Definitions of relapse in trials comparing antipsychotic maintenance with discontinuation or reduction for schizophrenia spectrum disorders: A systematic review

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ABSTRACT

Introduction: Avoidance of relapse is the main aim of long-term antipsychotic treatment in schizophrenia, yet how 'relapse' is defined in trials is not well-known.
Methods: We conducted a systematic review of definitions of relapse in trials of continuous antipsychotic treatment compared with discontinuation, intermittent treatment or dose reduction for people with schizophrenia spectrum disorders.
Trials were identified from previous Cochrane reviews and a new search. The quality of relapse definitions was rated in terms of reliability and clinical relevance and associations between quality of definitions and trial characteristics and outcome were explored.
Results: We identified 82 reports of 81 trials which employed 54 different definitions of relapse. There were 33 definitions in the 35 trials published since 1990, with recent trials employing complex definitions often involving alternative criteria. Only ten primary definitions of relapse required the presence of psychotic symptoms in all cases, and only three specified this in combination with a measure of overall severity or functional decline. Only two definitions specified a duration longer than two days. Relapse definitions were rated as showing good reliability in 37 trials, but only seven showed good clinical relevance. Six trials with definitions that were both reliable and clinically relevant were slightly longer, but did not differ from remaining trials in other characteristics and overall or relative risk of relapse.
Conclusions: Antipsychotic trials define relapse in numerous different ways, and few definitions consistently reflect suggested indications of a clinically significant relapse.

1. Introduction

Current recommendations for long-term antipsychotic treatment for people with schizophrenia and related disorders are based on trials that report lower rates of relapse with continuous antipsychotic medication compared with alternative strategies such as discontinuation or intermittent treatment (Leucht et al., 2012). What constitutes a 'relapse' is not straightforward, however, and previous reviews have highlighted the lack of consensus on how to define or measure it (Burns et al., 2000; Eisner et al., 2013; Falloon et al., 1983; Gleeson et al., 2010; Nuechterlein et al., 2006; Olivares et al., 2013; San et al., 2015). Different criteria may lead to different estimates of relapse, which may also vary between groups in trials of antipsychotics, if definitions are broad and likely to include situations that reflect withdrawal effects of antipsychotics rather than the re-emergence of an underlying psychotic condition(Dilsaver and Alessi, 1988).

Two Delphi panel exercises on clinicians' conceptions of relapse highlighted the complexity of the issue, but showed agreement that relapse was typically characterised by recurrence of psychotic symptoms and significant changes in functioning or behaviour (Burns et al., 2000; San et al., 2015). Other recommendations include a minimum duration of seven days, use of criteria based on rating scales or consumption of health resources and distinguishing relapses in people who have complete remission from those with chronic symptoms (Bebbington et al., 2006; Gleeson et al., 2010; San et al., 2015).

Whereas previous reviews of relapse definitions in research have focused on observational studies or trials in first episode

populations, little attention has been paid to how relapse is defined in the majority of randomised trials that form the evidence base for current practice. The current review aims to describe the definitions of relapse that have been employed in randomised controlled trials of antipsychotic maintenance treatment compared with placebo, intermittent treatment or guided discontinuation or reduction involving people with schizophrenia or psychosis. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

2. Methods

2.1. Eligibility criteria

Studies were included if they were randomised trials involving a comparison between antipsychotic maintenance treatment and placebo, gradual antipsychotic withdrawal or reduction or intermittent treatment for people with schizophrenia or schizophrenia-like psychoses. Included studies had to report 'relapse' or a similar outcome such as 'deterioration,' 'treatment failure' or hospitalisation. Studies not published in the Latin based alphabet were excluded.

2.2. Searches

We assessed the eligibility of all studies included in recent Cochrane reviews of antipsychotic maintenance treatment (Leucht et al., 2012) and intermittent antipsychotic treatment (Sampson et al., 2013). In addition, we conducted an additional search of MEDLINE, EMBASE and PsycINFO from June 2011 until October 2018 (date of last search) to identify studies published since publication of the previous reviews. The search employed the following combination of terms derived from these reviews:(cessation* OR withdraw* OR discontinu* OR halt* OR stop* OR drug?holiday* OR drug?free* OR drop-out* OR dropout* OR drop out OR rehospitalis* OR relaps* OR maintain* OR maintenance* OR recur* OR intermittent*) AND schizophr* OR schizoaff*.

2.3. Data extraction

Data on definitions of relapse, trial characteristics and relapse rates were extracted. Information on how relapse was assessed was extracted where documented, including time intervals between assessments and whether additional assessments were performed at the time of relapse.

2.4. Analysis and quality rating

The different criteria used to define relapse were tabulated and definitions used in studies conducted prior to 1990 were contrasted with those used in trials published since this year.

We evaluated the quality of relapse definitions in individual trials in terms of both reliability and clinical relevance. Trials were rated as showing good reliability if they: used objective criteria like hospitalisation, resumption of antipsychotics, precisely specified rating scale changes or if they provided precise descriptions of other methods used, such as would be easily replicable. These requirements had to apply to all relapse criteria included in the trial.

The clinical relevance of relapse definitions was based on findings of previous studies of clinicians' understandings of relapse which suggest the presence of positive psychotic symptoms and changes in functioning or behaviour (Burns et al., 2000; San et al., 2015). Hence relapse criteria were considered clinically relevant if they specified an increase in positive psychotic symptoms (according to any measure) and global, behavioural or functional

deterioration of at least a moderate degree, measured by rating scales or clinical evaluation, for all cases of relapse. Trials that defined relapse solely as hospitalisation or 'necessary' hospitalisation were also included.

Two authors (JM and TS) independently rated trial quality initially using the above criteria. Discrepancies were resolved by discussion and consensus to produce final ratings. Trials in which relapse definitions showed good reliability and clinical relevance were compared with other trials, exploring differences in year of publication, sample size, trial duration, number of criteria used in relapse definitions, reported blinding of assessors, reported pharmaceutical industry sponsorship and overall risk and relative risk of relapse. All analyses were conducted using SPSS version 22. To calculate relative risk, we applied a continuity correction of 0.5 in order to include data from trials in which there were zero relapses in one group.

3. Results

Eighty two analyses of 81 trials that provided a definition of relapse or deterioration were included, involving a total of 11,437 participants (see Fig. 1). Two follow-ups of the same trial cohort were included as distinct analyses since they employed different definitions of relapse (Wunderink et al., 2013; Wunderink et al., 2007).

3.1. Study characteristics

Table 1 summarises the design and characteristics of the included studies (detailed in the Supplementary information). Most consisted of placebo-controlled antipsychotic withdrawal trials. There were a total of eight trials that evaluated intermittent treatment (one in parallel with placebo-controlled withdrawal), and 11 fixed or flexible dose reduction studies.

3.2. Definitions of relapse

Among the 82 trial reports, there were a total of 54 different primary definitions of relapse (see Supplementary information). Table 2 shows the most common criteria used in in trials published before and since 1990. Many trials, especially more recent ones, used combinations of different criteria. There were 25 different primary definitions of relapse among the 47 trials published before 1990. For the 35 trials published since 1990, there were 33 different primary definitions. Four trials also provided one or more secondary definitions of relapse.

Among studies published before 1990, resumption of antipsychotics was the most common criteria, followed by clinician or assessor judgement. Ten trials provided no account of how relapse was defined. All trials published from 1990 provided some definition and definitions were increasingly likely to include criteria derived from rating scales. Definitions became increasingly complex over time. The mean number of alternative criteria for the primary definition of relapse across the whole sample of trials was 2.1 (s.d. 2.2), and it was strongly correlated with year of publication (Spearman's rho 0.60, $p < 0.001$). Studies published before 1990 used a mean of 1.1 (s.d. 0.80) definitions per study, compared with a mean of 3.5 (s.d. 2.7) per study for trials published in 1990 or later. Trials published since 2000 frequently involved four or five alternative criteria of relapse; the highest being ten.

No trials distinguished relapses among those participants who had experienced complete remission from those who had ongoing symptoms. A total of 16 reports specified a duration of relapse, although usually only for criteria involving increased symptoms. The specified minimum duration was 1 to 2 days in fourteen studies, with only two reports of the same trial specifying a longer
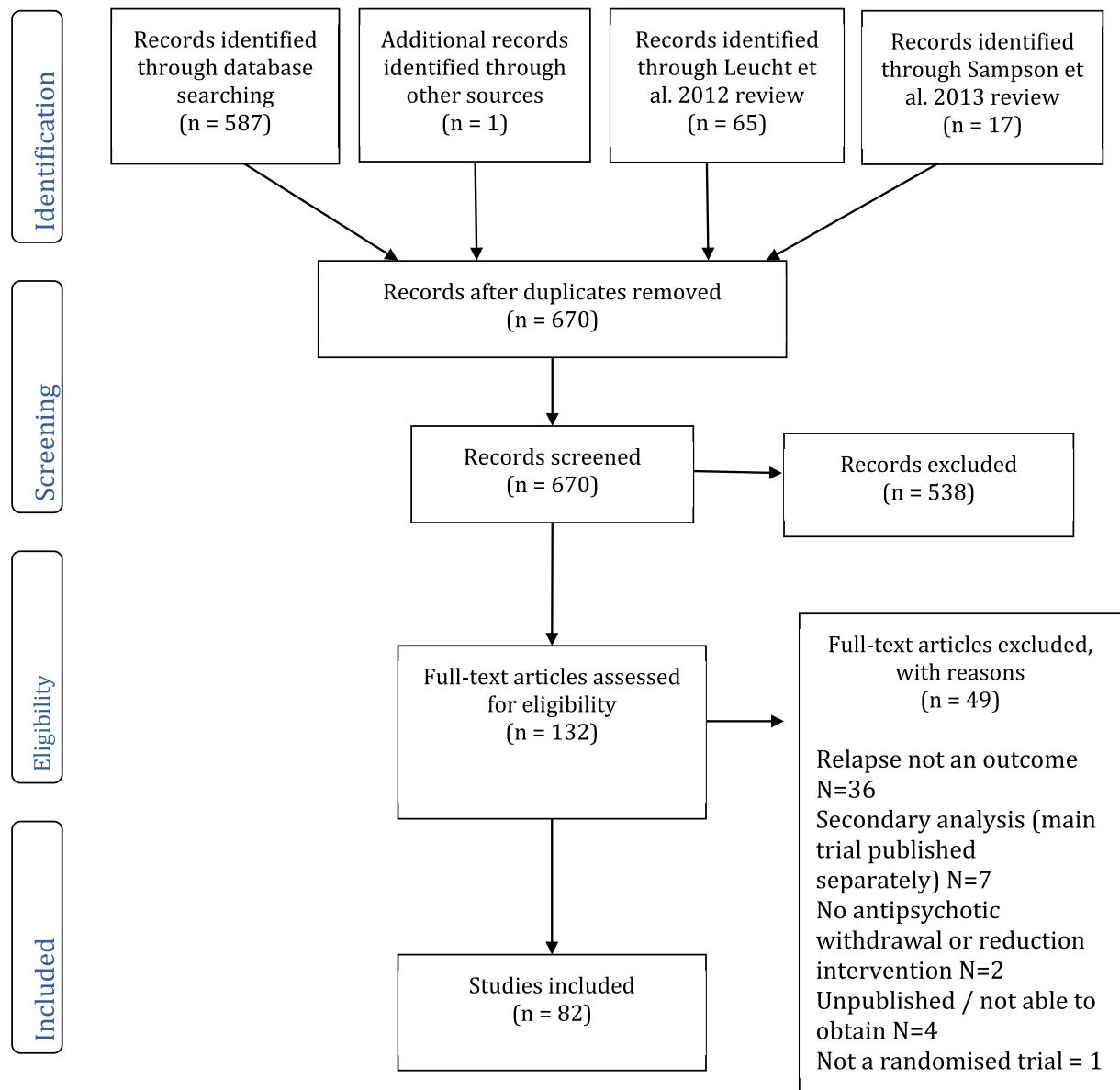
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

duration of at least 7 days (Wunderink et al., 2013; Wunderink et al., 2007).

There was considerable variation in the nature of criteria based on rating scales. The 23 studies that used the Positive and Negative Syndrome Scale (PANSS) in the primary definition, for example, used eighteen different sets of PANSS-based criteria (see Supplementary information). Specified levels of change in PANSS total scores varied from a 10 point increase to a 30 point or 30% increase, there was variation in individual items specified, and scores required on those items ranged from 3 (mild) to 6 (severe).

Although 27 trials included criteria specifying an increase in psychotic symptoms, primary definitions *required* an increase in at least one psychotic symptom in all participants defined as relapsed in only ten studies (12.2% of the total). Seven of these were published since 1990. Similarly, many recent studies used the Clinical Global Impressions (CGI) Severity (−S) or Improvement (−I) scales, but only three required change on this measure for all participants defined as relapsing. Moreover, thresholds varied between CGI-S of 3 (mildly ill) to CGI-S of 6 (severely ill) and CGI-I of 6 (much worse). Apart from hospitalisation, or 'necessary' or 'immanent'

hospitalisation, which was the sole primary definition of relapse in four studies, few of the definitions included evaluations of functioning or behaviour, or other measures that indicate tangible consequences of deterioration.

3.3. Quality of relapse definitions

In the initial rating exercise, the two raters agreed 93.9% of the time on reliability and 98.8% on clinical relevance. In the final ratings, 37 trials (45.1%) were rated as showing good reliability of relapse definition (Table 1), 19 of which were published since 1990 (54.3% of the 35 trials published since 1990). Seven trials (8.5%) specified definitions of relapse that indicated good clinical relevance, 4 published before 1990 and 3 since. Although ten studies included an increase in positive symptoms plus a measure of increased overall severity as a criterion of relapse, only three applied this definition to all cases of relapse (Chen et al., 2010; Gaebel et al., 2011; Pietzcker et al., 1993) and one of these trials specified that it had used 'liberal' thresholds, using CGI-S scores of 3 (mildly ill) and PANSS items scores of between 3 (mild) and 5

Table 1
Characteristics of included studies.

Trial characteristic	Number of studies (%) Total = 82
Design:	
Placebo controlled antipsychotic discontinuation	55 (67%)
Intermittent treatment	7 (9%)
Flexible dose reduction	5 (6%)
Fixed dose reduction	6 (7%)
Benzodiazepine substitution	1 (1%)
Open withdrawal	1 (1%)
Mixed	7 (9%)
Year of publication:	
1955−1969	14 (17%)
1970−1979	14 (17%)
1980−1989	19 (23%)
1990−2000	9 (11%)
2001−2018	26 (32%)
Region of origin:	
North America	33 (40%)
Europe	25 (31%)
Asia	9 (11%)
Africa	1 (1%)
Multi-region	13 (16%)
Not reported	1 (1%)
Setting:	
Inpatients	24 (29%)
Outpatients	39 (48%)
Mixed	9 (11%)
Not reported	10 (12%)
Participant diagnoses:	
Schizophrenia spectrum disorder	75 (91%)
First episode psychosis	6 (7%)
Mixed psychosis (including affective psychoses)	1 (1%)
Blinding of assessments reported:	
Yes	52 (63%)
No	30 (37%)
Pharmaceutical industry funding reported:	
Yes	26 (32%)
No	56 (68%)
Quality of relapse definition: reliability	
Good	37 (45%)
Poor or unknown	45 (55%)
Quality of relapse definition: clinical relevance	
Good	7 (9%)
Poor or unknown	75 (91%)
Trial characteristic	**Mean (s.d.)**
Sample size	139.7 (155.3)
Duration	11.6 (10.9)

(moderate severe) (Chen et al., 2010). Only six trials showed both good reliability and clinical relevance of the primary definition of relapse and four of these used hospitalisation as the sole relapse criterion (Carpenter et al., 1990; Carpenter et al., 1987; Gaebel et al., 2011; Hogarty et al., 1974; McCreadie et al., 1989; Pietzcker et al., 1993).

Comparisons indicated that the six trials with higher quality relapse definitions were twice as long as other trials (Table 3). There were no differences in other characteristics. Trials with high quality relapse definitions did not find different rates of overall relapse or relative risk of relapse compared with other trials. Trials with relapse definitions rated as reliable regardless of clinical relevance did not differ from other trials on trial characteristics or relapse measures. Trials with high clinical relevance of relapse definitions with or without high reliability showed a trend towards longer duration than other trials ($t = 1.87$; $p = 0.07$) and use of fewer relapse criteria (Wald test $p = 0.07$), but there were no other differences.

3.4. Assessment procedures

The frequency of routine assessments during which measures used to define relapse were completed was specified in 37 trials. In 22 of these, assessments were conducted at least once a month, and in 12 they were conducted every two weeks or more. Nineteen trials specified that additional assessments were done when a relapse was identified, and some others seem likely to have done this although it was not described. No publications discussed the potential difficulties of completing measures that require patient cooperation and response (like the PANSS) with people who are unwell.

Where rating scales were used to define relapse, they appear to have been administered during face to face interviews in all but one trial, which used a retrospective notes review to identify changes in PANSS positive item scores (Wunderink et al., 2013).

Among trials that used more than two alternative criteria for defining relapse and reported on which criteria were most frequently met, changes in overall rating scale scores, psychosis item scores and clinical judgement were the most commonly endorsed criteria, and hospitalisation and suicidal or aggressive behaviour were less frequently fulfilled (Durgam et al., 2016; Fu et al., 2015; Kane et al., 2011; Rui et al., 2014; Tandon et al., 2016). One study reported that most relapses were detected at routine assessments conducted every two weeks (Beasley et al., 2003). Five trials specified that 'prodromal' or non-psychotic symptoms were included in the primary definition of relapse (Kane et al., 1979;

Table 2
Definitions of relapse.

Type of definition	Published prior to 1990 ($n = 47$)		Published 1990 or later ($n = 35$)	
	Number (%) of studies using definition as part of primary definition of relapse	Number (%) of studies requiring this criteria (for all participants considered to have relapsed)	Number (%) of studies using definition as part of primary definition of relapse	Number (%) of studies requiring this criteria
Hospitalisation	6 (13%)	3 (6%)	15 (43%)	0
Resumption or increase in antipsychotics	18 (38%)	10 (21%)	5 (14%)	0
Increase or change in any other type of treatment (e.g. increased visits, other drugs, ECT)	6 (13%)	0	5 (14%)	0
Clinical judgement	17 (36%)	13 (28%)	2 (6%)	0
Increase in BPRS total score	0	0	3 (9%)	1 (3%)
Increase in PANSS total score	0	0	12 (34%)	0
Increase in BPRS psychosis factor score	0	0	5 (14%)	3 (9%)
Increase in any PANSS positive items or other specified items	0	0	20 (57%)	4 (11%)
Changes in CGI-I or CGI-S	0	0	18 (51%)	3 (9%)
Impact on functioning or behaviour	4 (9%)	1 (2%)	4 (11%)	3 (9%)
Increase in any positive symptom measure plus measure of overall severity, functioning or behaviour	0	0	9 (26%)	3 (9%)
Self-harm, suicide or suicidal ideation	0	0	14 (40%)	0
Violence to others or property or homicidal ideation	0	0	14 (40%)	0
Criteria not reported	11 (23%)	–	0	–

ECT electro convulsive therapy; BPRS Brief Psychiatric Rating Scale; PANSS Positive and Negative Syndrome Scale; CGI-I Clinical Global Impressions-Improvement; CGI-S Clinical Global Impressions-Severity.

Nishikawa et al., 1989; Nishikawa et al., 1982; Ruskin and Nyman, 1991; Spohn et al., 1986) and a further nine trials described their criteria as indicating mild or early deterioration, or 'immanent' rather than full-blown relapse (Chen et al., 2010; Correll et al., 2017; Fleischhacker et al., 2016; Fleischhacker et al., 2014; Fu et al., 2015; Kane et al., 2012; Kane et al., 2011; Weiden et al., 2016; Wunderink et al., 2007).

4. Discussion

4.1. Main findings

The review reveals that there is considerable variation in the way that relapse has been defined in trials of long-term antipsychotic treatment in people with schizophrenia or psychosis. Compared to earlier trials, recent trials are more likely to report detailed definitions of relapse, and to employ rating scales to identify relapse in at least some cases. However, as in observational studies (Olivares et al., 2013) definitions in trials have become even more variable in the last three decades, as trials employ complex definitions involving combinations of alternative criteria based on rating scales and other events. Indeed, since 1990, there are almost as many definitions as trials. Only one trial (Wang et al., 2010) used criteria suggested by Csernansky et al, 2002 and three others used similar criteria but with modifications (Hough et al., 2010; Kramer et al., 2007; Rui et al., 2014).

Although use of the BPRS and then the PANSS has become universal across trials since 2000, the way the scales are used and the thresholds specified vary widely. This reflects the fact that there is no generally agreed threshold for change in individual symptoms or total scores at which a relapse or significant deterioration can be held to have occurred. An additional source of variation is that the majority of studies using rating scale-based definitions combined these with various alternative definitions of relapse, including clinician judgement, need for additional treatment and suicidal or aggressive behaviour.

While 45% of studies used relatively objective and reliable measures of relapse, only 8.5% defined relapse in a clinically relevant manner that would coincide with most clinicians' views of what constitutes a relapse (Burns et al., 2000; San et al., 2015). Just over one in ten studies required that everyone who relapsed should show positive psychotic symptoms, but only three combined this with a measure indicating a significant decline in behaviour, functioning or global state. Most trials also did not specify a minimum duration of symptoms, and only two analyses, both of the same study cohort, required that relapse symptoms persisted for at least 7 days (Wunderink et al., 2013; Wunderink et al., 2007). A previous study found that almost a third fewer relapses were identified using a 7-day minimum duration criteria (Linszen et al., 1994). Moreover, several trials reported that most relapses were identified through changes in rating scale scores during routine assessments, and none discussed the practical and ethical problems

Table 3
Characteristics of trials with high reliability and clinical relevance of relapse definitions compared with other trials.

	Trials with good quality definitions ($n = 6$)	Other trials ($n = 76$)
Sample size (median, IQR.)	70.5 (164.3)	80.0 (332.0)
Duration (mean, s.d.)[*]	20.0 (6.2)	10.9 (11.0)
Year of publication (mean, s.d.)	1990.7 (11.9)	1988.1 (18.4)
Number of alternative relapse criteria (median, IQR)	1.0 (2.0)	1.0 (0)
Pharmaceutical industry funding (%)	16.7%	32.9%
Blinding of assessors (%)	33.3%	65.8%
Overall risk of relapse (mean, s.d.)	0.37 (0.16)	0.48 (1.53)
Relative risk of relapse (mean, s.d.)	4.4 (4.0)	5.2 (6.0)

s.d. standard deviation; IQR interquartile range (medians and IQR are presented for non-normally distributed data).
[*] *t*-test yielded $p = 0.049$.

of conducting assessments with people who were unwell. It appears, therefore, that in many trials some relapses, at least, may reflect mild and potentially short-lived fluctuations in symptoms that may not reflect real world understandings of relapse, and might more accurately be described as 'deteriorations.'

Recent relapse prevention trials are conducted for approval and marketing purposes and reflect the lower costs of conducting placebo-controlled trials versus comparative studies. In these situations, the focus on milder cases of relapse is understandable given that the use of placebo has been criticised as being redundant and unethical, and trial lists therefore wish to avoid the occurrence of severe relapses (Lawrence et al., 2019). Indeed, several recent definitions were described as referring to 'impending,' rather than full-blown relapse. However, these trials are presented as relapse prevention studies, and included in meta-analysis of relapse prevention, yet mild symptom deteriorations are not necessarily reliable indicators of relapse. Previous research shows that 'prodromal' or early symptoms occur frequently and do not reliably predict subsequent relapse, although psychotic exacerbations, though rarer, show better specificity (Gaebel and Riesbeck, 2007). Moreover, increases in non-specific symptoms may include adverse effects related to antipsychotic withdrawal, such as anxiety and insomnia (Dilsaver and Alessi, 1988).

Although trials that used higher quality definitions were longer than other trials, we did not demonstrate that the reliability or clinical relevance of relapse definitions affected the overall or differential risk of relapse detected in the trials. Small numbers of trials with high quality definitions limited the power of these comparisons, and lack of detail made it difficult to assess how definitions were applied in practice, however.

4.2. Further research

Further research is required into how to define relapse in a way that represents a clinically significant event, as well as how it can be measured in reliable ways. Other reviews have recommended the use of rating scales (Gleeson et al., 2010), but previous research has shown little concordance between clinical ratings of relapse and those based on measuring scale criteria (Linszen et al., 1994). Moreover, what constitutes a clinically significant change in rating scale scores needs clarifying. Leucht et al. examined the clinical significance of differences in PANSS scores in trials of acute treatment by comparing them with CGI ratings (Leucht et al., 2006; Leucht et al., 2005). A change of 33 points or between 40% and 53% was required to be classified as showing more than a 'minimal' level of improvement on the CGI-I (Leucht et al., 2006, Leucht et al., 2005). If the relationship between the PANSS and CGI-I is linear, this would imply that most current definitions of relapse reflect only limited degrees of change. However, the analysis was not based on trials that were assessing relapse. A linking analysis of this sort would be useful to identify levels of change in symptom scores that correspond to clinically significant degrees of deterioration. Further research is also required into how to measure changes in functioning and other impacts of symptom deterioration, to assess the personal and social significance of the episode. Questions about the necessary duration of the deterioration and whether positive symptoms should be specified in order to exclude non-psychotic antipsychotic withdrawal effects or other non-specific fluctuations in mental state also need to be resolved.

There also remains the difficulty of how to administer rating scales if someone is having a full-blown relapse. An alternative approach of assessing relapse retrospectively based on information derived from clinical case notes may be useful to circumvent this problem. This approach also requires operationalisation of criteria for relapse, but use of common rating scales is complicated since

they have been designed for face to face assessments. A method of this sort was devised for a study of an Early Intervention in psychosis programme and reasonable inter-rater reliability was achieved (kappa 0.71) (Bebbington et al., 2006). Unblinding of raters occurred, but this may also occur in face to face assessments. We suggest there is a need to develop this approach further, using criteria that reflect a clinical conception of relapse, namely the return or increase of psychotic symptoms along with significant deterioration in functioning, behaviour or increased risk, and using a relevant minimum duration of symptoms to exclude short-lived fluctuations in mental state.

4.3. Limitations

Exploring how relapse was defined was limited by the level of detail reported, especially in older studies, and this also constrained evaluation of the quality of definitions, particularly regarding their clinical relevance. Subjective criteria like clinician judgement and objective ones, such as restarting antipsychotics, are likely to be influenced by local and historical factors that are unlikely to be recorded. Hence some studies using apparently broad criteria may have identified more severe cases in practice. Evaluating quality was also difficult in the many modern trials that use numerous alternative criteria since there was rarely information about which criteria had been applied most commonly. We were unable to explore the effects of definitions including a duration criterion since so few trials stipulated any duration of relapse symptoms, and where they did it was usually very short.

4.4. Clinical implications

Recommendations for the long-term treatment of people diagnosed with schizophrenia and psychotic disorders are based on trials whose main outcome is relapse. It is important, therefore, to understand what is meant by relapse in these studies. It transpires that there is no single or even common definition, and that the definitions that have been constructed only rarely reflect, at least consistently, the sort of situation that clinicians would consider to be characteristic of relapse in the real world. Implications for treatment decisions might therefore be different from what is presently understood.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.08.035.

Contributors

JM, NC and ML were responsible for the study concept and design. JM, NC, ML, RC and TS did the searching and data extraction. JM, NC and TS performed quality ratings and JM conducted the statistical analysis. JM wrote the first draft of the manuscript. All authors helped revise it and all accept the final version.

Conflicts of interest

JM is Chief Investigator for the NIHR-funded RADAR (Reserch into Antipsychotic Discontinuation And Reduction) programme which includes a trial comparing antipsychotic reduction with maintenance treatment. Other authors are, or have, been employed

on the RADAR programme. No authors have any financial conflicts of interest.

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