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Review

Risk of symptom recurrence with medication discontinuation in first-episode psychosis: A systematic review

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ABSTRACT

The large majority of individuals with a first episode of schizophrenia will experience a remission of symptoms within their first year of treatment. It is not clear how long treatment with antipsychotic medications should be continued in this situation. The possibility that a percentage of patients may not require ongoing treatment and may be unnecessarily exposed to the long-term risks of antipsychotic medications has led to the development of a number of studies to address this question. We carried out a systematic review to determine the risk of experiencing a recurrence of psychotic symptoms in individuals who have discontinued antipsychotic medications after achieving symptomatic remission from a first episode of non-affective psychosis (FEP). Six studies were identified that met our criteria and these reported a weighted mean one-year recurrence rate of 77% following discontinuation of antipsychotic medication. By two years, the risk of recurrence had increased to over 90%. By comparison, we estimated the one-year recurrence rate for patients who continued antipsychotic medication to be 3%. These findings suggest that in the absence of uncertainty about the diagnosis or concerns about the contribution of medication side effects to problems with health or functioning, a trial off of antipsychotic medications is associated with a very high risk of symptom recurrence and should thus not be recommended.

1. Introduction

Specialized programs have been developed at many centers around the world for individuals experiencing a first episode of schizophrenia and related non-affective psychoses (FEP) with the goal of optimizing clinical outcomes and reducing morbidity (Jackson and McGorry, 2009; Zipursky and Schulz, 2001). Over most of the past century, schizophrenia has been thought of as a progressive deteriorating illness that inevitably leads to poor outcomes (Jablensky et al., 1993). It is now appreciated, however, that approximately 80% of people will experience a remission of symptoms following a FEP (Lieberman et al., 1993) and that with intensive efforts, both sustained remission and functional recovery may be achieved (Girgis et al., 2011; Lambert et al., 2008; Menezes et al., 2006; Zipursky et al., in press). The observation of high rates of symptomatic remission has raised the question of whether all such patients require long-term prophylaxis with antipsychotic medication. Given the long-term medical risks of remaining on antipsychotic medication, in particular tardive dyskinesia (Correll et al., 2004), obesity and metabolic problems (Allison et al., 2009), it has been important to determine whether there are some patients who may not require ongoing maintenance treatment.

It is now known that the large majority of remitted FEP patients will experience a relapse following their remission, but less clear how this risk is related to medication discontinuation. Robinson et al. (1999) reported that 82% of remitted FEP patients had a relapse in the first five years, with those who discontinued their medication having a five times greater risk of relapse than those who remained on medications. Published treatment guidelines and algorithms have been unclear about how long antipsychotic medications should be continued in remitted FEP patients. Takeuchi et al. (2012) reported that of the 11 published treatment guidelines and algorithms that address the issue of medication discontinuation in first-episode schizophrenia, six do not argue against discontinuing antipsychotics after one to two years of treatment. For example, the Canadian clinical practice guidelines for the treatment of schizophrenia (1998) suggest that it is pragmatic to recommend that "patients who have made a functional recovery and have been in remission on medication for at least one to two years may be considered candidates for a trial of no medication". The Practice Guideline for the Treatment of Patients with Schizophrenia published by the American Psychiatric Association (Lehman et al., 2004) recommends indefinite antipsychotic maintenance medication for patients who have had multiple prior episodes or two episodes within five years. In the case of remitted FEP patients, however, it is suggested that clinicians discuss two possible options with their patients, either

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indefinite antipsychotic maintenance medication or discontinuation following at least one year of symptom remission.

Discussing a trial of medication discontinuation requires a clear articulation of the risks and costs of relapse. A second episode of schizophrenia may be experienced as a major setback for patients who have made a good recovery from their FEP; it can lead to losses in hard-won social and vocational gains, and may increase the risk of violence and suicide (Amore et al., 2008; Hor and Taylor, 2010; Llorca, 2008; Masand et al., 2009). Tragically, some patients are not able to achieve a remission following their second episode and develop chronic treatment resistant symptoms (Lieberman, 1993; Wiersma et al., 1998).

Studies to date have yielded a wide range of recurrence and relapse rates after a remitted FEP when patients discontinue their medications. The risk of relapse in schizophrenia with and without maintenance treatment has been the subject of a recent meta-analysis by Leucht et al. (2012) who reported that one-year relapse rates averaged 65% in patients who had discontinued and 27% in those who had continued medication. These rates were not found to differ when the analysis was limited to studies of patients with a FEP. However, methodological issues in many of the included studies limit their relevance to addressing the clinical dilemma that clinicians face in determining whether to recommend a trial off antipsychotic medications for patients who have remitted from a FEP. In this study, we carried out a systematic review to determine the risk of psychotic symptom recurrence after medication discontinuation in patients who have remitted from a FEP.

2. Materials and methods

2.1. Search strategy

A systematic computerized search was performed to find relevant English language articles published before Oct. 10, 2012, using the following keywords: "[schizophrenia or psychotic disorders]" and "[first episode or early episode]", and "antipsychotic agents", and "[recurrence or relapse or withdrawal or discontinuation or taper]". The following databases were searched for title, abstract and index terms of reference: Medline, PsycINFO, Embase, and Cochrane. Furthermore, the references of retrieved articles were manually searched for additional references. Abstracts were perused for relevance to the systematic review. If relevant studies did not provide the data being sought, individual authors were contacted personally to obtain missing data.

2.2. Selection criteria

Studies were included in the systematic review if: (1) they included a first episode non-affective psychosis population; (2) the population had responded to treatment or experienced a remission of symptoms (e.g. was out of the acute phase of illness and in the maintenance phase) for a minimum of six months prior to medication discontinuation; and (3) the study reported some measure of symptom recurrence, worsening, or relapse as an outcome of interest a minimum of six months after medication discontinuation.

While the primary objective of this review was to estimate the rate of symptom recurrence off of medications, we were also interested in estimating the rate of symptom recurrence with continued treatment. From those studies that met our inclusion criteria above, we also extracted the rate of symptom recurrence if: 1) subjects were randomized to medication continuation for the duration of the follow-up period, and 2) medication continuation did not involve switching to a different medication.

2.3. Data extraction

Two authors (RBZ and NMM) independently reviewed all abstracts and studies, applied the selection criteria, and extracted information about study design, treatment, and outcome. Any discrepancies were resolved by consensus.

2.4. Statistical analysis

As studies varied in their criteria for relapse and symptom recurrence, it was necessary to select criteria for each study that could be used to compare results. When a study used multiple measures of relapse and recurrence, we elected to use the lowest threshold for clinical deterioration as our aim was to estimate the risk of symptom recurrence off of medications rather than the risk of a full relapse. This was also necessary as some studies reinstituted antipsychotic treatment at these lower thresholds in order to prevent relapses and hospitalizations. As a result, many patients who experienced an exacerbation of symptoms off of medications were prevented from deteriorating to a point where they would meet the criteria for the higher threshold of relapse. A weighted mean one-year recurrence rate was calculated by multiplying the mean one-year recurrence rate reported for each study by the number of subjects in the group, summing these, and dividing by the total number of subjects in all studies combined.

3. Results

Two hundred and eighty-six abstracts were reviewed through database searching. Twenty-seven full-text articles, representing 19 unique cohorts, were assessed for eligibility. Six studies met selection criteria and were included in the systematic review (Boonstra et al., 2011; Chen et al., 2010; Emsley et al., 2012; Gaebel et al., 2011; Gitlin et al., 2001; McCreadie et al., 1989). Details of the six studies included are presented in Table 1. Studies were excluded if they did not include a distinct group whose medications were discontinued (Crespo-Facorro et al., 2011; Emsley et al., 2008; Gaebel et al., 2007; Gleeson et al., 2009; Harrow et al., 2012; Malla et al., 2008; Wunderink et al., 2007), if they involved patients who had not been stable on treatment for at least 6 months prior to discontinuing medications (Crow et al., 1986; Gaebel et al., 2002; Hogarty and Ulrich, 1998; Jolley et al., 1990; Kane et al., 1982; Rabiner et al., 1986; Rifkin et al., 1977; Robinson et al., 1999), or if they included patients who had more than one episode of psychosis (Jolley et al., 1990; Herz et al., 1991). Three of the six studies provided estimates of the rate of symptom recurrence with medication continuation that met our criteria for inclusion (Boonstra et al., 2011; Gaebel et al., 2011; McCreadie et al., 1989). Two studies did not have a medication continuation group (Emsley et al., 2012; Gitlin et al., 2001) and one study was excluded because subjects in the continuation arm had been switched to a different medication (Chen et al., 2010).

3.1. Methodological aspects of the studies reviewed

3.1.1. Study design

Of the six studies included, four were randomized-controlled trials, of which two involved placebo groups (Chen et al., 2010; McCreadie et al., 1989) and two involved open medication discontinuation (Boonstra et al., 2011; Gaebel et al., 2011). The other two studies were non-randomized interventions involving medication discontinuation (Emsley et al., 2012; Gitlin et al., 2001). Two of the six studies evaluated intermittent treatment or early targeted intervention (Emsley et al., 2012; Gaebel et al., 2011), with the endpoint of relevance to this review being relapse or symptom recurrence requiring medication resumption.

3.1.2. Sample size

Sample sizes ranged from 7 to 89 patients in the included studies for a total of 209 patients in the medication discontinuation groups.

3.1.3. Diagnostic criteria

All studies included first episode non-affective psychosis patients with schizophrenia-related disorders (schizophrenia, schizoaffective

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