a significant advantage of maintenance medication, either in terms of the proportion of patients admitted (Pietzcker et al., 1993), time to admission (Carpenter et al., 1990), or both of these (Jolley et al., 1990; Schooler et al., 1997).

There are three possible alternative, but not mutually exclusive, explanations as to why the effects for hospitalization appear to be weaker than relapse effects. Firstly, assessment of hospitalization was unlikely to have been blind, since this is extremely difficult to achieve in practice. Thus clinicians may bias the number of patients admitted by being more reluctant to admit those in the intermittent medication group, despite them relapsing more often. Secondly, it is possible that those treated with intermittent medication experienced less severe relapses than those prescribed maintenance medication. Thus, although intermittently treated patients met criteria for relapse more often, these relapses were not always severe enough to warrant hospitalization. Thirdly, it is worth noting that the largest two studies (Pietzcker et al., 1993; Schooler et al., 1997) did find a difference in hospitalization. It is possible that some of the smaller studies were simply underpowered to detect differences between the groups. Since

all of the reviewed studies are 'non-inferiority' studies, they should have been powered to detect a small difference between treatments (D'Agostino, Massaro, & Sullivan, 2003) but this was rarely the case.

4.4.2.3. Medication side effects. In all studies, patients treated with maintenance medication were prescribed a significantly higher total dose of medication over the course of the study than those in intermittent targeted medication conditions (Table 6). However, in all but one study (Jolley et al., 1990) this did not translate into a difference in side effects reported by the two groups. There are several possible explanations for this. Firstly, it may be that the amount of medication actually taken did not differ between groups, since only information on the doses prescribed is given without an indication of levels of adherence, which may have differed between groups. Secondly, the assessments used may not have been sufficiently sensitive to changes in side effects. Thirdly, frequent titration of medication in intermittent treatment may have meant that some side effects were higher in the short term counteracting the effect of reducing the dosage. Even if this was the case, intermittent medication may still have benefits in terms of reducing long term side effects such as tardive dyskinesia, a syndrome of extra-pyramidal symptoms which is proportional to the total lifetime antipsychotic dose (Kane, Woerner, Borenstein, Wegner, & Lieberman, 1986; Kane, Woerner, & Lieberman, 1988). Finally, as with the other outcomes, there may have been insufficient power to detect a difference.

4.4.2.4. First episode subgroup analysis. In an exploratory re-analysis of Pietzcker et al.'s (1993) study, Gaebel et al. (2002) hypothesized that an intermittent targeted medication strategy may be more effective for preventing relapse among service users with first episode psychosis than for those who had already experienced multiple episodes. The authors of the re-analysis concluded that this was indeed the case. However, only the results from the per-protocol analysis, rather than the intention-to-treat analysis, actually supported this conclusion. Furthermore, these analyses were all post hoc and participants had not been randomized with respect to whether they had experienced one or a number of episodes of psychosis. Little weight can therefore be attached to the authors' conclusion.

However, the result prompted two further trials, directly comparing maintenance and intermittent targeted treatment strategies in purely first episode samples (Gaebel et al., 2011; Wunderink et al., 2007). As already discussed the proportion of patients relapsing in these studies was significantly higher in the groups receiving intermittent targeted (43%; 19%) rather than maintenance (21%; 0%) medication. Contrary to Gaebel et al.'s (2002) suggestion, it appears that intermittent targeted medication is not as effective in first episode patients as maintenance medication, in line with findings among those who have experienced multiple episodes.

4.4.3. Methodological considerations

On the whole, in the reviewed studies, intermittent targeted treatment was not an effective alternative to maintenance medication. However, before reaching a firm conclusion in this regard, the methods used in the eight studies are discussed below.

4.4.3.1. Early signs monitoring. Optimal methods for defining and monitoring early signs were rarely used in the reviewed studies (see Table 4). Some did not use a structured assessment of early signs (Carpenter & Heinrichs, 1983; Carpenter et al., 1987; Carpenter et al., 1990; Herz et al., 1991; Ruskin et al., 1994; Wiedemann et al., 2001); others monitored early signs too infrequently (Pietzcker et al., 1993) or failed to specify monitoring frequency (Schooler et al., 1997); some were poor in both these respects (Jolley et al., 1990; Wunderink et al., 2007). Had better early signs monitoring been employed, intermittent targeted medication may have fared better when compared to maintenance medication.

Table 4

Design and methods of studies comparing maintenance and intermittent targeted medication strategies (see Table 5 for details of relapse definitions).

Study	Treatment groups (numbers randomized)	Length of follow up	Design	Early warning signs definition and monitoring	Inclusion criteria	Notable exclusion criteria	Treatment dropout
Carpenter and Heinrichs (1983)	Maintenance + targeted (n = 27) Intermittent targeted + psychosocial support (n = 14)	0.5 years	Open RCT	EWS not defined; weekly monitoring with assistance of case manager and family	Schizophrenia or schizoaffective (RDC)	None	Not reported
Carpenter et al. (1987)	Maintenance + targeted (n = 21) Intermittent targeted + psychosocial support (n = 21)	2 years	Open RCT	EWS not defined; weekly monitoring with assistance of case manager and family	Schizophrenia or schizoaffective (RDC)	Drug or alcohol abuse	M = 43% I = 33%
Carpenter et al. (1990)	Maintenance + targeted (n = 59) Intermittent targeted (n = 57) *Both groups also received psychosocial support*	2 years	Single blind RCT	Dysphoria, insomnia or attenuated psychotic symptoms; monitored weekly with assistance of case manager and family	Chronic schizophrenia; recent psychotic episode	Recent alcoholism or clinically significant drug abuse	M = 19% I = 51%
Jolley et al. (1990)	Maintenance + targeted (n = 27) Intermittent targeted (n = 27)	2 years	Double blind RCT	Neurotic or dysphoric symptoms lasting ≥2 days and causing distress; assessed monthly; family involved	Schizophrenia (DSM-III); free from florid symptoms ≥ 6 months	None	M = 33% I = 56%
Herz et al. (1991)	Maintenance + targeted (n = 51) Intermittent targeted (n = 50) *Both groups also received psychosocial support*	2 years	Double blind RCT	Increase in psychotic symptoms, PAS role functioning or PAS non-psychotic symptom item for ≥ 1 day; monitored weekly in group therapy; family involved	Schizophrenia or schizoaffective (RDC); stable for ≥ 3 months	Alcohol or drug dependence; past un-cooperativeness with treatment; EWS in pre-study washout period	M = 27% I = 62%
Pietzcker et al. (1993)	Maintenance (n = 122) Intermittent targeted (n = 127) Crisis medication (n = 115)	2 years	Open RCT	EWS defined using items from the Early Signs Questionnaire; monthly assessment	Schizophrenia or schizoaffective (RDC); schizophrenia (ICD-10)	Drug and alcohol use	M = 43% I = 60% C = 67%
Ruskin et al. (1994)	Maintenance + targeted (n = 17) Intermittent targeted (n = 14)	1 year	Double blind RCT	Pre-defined BPRS item increase and clinician judges intervention necessary *or* insomnia; assessed fortnightly; family involved	Schizophrenia or schizoaffective (DSM-III); over 50 years of age; recent stability (no recent hospital admissions)	Alcohol abuse; Mini Mental State Examination <21	M = 29% I = 50%
Schooler et al. (1997)	Medium dose maintenance + targeted (n = 107) Low dose maintenance + targeted (n = 107) Intermittent targeted (n = 100) *All participants were also randomized to supportive or applied family therapy (3 × 2 design)*	2 years	Double blind RCT	EWS defined using modified Early Signs Questionnaire plus idiosyncratic signs; nurse assessed but frequency not specified	Schizophrenia or schizoaffective (DSM-III); ≥4 h per week contact with a relative	Substance dependence; those not successfully stabilized on study medication	Not reported
Wiedemann et al. (2001)[a]	Maintenance (n = 42)[a] Intermittent targeted (n = 45)[a] *Both groups also received behavioral family management*	1.5 years	Open RCT	Selected items from the Early Signs Scale plus idiosyncratic early signs; assessed at each contact (weekly, fortnightly or monthly); family involved	Schizophrenia or schizoaffective (ICD-10/RDC); ≥10 h per week contact with a relative	Substance abuse/ dependence	M = 36% I = 47%
Wunderink et al. (2007)[b]	Maintenance (n = 63)[b] Intermittent targeted (n = 68)[b]	2 years	Single blind RCT	Not specified	First episode of schizophrenia or a related psychotic disorder	None	M = 0% I = 6%
Gaebel et al. (2011)	Maintenance + targeted (n = 29) Intermittent targeted (n = 30) *Participants were randomized to receive either a targeted antipsychotic or targeted benzodiazepine (2 × 2 design)*	1 year	Open RCT	Increased severity of psychotic symptom items or items from the modified Early Signs Questionnaire, or judged to be at high risk of relapse by the clinician; assessed fortnightly	First episode of schizophrenia; recent stability (no relapse in the past year)	Substance dependence; non-attendance of appointments in the past year	M = 34% I = 73%

Notes: in some trials with a single blind design, those assessing *relapse* were not blind to treatment allocation; RCT = randomized controlled trial; EWS = early warning signs; PAS = Problem Appraisal Scale; BPRS = Brief Psychiatric Rating Scale; RDC = research diagnostic criteria; DSM = diagnostic and statistical manual of mental disorders; ICD = International Classification of Diseases; M = maintenance; I = intermittent; C = crisis medication.

[a] Note that the exact number initially randomized to each group is not consistently reported in the original paper.

[b] 26 further participants were randomized but their distribution between the trial arms was not reported.

Table 5
Definition and assessment of relapse outcomes in studies comparing maintenance and intermittent targeted medication strategies.

Study	Relapse definition	Severity specified a priori?	Duration specified a priori?	Objective rating instrument(s) used?	Blind assessment?	Inter-rater reliability assessed?	Frequency of assessment
Carpenter et al. (1990)	Worse functioning and/or symptoms, judged jointly by the therapist and research psychiatrist; weekly BPRS	No	No	Yes but clinician judgment too	No	No	Weekly
Jolley et al. (1990)	Re-emergence of florid psychotic symptoms or hospital admission due to symptom deterioration	No	No	No	Yes	No	Monthly
Herz et al. (1991)	Increase in PAS psychotic symptom item to moderate/severe and GAS score ≤ 30 for more than 2 days or by consensus judgment, e.g. if admitted to hospital	Yes	Yes	Yes but clinician judgment too	Yes	No	Monthly
Pietzcker et al. (1993)	BPRS psychosis factor change ≥ 10; GAS change ≤ 20; CGI change ≥ 6	Yes	No	Yes	No	Yes	Monthly; fortnightly if unstable
Ruskin et al. (1994)	Clinician judgment that significantly worse and an increase of ≥3 points per item or ≥5 points total on certain BPRS items	Yes	No	Yes but clinician judgment too	Yes	No	Monthly
Schooler et al. (1997)	≥2 point increase on any BPRS psychosis item to moderate or greater for 2 monthly ratings or at 1 monthly rating and at rescue medication assessment	Yes	Yes	Yes	Yes	No	Monthly; weekly when receiving targeted medication
Wiedemann et al. (2001)	Increase of ≥2 points to a score of ≥6 on any BPRS psychosis item	Yes	No	Yes	No	No	Monthly for first year, then 6 months later
Wunderink et al. (2007)	Clinical deterioration for ≥ 1 week causing a management change; reported by clinician and research team confirmed (any PANSS positive item ≥ 5)	Yes	Yes	Yes	Yes	Yes	When clinicians reported clinical deterioration
Gaebel et al. (2011)	Increase in PANSS positive score >10 and decrease in GAF >20 and CGI-change ≥ 6	Yes	No	Yes	No	Yes (PANSS)	Fortnightly

Notes: BPRS = Brief Psychiatric Rating Scale; PAS = Problem Appraisal Scale; GAS = Global Assessment Scale; CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale; GAF = Global Assessment of Functioning.

Regular early signs monitoring requires commitment and motivation from the participating service user. In all of the studies reviewed in Table 4 the participant was assisted in the monitoring process, either by a clinician, a significant other or via group therapy sessions. Nevertheless, there was some variety in the level of psychosocial support offered to participants. For example, Jolley et al. (1990) acknowledge that their study involved much less support than previous studies (e.g. Carpenter et al., 1987). The extent of assistance provided is likely to influence the quality of the early signs monitoring and thus the effectiveness of an intervention in predicting and preventing relapse. The level of support may also affect relapse outcomes more directly, potentially confounding the specific effect of the early signs intervention.

4.4.3.2. Definitions of relapse. In Table 5, nine studies are evaluated against Gleeson et al.'s (2010) recommendations regarding relapse assessment. The remaining two studies (Carpenter & Heinrichs, 1983; Carpenter et al., 1987) provided hospital admission data only

rather than assessing relapse specifically. None of the nine studies were entirely robust in their definition and assessment of relapse. Some relied on clinical opinion rather than using an objective rating scale; in some cases those assessing relapse were not blind to the treatment condition (Gaebel et al., 2011; Pietzcker et al., 1993); some assessed relapse insufficiently frequently (Schooler et al., 1997; Wunderink et al., 2007); some had a combination of these and other flaws (Carpenter et al., 1990; Herz et al., 1991; Jolley et al., 1990; Ruskin et al., 1994; Wiedemann et al., 2001).

Although most studies stated that participants must be 'clinically stable' prior to commencing the intervention (often assessed during an initial stabilization phase of the study) this criterion was rarely (e.g. Ruskin et al., 1994; Schooler et al., 1997) well defined. Similarly, despite participants in several studies (Gaebel et al., 2011; Herz et al., 1991; Jolley et al., 1990; Pietzcker et al., 1993) continuing the intervention after an initial relapse, only one study (Gaebel et al., 2011) defined specific remission criteria to indicate when these participants became eligible for a further relapse.

Table 6
Relapse, admission and medication outcomes in studies comparing maintenance and intermittent targeted medication strategies.

Study	Proportion relapsing		Proportion admitted		Comparison of maintenance and intermittent medication					
	Maintenance medication	Intermittent medication	Maintenance medication	Intermittent medication	Proportion relapsing	Time to relapse	Proportion admitted	Time to admission	Medication (total dose)	Side effects
Carpenter and Heinrichs (1983)	–	–	2/27 (7%)	4/14 (29%)	–	–	n.s.	–	**M > I**	–
Carpenter et al. (1987)	–	–	9/20 (45%)	11/21 (52%)	–	–	n.s.	–	**M > I**	–
Carpenter et al. (1990)	–	–	21/58 (36%)	30/57 (53%)	–	–	n.s.	**M > I**	**M > I**	–
Jolley et al. (1990)	3/25 (12%)	12/24 (50%)	2/27 (7%)	8/27 (30%)	**M < I**	**M > I**	**M < I**	**M > I**	**M > I**	**M > I**
Herz et al. (1991)	8/51 (16%)	15/50 (30%)	8/51 (16%)	12/50 (24%)	n.s.	**M > I**	n.s.	n.s	**M > I**	n.s.
Pietzcker et al. (1993)	28/122 (23%)	62/127 (49%)	29/122 (24%)	47/127 (37%)	**M < I**	**M > I**	**M < I**	n.s	**M > I**	n.s.
Ruskin et al. (1994)	2/17 (12%)	7/14 (50%)	2/17 (12%)	3/14 (21%)	**M < I**	**M > I**	n.s.	n.s	**M > I**	n.s.
Schooler et al. (1997)	–	–	27/107 (25%)	46/100 (46%)	–	**M > I**	**M < I**	**M > I**	**M > I**	–
Wiedemann et al. (2001)	1/24 (4%)	8/23 (35%)	–	–	**M < I**	**M > I**	–	–	**M > I**	n.s.
Wunderink et al. (2007)	13/63 (21%)	28/65 (43%)	–	–	**M < I**	–	–	–	–	n.s.
Gaebel et al. (2011)	0/23 (0%)	4/21 (19%)	–	–	**M < I**	**M > I**	–	–	**M > I**	n.s.
Total proportion (2 year follow up studies, n = 7)	52/261 (20%)	117/266 (44%)	96/385 (25%)	154/382 (40%)						

Notes: results are for the full study follow-up period (as detailed in Table 4); statistically significant results (p < 0.05) are indicated in bold type; n.s. = not statistically significant at p = 0.05; M = maintenance group; I = Intermittent group.

4.4.3.3. Sampling considerations. All the study samples consisted of participants with a diagnosis of schizophrenia, schizoaffective, or a related psychotic disorder (see Table 4) and, on the whole, standard diagnostic criteria were used. In some studies, additional inclusion criteria were specified, such as recent stability (Gaebel et al., 2011; Herz et al., 1991; Jolley et al., 1990; Ruskin et al., 1994), a recent psychotic episode (Carpenter et al., 1990) or regular contact with a relative (Schooler et al., 1997; Wiedemann et al., 2001). The latter criterion reduces the external validity of the study to some extent, since not all of those with psychosis have family contact and those who do may respond better to psychological interventions (Garety et al., 2008).

Similarly some of the study exclusion criteria led to relatively unimpaired samples being selected for participation in the study. Several studies excluded those with drug or alcohol abuse (Carpenter et al., 1987; Carpenter et al., 1990; Gaebel et al., 2011; Herz et al., 1991; Pietzcker et al., 1993; Ruskin et al., 1994; Schooler et al., 1997; Wiedemann et al., 2001) which, as discussed earlier, may reduce external validity. Herz et al. (1991) further selected their sample by excluding those who had displayed "uncooperativeness with treatment in the past" and those who could not be successfully withdrawn from medication during an eight week pre-study washout period.

In addition to the sampling bias inherent in the study inclusion and exclusion criteria, further bias may have been introduced by the unequal dropout from the different treatment conditions. Where reported, dropout tended to be higher in intermittently treated groups. However, most studies did not report whether those dropping out of treatment did so before or after relapse. Thus it is unclear whether dropout biased the results. Nevertheless, the consistently higher dropout rate in intermittent treatment across studies may indicate that this strategy is less acceptable to service users than maintenance medication or perhaps less feasible to adhere to in the long term.

4.4.4. Conclusions regarding targeted medication

Intermittent targeted medication appears to be less effective than moderate dose maintenance medication in terms of relapse. Results for hospitalization were more mixed but overall they suggested that maintenance medication was superior. Examination of the methodological characteristics of these studies indicated that early signs monitoring was rarely optimal. Improved accuracy of such assessments may improve the effectiveness of intermittent targeted medication. Furthermore, assessment of relapse itself was not always robust and study samples tended to be highly selected meaning that the results may not be generalizable to all service users with psychosis.

In the single study that evaluated a combined maintenance and targeted medication strategy, there was limited evidence that this improved relapse outcomes. Further studies investigating this specific question are warranted.

4.5. Early signs intervention studies: general conclusions

Studies evaluating early signs interventions using targeted psychological therapy (n = 1), multi-component relapse prevention techniques (n = 4) and targeted medication (n = 12) have been reviewed. Although targeted CBT appeared to have a positive effect on relapse outcomes compared to usual treatment, relapse assessment was not blind, so a full replication of this study is needed before firm conclusions can be drawn. Studies evaluating multi-component early signs interventions suggest that these may be effective in relapse prevention, although one study was very methodologically poor and a second was considerably underpowered.

On the whole, intermittent targeted medication was less effective than moderate dose maintenance medication, although early signs assessment was noted to be poor in these studies. Only one study evaluated the effect of adding targeted medication to maintenance medication. There was some indication from post hoc analyses that this may have improved relapse outcomes but no firm conclusions

can be drawn unless this finding is replicated. It is interesting to note that early signs monitoring methods were most robust in the targeted CBT and multi-component studies. Other methodological considerations notwithstanding, this may have contributed to the better outcomes in these compared to the targeted medication studies.

5. Suggested complementary paradigm for relapse prediction: basic symptoms

5.1. The basic symptoms concept

5.1.1. The need for accurate assessment of relapse risk

There was some indication from the studies reviewed in the previous section that the addition of early signs interventions to usual care may improve relapse outcomes. As emphasized throughout this review, accurate assessment of relapse risk is of key clinical importance. Improving such assessment is likely to improve early signs based relapse prevention interventions. A number of early signs assessments were evaluated in Section 3 in terms of their predictive validity. They tended to be modestly predictive of relapse but could nevertheless be further improved. It has been suggested that the addition of 'basic symptoms' to conventional early signs assessments may improve prospective evaluation of relapse risk (Birchwood, 1995; Gross & Huber, 2010; Sass & Parnas, 2001; Schultze-Lutter, 2009).

5.1.2. What are basic symptoms?

Basic symptoms are subtle, sub-clinical, qualitative disturbances in one's experience of oneself and the world, for example: changes in perceptions, such as increased vividness of color vision; mild subjective cognitive problems; impaired tolerance to certain stressors; changes in emotional reactivity; subjective difficulty finding or understanding common words (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). The basic symptom concept is widely used in German clinical practice, having originated in clinical observations by German psychiatrists during the 1950s (Gross & Huber, 2010). Similar concepts can be found in Anglo-American (Chapman, 1966; Varsamis & Adamson, 1971) and Danish (Parnas, Handest, Jansson, & Saebye, 2005) psychiatry where phenomenological methods have been used to investigate early experiences of psychosis (Schultze-Lutter, 2009).

In the psychiatric literature, basic symptoms have been regarded as the most immediate symptomatic manifestations of the underlying neurobiological disruption thought to occur during psychosis (Schultze-Lutter, 2009). However, it may also be possible to conceptualize basic symptoms in the context of *psychological* models of psychosis development (e.g. Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001) and relapse (e.g. Birchwood, 1995; Gumley et al., 1999). For example, Garety and colleagues propose that, in a pre-disposed individual, a sufficiently stressful trigger may lead to 'anomalous experiences' which, along with emotional changes, precipitate a search for meaning that eventually results in psychotic symptoms (Garety et al., 2001). One might argue that these anomalous experiences are the same phenomena as the basic symptoms described in the German psychiatric literature. Similarly, as has already been discussed, two existing cognitive models of psychosis relapse (Birchwood, 1995; Gumley et al., 1999) propose that dysphoric early signs (e.g. anxiety, depression, insomnia) are responses to internal or external events resembling the early stages of previous episodes. Birchwood (1995) gives several examples of these 'internal events' that echo previous descriptions of basic symptoms.

5.1.3. Could basic symptoms be used as predictors of relapse?

Basic symptoms have been anecdotally reported at all stages of psychosis, including prior to a first episode, during acute psychosis, during remission and prior to relapse (Gross, 1989; Huber & Gross, 1989). Several authors have suggested that, like early signs, basic symptoms could be used to assess relapse risk in those with

established psychosis (Birchwood, 1995; Gross & Huber, 2010; Sass & Parnas, 2001; Schultze-Lutter, 2009). In the remainder of this review, evidence from the literature in support of this suggestion will be evaluated.

Several characteristics of basic symptoms suggest that they may be particularly suitable for early signs monitoring. It has been suggested that, unlike later attenuated or frank psychotic symptoms, service users tend to recognize basic symptoms as disturbances in their experience rather than real phenomena (Schultze-Lutter, 2009). It is also notable that basic symptoms are state rather than trait phenomena, meaning that individuals can distinguish fluctuating basic symptoms from their normal condition (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). Moreover, anecdotally most service users find them an irritation and are not reluctant to discuss them (Schultze-Lutter, 2009).

Only one study, to date, has formally investigated whether basic symptoms occur prior to relapse in those with established psychosis. In a retrospective design, a remitted psychosis sample (n = 27) was compared to a remitted depression sample (n = 24) in terms of their experiences of basic symptoms prior to their most recent episode of their mental illness (Bechdolf, Schultze-Lutter, & Klosterkötter, 2002). Basic symptoms were assessed using the Bonn Scale for the Assessment of Basic Symptoms (BSABS) semi-structured interview. Whilst there was some overlap between the prodromal symptoms experienced by the two groups, there were also significant differences. The 'increased emotional reactivity' cluster of the BSABS was significantly more common and the 'disorders of emotion and affect' cluster significantly less common in the psychosis group compared to the depression group. In terms of individual items, four basic symptoms were identified as being significantly more frequent in the psychosis group (feeling overwhelmed by stimuli; changes in perceived intensity or quality of acoustic stimuli; decrease in facial expression, intonation and communication gestures; unstable ideas of reference) and nine as more frequent in the depression group (decreased resilience and energy; decreased drive, activity, vitality and initiative; changes in mood and emotional responsiveness; decrease in positive emotional responsiveness towards others; decrease in the need for contact with others; increased self-reflection; decreased spontaneity; difficulties concentrating; difficulties holding things in mind for seconds; difficulties holding things in mind for less than half an hour).

This single study is not without limitations such as its retrospective design and small sample, all of whom were recruited via a university hospital. Furthermore, only those with the paranoid subtype of schizophrenia who had no residual symptoms were included in the psychosis sample, limiting the generalizability of the findings. It is clear that further studies with more robust methodology are needed. However this study provides preliminary evidence that an increase in certain basic symptoms may occur prior to relapses of psychosis, and that the latter can be distinguished from developing depressive episodes.

Since the empirical literature directly investigating basic symptoms as predictors of relapse is currently so sparse, one must refer to other aspects of the basic symptoms literature. Evidence from two other key lines of research will be reviewed. Firstly, in Section 5.2, studies concerning the frequency of basic symptom experiences in those with psychosis, compared with other diagnostic groups and the general population, will be reviewed. Secondly, in Section 5.3, studies assessing the validity of basic symptoms as predictors of a first episode of psychosis will be examined. Conclusions will be drawn regarding the suggestion that basic symptoms could be used, alongside conventional early signs, to assess relapse risk in those with psychosis.

5.2. Specificity of basic symptoms to psychotic disorders

A number of studies have compared levels of basic symptoms in people with psychosis to other groups. Three general conclusions can be drawn from this extensive literature. Firstly, basic symptoms

appear to be much less prevalent in the general population than in those with psychosis. Only 30% of adolescents from a general population sample reported at least one basic symptom, compared to 97% in a sample diagnosed with first episode psychosis (Meng et al., 2009). The mean number of basic symptoms reported in total and on each BSABS subscale was also significantly higher in the first episode sample (Meng et al., 2009). Similarly, only 21% (158/758) of a randomly selected general population sample, who were interviewed by telephone, reported at least one basic symptom (Schultze-Lutter, Michel, & Schimmelmann, 2012). However, it is interesting to note that in healthy controls from the general population, cannabis users had a higher total number of basic symptoms than non-cannabis users (Korver et al., 2010).

Secondly, those with psychosis can be distinguished from groups with other psychiatric diagnoses in terms of total and/or subscale BSABS scores. This appears to be the case for affective disorders, such as depression (Klosterkötter, Ebel, Schultze-Lutter, & Steinmeyer, 1996; Schultze-Lutter et al., 2007) or bipolar disorder (Parnas, Handest, Saebye, & Jansson, 2003), as well as for those with other diagnoses such as obsessive–compulsive disorder, anxiety, eating disorders, personality disorders and organic mental disorders (Klosterkötter et al., 1996; Meng et al., 2009; Parnas et al., 2005).

Finally, it is notable that levels of basic symptoms do not appear to differ between those with various schizophrenia spectrum diagnoses, including schizotypal disorder (Parnas et al., 2005; Peralta & Cuesta, 1998). Furthermore, in terms of basic symptoms, those defined as at risk of psychosis could not be distinguished from those with psychosis (Schultze-Lutter, Ruhrmann et al., 2007; Schultze-Lutter, Steinmeyer, Ruhrmann, & Klosterkötter, 2008) and there was no difference between cannabis users and non-cannabis users in an at risk sample (Korver et al., 2010).

In summary, basic symptoms appear to be more common in people with psychosis, or at risk of psychosis, than in other groups, including those with other psychiatric diagnoses and individuals from the general population. If this were not the case, one might assume that basic symptoms were merely fluctuations in everyday experience and so of little value in predicting relapse. Since basic symptoms appear to be relatively specific to those diagnosed with psychosis, it is plausible that changes in basic symptoms may be related to changes in psychotic symptoms. As has already been discussed, there is preliminary evidence that basic symptoms occur prior to relapses of psychosis (Bechdolf et al., 2002). Relevant aspects of the somewhat larger research literature on the occurrence of basic symptoms prior to first episodes of psychosis are reviewed below.

5.3. Basic symptoms in individuals at risk of a first episode of psychosis

Retrospective reports from large samples suggest that the majority of patients experience signs of deterioration for several years prior to developing a first episode of psychosis (Hafner et al., 1998; Yung, 2007). This deterioration may include one or more of the following: basic symptoms, non-specific symptoms (e.g. sleep disturbances, increased worrying), attenuated psychotic symptoms, or brief intermittent psychotic symptoms (Gross, 1969; Hafner et al., 1998). The evaluation of these signs as predictors of first episode psychosis has become the focus of much research. It is hoped that accurate early detection of first episode psychosis will allow early treatment, potentially preventing or postponing psychosis onset and improving outcomes (McGorry et al., 2009).

Whilst the Anglo-American-Australian literature has examined certain 'ultra high risk' criteria including attenuated psychotic symptoms, the predictive value of *basic symptoms* has been a key focus in the German early psychosis literature (Fusar-Poli et al., 2012; Klosterkötter, Schultze-Lutter, Bechdolf, & Ruhrmann, 2011). Klosterkötter and colleagues conducted two studies investigating whether the presence of at least one basic symptom at baseline predicted conversion to first

episode psychosis during an 8 year (Klosterkötter, Schultze-Lutter, Gross, Huber, & Steinmeyer, 1997) or 10 year follow up period (Klosterkötter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001). In both studies, participants were help seeking individuals who had been referred to the university psychiatric department for diagnostic clarification. In the first study participants were identified retrospectively (Klosterkötter et al., 1997), whereas the second study had a fully prospective design (Klosterkötter et al., 2001).

Regarding the question of whether having at least one basic symptom predicted conversion to first episode psychosis, high sensitivity (100% and 98%, respectively) and moderate specificity (45% and 59%) were reported (Klosterkötter et al., 1997, 2001). In both studies, additional analyses examined which BSABS subscales and individual items were most predictive of conversion to psychosis. The earlier study (Klosterkötter et al., 1997) identified three subscales (cognitive, motor and perceptual disturbances) and 24 individual items that were significantly more likely to occur in people who went on to develop psychosis than in those who did not. In the later Cologne Early Recognition study (Klosterkötter et al., 2001), the BSABS cluster measuring cognitive, linguistic, perceptual and motor disturbances was by far the best predictor of conversion to psychosis. Ten individual items with sensitivity over 25% and specificity over 70% were also identified.

Based on these observations, two criteria for identifying an initial prodrome of psychosis have been developed as part of the SPI-A (Schizophrenia Proneness Index, Adult Version) assessment: the 'CODGIS' (Cognitive Disturbances) and 'COPER' (Cognitive–Perceptive basic symptoms) criteria (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). To meet CODGIS criteria, an individual must display at least two of the nine basic symptoms in the cognitive disturbances cluster and have a total SPI-A score of ≥3 within the last three months. To meet COPER criteria, an individual must have at least one of the ten identified basic symptoms, with a SPI-A score of >3 in the last three months and first occurrence at least twelve months ago.

In the Cologne Early Recognition study (Klosterkötter et al., 2001), sensitivity figures for COPER and CODGIS were 87% and 67%, respectively, and specificity figures were 54% and 83%. Yearly rates of conversion to psychosis for those meeting the criteria in this study are given in Table 7. Conversion rates during the first year were replicated in a further prospective study (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer, & Ruhrmann, 2007), although lower conversion rates were found in the second year (Table 7). The authors suggest that this may be due to the high dropout rate, since dropouts were treated as non-convertors in the analysis. Unlike the Cologne Early Recognition study, other measures of predictive accuracy, such as sensitivity and specificity, cannot be evaluated since all participants had basic symptoms at baseline.

It is important to emphasize that COPER and CODGIS were defined post hoc in the Cologne Early Recognition study. Thus, replication of the study's sensitivity and specificity figures in another prospective

study, in which the criteria are specified a priori, is needed. Nevertheless, it is useful to see that basic symptoms appear to be modestly effective predictors of first episode psychosis. The sensitivity and specificity of CODGIS and COPER are comparable to those of the Anglo-American-Australian 'ultra high risk' criteria in predicting first episode psychosis in help seeking samples (Fusar-Poli et al., 2012; Klosterkötter et al., 2011). Various authors (Ruhrmann et al., 2010; Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007; Schultze-Lutter et al., 2012; Simon et al., 2006) have suggested that it may be useful to combine the two approaches to predicting first episode psychosis. This has been partly motivated by an assumption in the literature that basic symptoms appear earlier than attenuated symptoms in those at risk of psychosis (Olsen & Rosenbaum, 2006; Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007; Yung, 2007). Thus, in some studies and early detection centers, the two approaches have been combined as early and late at risk states. However, the relative timescales of the two have only recently been empirically examined (Schultze-Lutter, Ruhrmann, Berning, Maier, & Klosterkötter, 2010).

Patients admitted to hospital for a first episode of psychosis (n = 138) were retrospectively interviewed using the ERIraos (Early Recognition Instrument based on the Instrument for the Retrospective Assessment of the Onset of Schizophrenia), which assesses experiences prior to first episode psychosis (Schultze-Lutter et al., 2010). Only two participants reported no prodromal symptoms, with other participants reporting pre-first episode experiences as follows: unspecific symptoms (n = 126); basic symptoms (n = 101); attenuated psychotic symptoms (n = 91). The relative timescales of these were examined. Contrary to expectations, the average onset of attenuated psychotic symptoms occurred earlier (3.9 years prior to admission) than the onset of basic symptoms (3.2 years), a non-significant difference. However, the early average onset of attenuated psychotic symptoms was mainly accounted for by 'magical thinking' and 'paranoia', and for people who had one of these symptoms and a basic symptom the basic symptom always occurred earlier.

Although the timing of symptoms was not significantly different in statistical terms, in clinical terms the fact that basic symptoms occurred earlier may still be important. This may be particularly relevant in the context of relapse prediction. Even if basic symptoms only occurred a few days earlier than conventional early signs of relapse, this extra time may be crucial in enabling preventative action to be taken to avoid a relapse. Any investigation of whether basic symptoms occur before relapse should compare the timing of these relative to early signs. This and other suggestions regarding future research directions are discussed in detail below.

6. Conclusions and future directions

The current model for assessing relapse risk uses conventional early signs such as dysphoric symptoms and attenuated psychotic symptoms. Retrospective and prospective studies suggest that these early signs appear in the few weeks before relapse, and that they have modest predictive validity. Studies that included a wide variety of possible early signs in monitoring assessments appeared to achieve the most sensitive assessment of relapse risk. This implies that early signs assessments may be further improved by the addition of other hypothesized predictors of relapse such as basic symptoms. This is of key interest since existing studies evaluating early signs interventions have shown mixed results. On the whole, targeted medication was not an effective alternative to moderate dose maintenance medication. However, there was some evidence that the *addition* of a multi-component early signs intervention or a targeted psychological intervention to usual care may improve relapse outcomes.

Evidence in support of the hypothesis that basic symptoms predict relapse was outlined in Section 5 of the review. Certain characteristics of basic symptoms make them plausible as relapse predictors. There

Table 7
Proportion of participants meeting CODGIS or COPER criteria who converted to psychosis.

		Percentage converting to psychosis			
		1st year	2nd year	3rd year	≥4th year
CODGIS	Klosterkötter et al. (2001)	24%	22%	15%	18%
	Schultze-Lutter, Klosterkötter et al. (2007)	25%	8%	–	–
COPER	Klosterkötter et al. (2001)	20%	17%	13%	15%
	Schultze-Lutter, Klosterkötter et al. (2007)	23%	9%	–	–
	Schultze-Lutter, Klosterkötter et al. and Schultze-Lutter, Ruhrmann et al. (2007)				

is preliminary evidence that increases in basic symptoms occur prior to relapses and considerable evidence that basic symptoms are relatively specific to psychosis and predictive of first episodes of psychosis. Nevertheless, the empirical literature directly investigating basic symptoms as predictors of relapse is currently extremely sparse so there are a number of potential avenues for future research.

Firstly, building on the preliminary work by Bechdolf et al. (2002), we suggest that a further retrospective study, using qualitative methods, would be valuable. In-depth interviews with those who have recently experienced a relapse of psychosis, exploring the pre-relapse period in detail, would allow one to map out events, feelings and other experiences commonly occurring at this stage. These may include basic symptoms and conventional early warning signs. It would be valuable to identify which of these pre-relapse experiences tend to be most salient to service users, which occur most commonly and what are the relative timescales of these experiences prior to relapse.

Secondly, a longitudinal prospective study would be essential in order to validate any signs derived from retrospective studies and to examine which combinations of these are most predictive, analogously to the 'ultra high risk' literature (e.g. Ruhrmann et al., 2010). Technology such as adapted smart phones or internet based questionnaires (Kimhy, Myin-Germeys, Palmier-Claus, & Swendsen, 2012) could be used to collect repeated measures of the proposed signs and relapse outcomes. Key lines of enquiry would include: whether, individually or in combination, the range of proposed signs (e.g. basic symptoms, dysphoric symptoms and attenuated psychotic symptoms) predict relapse better than chance; the sensitivity and specificity of the proposed signs as predictors of relapse; the relative timing of the proposed signs during the pre-relapse period; the optimum combination of the proposed signs for predicting relapse.

Thirdly, it would be important to design and validate a measure that would be suitable for ongoing monitoring of the proposed signs such as basic symptoms. A brief, self-report measure would be most practical for regular monitoring, both for research purposes and in clinical practice, as it could be administered quickly, with limited training and via various means (e.g. face to face, or by post, internet or text message). The development of such a measure could be informed by qualitative interview data as well as by existing semi-structured interview measures of basic symptoms (e.g. SPI-A; Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007). The measure's preliminary psychometric properties would need to be assessed. For example a psychosis sample's self reported basic symptoms could be compared to: their basic symptoms assessed using the SPI-A (convergent validity); their own self report at a later time point (retest reliability); and to a non-psychosis sample's self report (discriminant validity).

Finally, in the longer term, the value of using a greater range of signs (e.g. basic symptoms) to assess relapse risk in the context of early signs interventions would need to be evaluated in a well-controlled manner. In Section 4 of the current review, existing studies evaluating the addition of early signs interventions to usual care were critically appraised. A number of methodological limitations were noted, such as non-blind assessment of relapse, lack of power and difficulty isolating the specific effect of the early signs components of the intervention. On this basis we recommended that further, methodologically robust trials should be conducted so that definitive conclusions may be drawn regarding the value of early signs interventions for relapse prevention. If the proposed additional signs (e.g. basic symptoms) are shown to be good predictors of relapse, they should be included in the early signs monitoring strategies used in such intervention studies.

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