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You say "schizophrenia" and I say "psychosis": Just tell me when I can come off this medication

Robert B. Zipursky [a,b,*], Gbolahan Odejayi [c,d], Ofer Agid [a,b], Gary Remington [a,b]

[a] Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[b] Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[c] Schizophrenia and Community Integration Service, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
[d] Department of Psychiatry and Behavioural Neurosciences, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada

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ABSTRACT

Individuals experiencing a first episode of psychosis are likely to respond well to treatment with antipsychotic medications. Of those treated for a first episode of schizophrenia, three out of four can expect to achieve remission. The question of how long antipsychotic medication should be continued has been a topic of heated debate in the field. Longitudinal studies of individuals diagnosed with a first episode of psychosis have reported that as many as 30% may be able to come off of medications without relapsing while treatment discontinuation studies have found that very few patients remain in remission off of medication. This paper reviews the literature on relapse rates following a first episode of schizophrenia and identifies factors that contribute to the discrepancies in the rates reported. These factors include sampling considerations, the distribution of psychiatric diagnoses, the duration of follow-up, the rate of medication discontinuation and the criteria used to define illness recurrence. We propose that individuals for whom the diagnosis of their first psychotic episode is determined with ongoing follow-up to be due to schizophrenia are at extremely high risk of relapse and should be advised to continue antipsychotic medication for the long-term. Those whose first episode of psychosis is determined to be due to other causes are also at high risk of illness recurrence off medications. Recommendations for maintenance treatment should be tailored to reflect the risk of relapse and sequelae of relapse associated with specific causes of first episode psychosis.

1. Introduction

Specialized treatment programs to provide comprehensive early intervention to individuals experiencing a first episode of schizophrenia have continued to be developed since the earlier research-focused programs were started in the 1980s and 1990s (Zipursky and Schulz, 2001). More recent programs have typically had a broader mandate to identify and treat first episodes of psychosis irrespective of diagnosis. It has been understood that at initial presentation it can be very challenging to differentiate those psychotic episodes due to schizophrenia from those due to other aetiologies such as bipolar disorder, psychotic depression and substance use.

Early research established that, even in those individuals diagnosed with schizophrenia at the time of their first episode, dramatic improvement in symptoms occurs with the administration of antipsychotic medication (Lieberman et al., 1993). The Remission in Schizophrenia Working Group (RSWG) (Andreasen et al., 2005) defined remission as, "a state in which patients have experienced an improvement in core signs and symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia." Complete recovery, is then understood to involve, "the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology" (Andreasen et al., 2005). These terms have unfortunately been used in quite different ways in the schizophrenia outcome literature, with some earlier studies defining full recovery as requiring only complete symptom remission without specification of functional ability (Rosen and Garety, 2005).

A recent meta-analysis using the RSWG criteria which required symptoms to be mild or absent in severity for at least 6 months reported initial remission rates from a first episode of psychosis of 56.9%, which increased to 57.9% when studies that did not apply the 6-month duration criteria were included (Lally et al., 2017). Using the latter criteria, remission rates from a first episode of schizophrenia were estimated at 56.0% with some studies reporting rates of remission of over 80% in the first year. In a recent multicentre study that involved standardized

* Corresponding author at: Centre for Addiction and Mental Health, 1001 Queen Street West, Toronto, Ontario M6J 1H4, Canada.
E-mail addresses: robert.zipursky@camh.ca (R.B. Zipursky), bodejayi@stjosham.on.ca (G. Odejayi), ofer.agid@camh.ca (O. Agid), gary.remington@camh.ca (G. Remington).

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treatment of patients with sequential trials of amisulpiride, olanzapine and clozapine, 76% of patients met criteria for remission within 6 months underscoring that schizophrenia is a highly treatable disorder for the majority of patients (Kahn et al., 2018).

While remission rates are high, the number of patients who achieve both sustained remission and functional improvement following a first episode of psychosis is estimated to be only 25.2% with comparable rates of recovery in those diagnosed with schizophrenia (Lally et al., 2017). Other measures of outcome reinforce the finding that the functional outcomes from schizophrenia remain poor. Only 5% of people with schizophrenia living in Israel were employed in work that pays more than the minimum wage (Davidson et al., 2016) while in Norway only 10% of people with schizophrenia were involved in competitive employment for at least 1 h per week (Evensen et al., 2016). Twenty-year follow-up of patients with a first episode of psychosis in the Suffolk County Mental Health Project found that only 4% of patients with schizophrenia were functioning in the normal range (Lally et al., 2017).

Despite strong evidence for poor functional outcomes following a first episode of schizophrenia, there has been a resurgence of interest in the question of whether those who have remitted from a first episode of schizophrenia require long-term treatment. A number of naturalistic longitudinal studies, which will be discussed in more detail below, have reported that a substantial number of individuals diagnosed with a first episode of schizophrenia are able to discontinue antipsychotic medication "without detriment in the long term"(Murray et al., 2016). In some of these studies, those who have discontinued medication have been reported to be functioning better than those who have stayed on medication. In contrast, studies designed to investigate how many individuals who have remitted from a first episode of schizophrenia are able to discontinue antipsychotic medication without a recurrence of psychosis have found that few if any patients remain well off of treatment (Zipursky et al., 2014). This major discrepancy in estimates of how many individuals are able to remain free of psychotic symptoms off of medication has led to polarized views on whether long-term medication should be recommended to all patients with schizophrenia including those with a first episode of schizophrenia or, alternatively, whether a trial of medication discontinuation should be considered in those who have experienced remission or recovery. This is a critically important question as relapse into a psychotic state is known to carry substantial risks beyond the immeasurable suffering that many patients and their families experience with a psychotic relapse.

Experiencing a psychotic relapse is not only associated with an increased risk of re-hospitalization, but also violent behaviour and suicide, homelessness, loss of jobs and relationships, as well as disruption of recovery trajectory (Kane, 2007). It is estimated that between one out of six to seven patients will fail to return to a remitted state following a relapse (Emsley et al., 2013; Lieberman et al., 1996; Wiersma et al., 1998), a tragic occurrence when remission had been achieved from earlier episodes. Psychotic relapse is associated with an attenuated response to antipsychotic medication (Emsley et al., 2012a; Lieberman et al., 1996; Takeuchi et al., 2012). Hui et al. (Hui et al., 2018b) reported that patients who were randomized to discontinue their medications for a period of one year after remitting from a first episode of schizophrenia were significantly more likely to have poor outcomes (defined as persistent positive symptoms of psychosis, requirement for clozapine treatment for treatment-resistant schizophrenia, or death by suicide) at 10-year follow-up than those randomized to maintenance antipsychotic treatment; the increase in poor outcomes was mediated to a significant degree by the increased risk of relapse during the 12-month period of randomization. These lines of evidence suggest that psychotic relapses contribute to the development of treatment resistance in schizophrenia, which should be a critical concern when considering a trial of medication discontinuation.

In this paper, we will address the factors that contribute to the discrepancy in the risk of relapse following a first episode of schizophrenia found across studies. We propose that the major source of variability in reported relapse rates relates to whether studies are naturalistic or involve a group whose medications are systemically discontinued, to differences in the distribution of diagnoses and when the diagnosis is made, to criteria used for recurrence and relapse, to the mode of medication discontinuation, and to the duration of follow-up. Many individuals who experience a first episode of psychosis will not turn out to have a diagnosis of schizophrenia. The likelihood that these individuals will experience a relapse will impact on the overall relapse rates reported in studies that follow cohorts of patients with more broadly defined first episode psychosis or non-affective psychosis. Recurrence rates for those cases of first episode psychosis not due to schizophrenia will be summarized. Finally, recommendations will be proposed for maintenance treatment following a first episode of schizophrenia.

2. Factors impacting on reported rates of relapse

2.1. Naturalistic studies

Longitudinal studies of individuals who have experienced a first episode of psychosis or schizophrenia have reported that some individuals are able to discontinue antipsychotic medications and to remain off of them for the long-term (Murray et al., 2016). Harrow et al. (Harrow and Jobe, 2013) followed 70 patients diagnosed with schizophrenia or schizoaffective disorder following their first or second admission to hospital, 59 of whom were assessed after 20 years. Twenty-four patients were on antipsychotics at every follow-up visit while 15 of 70 patients were not on antipsychotics at any of the follow-up visits between 2 and 20 years. Beginning at the 4.5-year follow-up, those in subgroup not on antipsychotics had lower ratings of psychotic symptoms and were more likely to have had a 1-year period of recovery. Of the 15 patients who had been off of medications, 13 (87%) experienced two or more years during which they were considered to have recovered. How many remained free of psychotic symptoms for the entire follow-up period is not described. While this study does suggest that some individuals with an initial diagnosis of schizophrenia are able to manage without long-term antipsychotic treatment, it does not provide compelling evidence that a substantial percentage of patients diagnosed with schizophrenia are able to remain in remitted or recovered state throughout 20 years of follow-up. Interpretation of this study is limited by the possibility of reverse causation, i.e. those with milder or remitting forms of psychotic illness may be less likely to require ongoing medications (Correll et al., 2018).

Alvarez-Jimenez (Alvarez-Jimenez et al., 2012) followed 209 patients with a first episode of non-affective psychosis for 7.5 years. They found that 26% met criteria for a full functional recovery, 61% of whom (15.9% of the entire sample) had not been on medications for the previous 2 years. Whether those who were able to stop medications were in remission or differed in their initial or follow-up diagnosis was not reported.

Moilanen et al. (Moilanen et al., 2013) followed 70 individuals diagnosed with schizophrenia spectrum psychoses including 58 with schizophrenia that were part of the Northern Finland 1966 Birth Cohort. At 10-year follow-up, 24/70 were not on medications of whom 15 were in remission. Of the 58 subjects with schizophrenia, 7 (12%) were in remission off of medication at follow-up of whom 4 (6.9%) had no history of relapse.

Lappin et al. (Lappin et al., 2018) carried out 10-year follow-up of 345 individuals with a first episode of psychosis in the AESOP10 study that also included individuals with primary affective disorders. They reported that 12.5% met criteria for Early Sustained Recovery (ESR), which was defined as having achieved remission within 6 months with no further psychotic episodes over the 10-year follow-up period. Only one of these ESR patients was on medication throughout the 10-year follow-up period. Five percent of ESR patients (i.e. two patients) did not take medication at the time of their first episode; 74.4% of the remaining

41 ESR patients stopped medication at some point and did not resume treatment. Those who met criteria for ESR were more likely to have a diagnosis other than schizophrenia, and in particular, mania. While this study provides some support to the view that a significant number of individuals who have had a first episode of psychosis may remain relapse free for many years following a first episode of psychosis, it does not seem as promising an option when the initial diagnosis is schizophrenia.

Wils et al. (Wils et al., 2017) reported on the 10-year follow-up of 496 patients with schizophrenia spectrum disorders, 79.2% with an initial diagnosis of schizophrenia. Sixty percent were available for 10-year follow-up of whom 30% were in remission and off of medication. No information was provided about how long these individuals had been off of medication. As in the case of the report by Lappin et al. (Lappin et al., 2018), updated diagnoses at the one- and two-year follow-up points were not provided. As a result, it is not possible to know how many patients with a confirmed diagnosis of schizophrenia were able to successfully discontinue medications.

Hui et al. (Hui et al., 2018a) evaluated 178 patients with a first episode of non-affective psychosis over a 10-year period to determine how to predict which patients will never relapse. They reported that 37/178 (21%) patients did not relapse of whom 18 had been initially diagnosed with schizophrenia spectrum disorders. Those who did not relapse were less likely to have been diagnosed with a schizophrenia spectrum disorder. This study was not able to investigate the association between risk of relapse and medication discontinuation as those patient groups with and without relapse had received antipsychotic medication for a mean of 112 months over the 120-month follow-up period.

A number of longitudinal studies have investigated how many individuals will have only a single episode of schizophrenia followed by full recovery (Rosen and Garety, 2005). Estimates have varied as a function of duration of follow-up and have ranged from as high as 50.3% at 2-year follow-up (Jablensky et al., 1992) to as low as 12.2% at 15-year follow-up. Based on their 15-year follow-up study, Wiersma (Wiersma et al., 1998), reported that approximately 70% relapsed from their first episode within the first five years and that no further relapses occurred between 10 and 15 years of follow-up in the remaining 15% with a single psychotic episode. This finding is consistent with the subsequent report by Rosen and Garrety (Rosen and Garety, 2005) who studied 436 patients assessed following a first episode of non-affective psychosis and followed for 6 to 19 years. Within the first six years of follow-up, 74.4% had relapsed with 15.6% having had a single episode with complete remission. Among those patients who relapsed over as long as 19 years of follow-up, 91.7% relapsed within 6 years, 98.1% within 9 years with the remainder relapsing between 10 and 15 years. How many single episode patients had remained on medication, and the relationship between medication discontinuation and years to relapse, was not described.

The results of naturalistic longitudinal studies are consistent in demonstrating that there are some patients with a first episode of psychosis who are able to achieve and sustain remission without long-term antipsychotic treatment. The percentage of patients who are able to remain relapse-free off of medications at 10-year follow-up varies from study to study with a low of 6.9% of patients with schizophrenia followed by Moilanan et al. (Moilanen et al., 2013) to a high of 30% among those patients with schizophrenia spectrum disorders available for follow-up described by Wils et al. (Wils et al., 2017). A number of studies have reported that those with an initial diagnosis of schizophrenia are less likely to remain in remission off of medications. It would then be expected that the likelihood of remaining in remission off of medication would vary depending on whether the sample includes only patients with schizophrenia, schizophrenia spectrum disorders, or a first episode of psychosis. What these studies also have in common is that the diagnosis used for the analysis was the diagnosis at the time of the first episode. However, it is unlikely that long-term treatment recommendations would be made on the basis of the initial diagnosis. This raises the question of how many patients whose diagnosis of schizophrenia is confirmed one to two years following their initial presentation are able to successfully discontinue antipsychotic medication.

2.2. Antipsychotic discontinuation studies

The efficacy of antipsychotic medication in preventing relapse in individuals with schizophrenia has been evaluated in discontinuation studies including a number that utilized randomized controlled trials (RCTs) that included a group that received placebo. These latter studies have been subjected to meta-analysis by Leucht et al. (Leucht et al., 2012) who found that, based on 65 RCTs involving 6493 subjects, 1-year relapse rates in patients with schizophrenia assigned to maintenance medication was 27% compared to 64% in those assigned to placebo. When the analysis was limited to studies of patients with a first episode of schizophrenia, the relapse rates were 26% with maintenance treatment and 61% with placebo. While this meta-analysis clearly established the benefit of maintenance treatment for relapse prevention, the absence of relapse data beyond one year precludes extrapolating this data to infer how many patients would continue to remain well off of treatment. Problems with treatment adherence in those assigned to maintenance treatment distort estimates of its efficacy for relapse prevention (Leucht et al., 2012). Furthermore, the analysis of first episode studies did not require that patients be highly responsive or remitted, that they have a minimum duration of stability prior to discontinuation, or a minimum duration of follow-up.

We carried out a systematic review of studies that involved medication discontinuation or randomization to placebo in patients with a first episode of non-affective psychosis to address the limitations of the meta-analysis by Leucht et al. (Leucht et al., 2012) outlined above (Zipursky et al., 2014). Our review was limited to those studies in which patients had responded to treatment or were in remission, had been treated for at least six months, and were followed up for a minimum of six months after stopping antipsychotic medications. We found six studies that included a total of 209 patients in the discontinuation groups that met our selection criteria. Mean risk of recurrence at 1-year was 77%. The two studies that included data beyond 1-year follow-up reported 2-year recurrence rates of 94% and 96%, and 3-year recurrence rates of 97% and 98%. Two of these six studies evaluated the risk of recurrence with maintenance treatment at 1-year; they reported recurrence rates of 0/8 and 1/23 (weighted mean 3%).

Thompson et al. (Thompson et al., 2018) carried out a more recent systematic review of relapse rates following a first episode of psychosis that included seven studies. They reported 1-year relapse rates of 53% with medication discontinuation versus 19% with maintenance treatment. In comparison with our previous review, their analysis was limited to randomized controlled trials, did not have a requirement for a minimum duration of stability prior to discontinuation, was not limited to subjects with non-affective psychoses, and used rates of relapse rather than rates of recurrence as the outcome measure.

Most recently, Kishi et al. (Kishi et al., 2019) carried out an updated meta-analysis that included 10 RCTs that compared relapse rates in first episode psychosis patients who received maintenance antipsychotics versus antipsychotic discontinuation. Five of these studies were limited to patients diagnosed with schizophrenia and five used broader diagnostic criteria for first episode psychosis. The outcome measure used in this study was relapse though criteria were not provided. They concluded that maintenance treatment prevented relapses beginning at the 2-month follow-up and through to the 24-month follow-up. However, they also pointed out that 45.7% who discontinued antipsychotics did not relapse in the first 12 months, which dropped to 39.4% after 18–24 months.

Randomized controlled trials and medication discontinuation studies show large and consistent differences when the outcome is recurrence or relapse. These studies also find that many patients who have discontinued medication will not experience a recurrence within the first year. However, discontinuation studies with longer follow-up

periods find that few if any patients diagnosed with schizophrenia remain free of symptoms after being off of antipsychotic medication for two to three years. This is a very different conclusion than that reached from the longitudinal studies summarized above.

The naturalistic longitudinal studies described have been interpreted as finding that those patients who have been able to sustain improvement off of medications may be less symptomatic and function better than those on medications, inferring that ongoing treatment with antipsychotic medication contributes to poorer outcomes. However, the association between maintenance medication and poorer outcomes may be better explained by reverse causation (i.e. those who require ongoing medications have a more severe and disabling disorder) or by confounding by association (i.e. those on medication differ in some way which lead both to their remaining on medication and to having poorer outcomes, such as having schizophrenia) (Correll et al., 2018).

As was the case for naturalistic longitudinal studies, estimates of recurrence and relapse rates following medication discontinuation vary across discontinuation studies and randomized-placebo controlled trials of maintenance treatment. Likelihood of relapse is clearly related to duration of follow-up as described above. Additional variance in reported rates of relapse is attributable to the criteria used for relapse and recurrence, the mode of discontinuation, and the psychiatric diagnoses included in the studies.

2.3. Relapse versus recurrence

More stringent thresholds for relapse such as hospitalizations will result in lower estimates of relapse on and off of medication. However, in experimental study designs such as RCTs and discontinuation studies, following patients until they meet the higher threshold criteria for relapse is not justifiable. In such studies, clinicians are bound to recommend treatment when, in their clinical judgment, failing to do so would put their patient at increased risk of adverse outcomes including hospitalization and harm to self or others. (Emsley, 2017; Emsley, 2018; Zipursky and Darby, 1999). The lower threshold concept of "recurrence" may result in higher estimates of the risk of worsening both on and off of medications. This limitation is unavoidable when studies are designed to meet standards for safety and ethics.

2.4. Mode of discontinuation and duration of follow-up

Antipsychotic response has been reported to be associated with a threshold level of D_2 receptor occupancy by antipsychotic medication in the brain (Kapur et al., 2000). It is likely that the risk of relapse increases when D_2 receptor occupancy drops below this threshold. How quickly D_2 receptor occupancy drops would be expected to be a function of the drug level prior to dosage reduction and the rate at which the dose is reduced. While it is commonly recommended that antipsychotic medication be reduced gradually rather than abruptly, there is no good evidence that this practice reduces the risk of recurrences. It is of note that the two studies that report the highest relapse rates (Emsley et al., 2012b; Gitlin et al., 2001) both involved discontinuation of long-acting medications. In addition, recurrences do not usually take place immediately after the drug has been eliminated from the body but rather with a latency that can be as long as a few years. Time to recurrence rather than risk of recurrence may be expected to vary as a function of rate of discontinuation. Studies with a shorter follow-up period would be more likely to underestimate recurrence rates if medication is gradually discontinued.

2.5. First episode psychosis versus first episode schizophrenia

The initial impetus for the development of specialized early intervention programs was to identify new approaches to improve the outcomes for people with schizophrenia. Identifying and treating individuals at the beginning of their illness provided unique opportunities to study the biology of schizophrenia before antipsychotic medication confounds interpretation of studies. Studying and treating people from the point of onset of schizophrenia also provided the opportunity to carry out longitudinal studies to evaluate the association between illness course and measures of brain structure and function. To identify individuals with a first episode of schizophrenia has required that individuals with a broader range of diagnoses be ascertained including those with psychotic affective disorders, drug-induced psychosis, as well as those with brief psychotic disorders and schizophreniform disorder. Longitudinal research has reinforced the importance of casting a broad diagnostic net in the early years of illness as shifts in diagnoses are more frequently towards rather than away from a diagnosis of schizophrenia (Bromet et al., 2011).

The question of how many patients who have had a first episode of psychosis can successfully remain off of antipsychotic medication over the long-term is very different from the question of how many patients with a diagnosis of schizophrenia who have remained on medication and have had their diagnosis confirmed one or more or more years later will remain well off of antipsychotic medication. This difference in sampling is likely key to understanding the disparate estimates of how many patients are likely to remain well off of antipsychotic medications. If the relapse rates off of medication vary across the different causes of a first episode of psychosis, it should not be surprising that the estimates of risk reported by studies to date should vary based on the distribution of diagnoses within their sample. In addition to differences in sampling, variability in diagnostic processes across sites and studies may also contribute to different distributions of diagnoses and in turn to differences in reported rates of relapse.

Estimated recurrence rates for studies with greater than one year of follow-up suggest that the risk of recurrence is extremely high for individuals diagnosed with schizophrenia and non-affective psychoses more broadly. Individuals whose first episode of psychosis is considered to have been due to causes other than schizophrenia may contribute disproportionately to those who are able to discontinue antipsychotic medication without experiencing a recurrence or relapse. Appreciating the risk of recurrence and relapse from a first episode of these disorders is important for understanding the discrepancy in relapse rates reported from naturalistic studies versus discontinuation studies. Individuals with these other disorders also face the difficult issue of how long to remain on antipsychotic medication following a first episode of psychosis. We will review below the evidence bearing on this issue for other causes of first episode psychosis: bipolar disorder, depression with psychotic features, unspecified psychotic disorders, brief psychotic disorders, and substance-induced psychoses.

3. Relapse rates associated with other causes of first episode psychosis

3.1. Bipolar disorder

Bipolar disorder is a common cause of psychosis. It has been estimated that 58% of bipolar patients will have at least one psychotic symptom in their lifetime, most commonly when manic (Dunayevich and Keck, 2000). Psychotic symptoms have been reported to be present in 75% of manic patients (Tohen et al., 2000). Of patients with a first episode of psychosis followed in the Suffolk County Mental Health Project, bipolar disorder was the second most common diagnosis (after schizophrenia spectrum disorders) at baseline (21.1%) and 10-year follow-up (24.0%) (Bromet et al., 2011). Manic patients are frequently treated with antipsychotic medications either alone or in combination with mood stabilizers.

Gignac et al. (Gignac et al., 2015) carried out a systematic review and meta-analysis of recovery and recurrence rates following a first episode of mania. Based on eight studies that included 734 patients with a first episode of mania, they reported syndromal recovery rates at one year of 84.2% and symptomatic recovery rates of 62.1%. At 1-year, 41.1% of

patients had a recurrence (manic, mixed or depressive), which increased to 59.7% by the end of 4 years. Rates of non-adherence ranged from 21% to 45.8% and as high as 65% when partial adherence was included. As these studies were all naturalistic in design, it is not possible to determine what the recurrence rates would be on versus off of recommended treatment. Vasquez et al. (Vazquez et al., 2015) compared recurrence rates in bipolar disorder estimated from naturalistic studies and randomized controlled studies. Their review was not limited to first episode cases or to those with a history of psychosis, and included studies in which index episodes and recurrences could have been either depressive or manic episodes. The average duration of follow-up in these studies was two years. The average risk of recurrence estimated from naturalistic studies was 55.2% (range of 40.4% - 66.0%). In randomized controlled trials, recurrence rates on active treatment were estimated at 39.3% compared to 60.6% in those randomized to placebo. It is not known how much higher these estimates of recurrence would have been with additional years of follow-up or if index cases had been limited to those with a first episode of psychosis.

3.2. Depression

Severe forms of depression may also include psychotic symptoms. Depression with psychosis is typically treated with a combination of antidepressant and antipsychotic medication, or alternatively with electroconvulsive therapy (ECT). Risk of relapse following an episode of psychotic depression has been less studied than in schizophrenia and bipolar disorder. Rothschild and Duval (2003) studied 40 patients with psychotic depression who were treated with fluoxetine and perphenazine for 5 weeks. Of these patients, 30 responded to treatment and were maintained on this treatment for an additional 3 months. Those who remained stable on treatment were gradually tapered off of perphenazine over the following 4 months; 7/30 patients experienced a recurrence of psychotic symptoms.

Clower (Clower, 1983) followed 10 patients with psychotic depression who had responded to a combination of antidepressant and antipsychotic medication. Over the 11-month follow-up period, three patients stopped their medication; all three relapsed and were rehospitalized. Aronson et al. (Aronson et al., 1988) reported on 52 patients with psychotic depression who were followed for an average of 32 months (range = 0.5–14 years), 36 of whom were treated for their first episode of psychotic depression. Of this latter group, 80.6% had at least one recurrence. Most relapses for the sample as a whole occurred in the first year and 86.6% occurred after antipsychotics were discontinued or reduced in dosage while still on antidepressants or lithium.

The recently reported results from the STOP-PD II study compared time to relapse in 126 patients who were randomized to antipsychotic discontinuation after having remitted from an episode of psychotic depression treated with a combination of sertraline and olanzapine (Flint et al., 2019). Time to relapse was significantly shorter in those randomized to sertraline monotherapy compared to the sertraline-olanzapine combination; over the course of the 36 week follow-up period, 54.8% relapsed in the sertraline monotherapy group compared to 20.3% in the sertraline-olanzapine group.

Taken together, the above studies of psychotic depression underscore the high risk of relapse associated with the disorder and the particular risk attributable to antipsychotic discontinuation.

3.3. Other psychotic disorders

Individuals who have experienced a first episode of non-affective psychosis may not meet criteria for schizophrenia as a result of the 6-month duration criteria for DSM-5 schizophrenia, and may then receive other diagnoses such as brief psychotic disorder, schizophreniform disorder, and other specified or unspecified schizophrenia spectrum disorders (Psychosis Not Otherwise Specified in DSM-IV).

The risk of recurrence following the diagnosis of brief psychotic disorder was evaluated by Fusar-Poli et al. (Fusar-Poli et al., 2016) who reported that 31% experienced a recurrence within 12 months and 53% within 36 months. How these estimates relate to medication discontinuation is not described. Bromet et al. (Bromet et al., 2011) reported on the 10-year follow-up of 470 patients with a first episode of psychosis of whom 118 were initially diagnosed with “Other or undetermined psychoses”, most commonly DSM-III-R Psychosis Not Otherwise Specified. At 10-year follow-up, 50% of this latter group met criteria for schizophrenia, 16% for bipolar disorder, and 8% for depression, all psychotic disorders that carry very high rates of relapse as summarized above.

3.4. Substance-induced psychosis

Many individuals will experience their first episode of psychosis in the context of substance use. The percentage of such individuals in studies will vary as a function of inclusion and exclusion criteria while the percentage with this diagnosis will also vary in different epidemiological samples as a function of usage patterns which may differ by drug and potency, by frequency of use, and by location and time. Individuals with substance-induced psychosis may have a recurrence of their psychosis because of ongoing substance use, medication discontinuation or the combination. When evaluating the likelihood of having a relapse related to medication discontinuation, it is important to understand how many individuals diagnosed with a substance-induced psychosis will go on to be diagnosed with a serious mental illness. Caton et al. (Caton et al., 2007) followed 319 patients with either early phase psychosis or substance-induced psychosis recruited from five emergency departments in New York City. Among those patients who received an initial diagnosis of substance-induced psychosis, 25% had a diagnosis of a primary psychotic disorder at 1-year follow-up. O'Connell et al. (O'Connell et al., 2019) reported on the follow-up of 56 patients with an initial diagnosis of substance-induced psychosis in Australia. After a mean follow-up of 84 weeks, 35.7% had a change of diagnosis to a schizophrenia spectrum disorder or bipolar disorder.

The question of how many individuals diagnosed with substance-induced psychosis go on to develop a primary psychotic disorder has been investigated in a number of nationwide registry studies. Arendt et al. (Arendt et al., 2005) utilized the Danish Psychiatric Central Register and identified 535 patients diagnosed with cannabis-induced psychosis. They reported that 45% were diagnosed with schizophrenia spectrum disorders at three-year follow-up, of whom 47% received the diagnosis within one year. A more recent Danish study utilizing the Danish Psychiatric Central Research Register and the Danish Civic Registration System reported on 6788 individuals diagnosed with a substance-induced psychosis (Starzer et al., 2018). In total, 32.2% of patients were re-diagnosed with either a schizophrenia spectrum disorder or bipolar disorder. Among those with an initial diagnosis of cannabis-induced psychosis, 47.4% converted to a diagnosis of schizophrenia or bipolar disorder, with the large majority (87%) converting to schizophrenia.

Niemi-Pynttari et al. (Niemi-Pynttari et al., 2013) used the national Finnish Hospital Discharge Register to identify 18,478 individuals who were admitted to hospital with a diagnosis of substance-induced psychosis. The 8-year cumulative risk for developing a schizophrenia spectrum disorder was 46% in those initially diagnosed with a cannabis-induced psychosis and 30% in those initially diagnosed with an amphetamine-induced psychosis. The majority of conversions took place in the first three years of follow-up.

That the percentage of individuals initially diagnosed with cannabis-induced psychosis who are re-diagnosed with either schizophrenia or bipolar approaches 50% underscores the very high risk of psychotic relapse to be expected in those whose first episode of psychosis is considered to have been due to substance use.

3.5. Varying distributions of initial diagnoses and risk of relapse

As relapse rates following a first episode of psychosis vary in the long-run from as low as 25% with some studies of stimulant-induced psychosis, to over 50% in naturalistic studies of patients with primary affective disorders, and as high as 100% for those with a first episode of schizophrenia who discontinue antipsychotic medication, the rates reported for any given sample of patients with a first episode psychosis would be expected to vary as a function of the distribution of initial diagnoses in a given sample. Relapse rates will also vary as a function of inclusion and exclusion criteria applied in different studies. Some studies will include those with primary mood disorders while others may exclude those thought to have substance-induced psychosis. As a result, samples will vary in the percentage of first episode psychosis patients who carry an initial diagnosis of schizophrenia. It should not be surprising that the number of patients who will remain well off of medication in some longitudinal samples of first episode psychosis may be as high as 30% at 10-year follow-up. It does not follow that a substantial percentage of patients who are diagnosed with schizophrenia and whose diagnoses remains schizophrenia will be able to safely manage without antipsychotics in the long run.

Based on the studies reviewed in this paper, the 1-year risk of recurrence following a first episode of schizophrenia can be estimated to be in the range of 60–80% with the few studies with 3-year follow-up finding that recurrence rates exceed 95%. Fewer randomized controlled trials and medication discontinuation trials have been carried out for patients whose first episode of psychosis was considered to be due to a primary affective disorder. However, the evidence from naturalistic studies as well as randomized controlled studies in broader samples of affective disorder patients suggest that relapse rates are likely greater than 50% and likely substantially higher when follow-up is extended to four years or more. It is likely that as many as 50% of patients with cannabis-induced psychosis will go on to meet criteria for schizophrenia and bipolar disorder. Similarly, 50% of those diagnosed with other psychotic disorders (i.e. DSM-5 specified and unspecified schizophrenia spectrum disorders, DSM-IV psychosis not otherwise specified) will likely go on to meet criteria for schizophrenia.

4. Recommendations for maintenance treatment of first episode schizophrenia

Prior to the surge of interest in early intervention, schizophrenia had for the most part been assumed to be a chronic, disabling illness with a course that is typically deteriorating (Zipursky et al., 2013). The report by Lieberman et al. (Lieberman et al., 1993) that over 80% of individuals experienced a remission of their psychotic symptoms in the first year of treatment shifted our understanding of the potential outcomes from schizophrenia. Prior to the publication of this research, clinicians often assumed that their patients probably did not have schizophrenia if treatment resulted in a full remission of psychotic symptoms. Given that standard doses of antipsychotics at the time were on the order of 20–40 mg per day of haloperidol (Lieberman et al., 1993) and were known to be associated with a high incidence and prevalence of tardive dyskinesia, it is not surprising that limiting exposure to antipsychotics medications was accepted as an important priority. That relapses occurred even in those whose symptoms fully remitted has contributed to the more conservative approach incorporated into the first generation of clinical practice guidelines which typically recommended that antipsychotics be continued for one to two years before considering a trial off of medications (Takeuchi et al., 2012).

For some clinicians and their patients, the recommendation that medications be continued for one to two years has been interpreted as meaning that it may be reasonable to undergo a trial off of medication when this time has elapsed. This recommendation, however, is better understood as a way of deferring advice until the underlying diagnosis and the extent of recovery achieved becomes clear. Most individuals for whom a diagnosis of schizophrenia is confirmed and who continue to experience psychotic symptoms despite substantial improvement with ongoing antipsychotic treatment will be advised to stay on antipsychotic medication for the long-term. When patients have achieved and sustained remission from their first episode of psychosis over the first year or two of treatment, knowing how to best advise them about the risks and benefits of medication discontinuation becomes much more challenging. It is very likely, however, that one to two years after the onset of the first psychotic episode, the diagnosis of the underlying illness should be discernable. At this stage, it should be possible to tailor the advice provided to the individual patient, based on the diagnosis established at this point, as well as individual considerations related to current symptoms, side effects, functioning, risks associated with previous episodes as well as their current family and work responsibilities.

We propose the following recommendations:

1. Following a first episode of psychosis, maintenance treatment should be continued until the diagnosis for the episode has been established with confidence. This may require a number of years of ongoing assessment and treatment in those who remain symptomatic and disabled, or shorter periods of time in individuals who have a sustained remission and made a full recovery from an affective psychosis or substance-induced psychotic disorder. Once the diagnosis is established with confidence, recommendations for maintenance treatment should be tailored to the specific diagnosis based on the existing evidence for the risks and benefits of maintenance medication, the risk and sequelae of recurrence, and current treatment guidelines.
2. As long as the diagnosis continues to be schizophrenia, maintenance medication with antipsychotic medication should be continued. This will mean long-term antipsychotic treatment for those with an established diagnosis of schizophrenia. This is consistent with the recommendation of the evidence-based guidelines from the British Association of Psychopharmacology that, "Established schizophrenia requires continued maintenance with doses of antipsychotic medication within the recommended range" (Barnes and Schizophrenia Consensus Group of British Association for Psychopharmacology, 2011).
3. For those with schizoaffective disorder, maintenance treatment with antipsychotic medication should be continued and, in some cases, may require concomitant mood stabilizers or antidepressants.
4. Individuals for whom the diagnosis of schizophrenia or schizoaffective disorder has been established and who have experienced a complete remission of symptoms are often eager to discontinue antipsychotic medication despite recommendations for maintenance treatment. While being free of psychotic symptoms is typically a precondition for a trial off of medications, Gaebel et al. have reported that patients who have responded well to antipsychotics are at higher risk of symptom exacerbation when medication is discontinued (Gaebel et al., 2016). While interpretation of this finding is limited by the study's small sample size, it is plausible that those patients whose psychotic symptoms are most responsive to antipsychotics are at greatest risk of deterioration without them. These patients and their families need to have a full appreciation of the risks of medication discontinuation. Many of these individuals will have made substantial gains in their recovery over the years they have been treated. This may include success in their educational pursuits and work, the development of important relationships, and improvement in housing and their quality of life more broadly. They require a clear understanding of the likelihood or relapse and its possible consequences including the development of treatment resistance. Given that even the most optimistic estimates suggest that fewer than one third of patients diagnosed with a first episode of schizophrenia will be able to sustain remission without antipsychotic medication, many individuals facing this decision may well choose to remain on maintenance treatment.

5. Individuals whose first episode of schizophrenia was associated with behaviours that put them or others at high risk of harm should be strongly advised against a trial off of medications. This would include individuals who were violent, attempted or planned suicide with highly lethal means, were driving dangerously while ill, or engaging in other dangerous or criminal behaviours.
6. Despite being made aware of the risks associated with discontinuing medications, many individuals will choose to undergo a trial off of medications. This should be done gradually with ongoing psychiatric follow-up for at least three years following discontinuation of medication. Families should be included in discussions about risk and, together with the patient, have a clear understanding of signs of recurrence as well as a safety plan to be initiated should symptoms return.

Recommendations for maintenance treatment for other causes of first episode of psychosis are beyond the scope of this paper. The issues to be considered are similar but differ in the specific medications or combinations of medications recommended. As in the case of schizophrenia, recommendations for patients who have experienced psychosis as a part of bipolar disorder have varied but have recently underscored the need for long-term treatment. As described in this paper, other major causes of a first episode of psychosis are also associated with a high risk of developing a serious mental illness in the long-term. For each of these disorders, the potential benefit of being off of medications will need to be weighed against the risk incurred by a substantial percentage of individuals when they experience their second episode of psychosis.

Contributors

Dr. Zipursky developed the project, directed the literature search and wrote the first draft of the manuscript. Dr. Odejayi conducted the literature search, summarized results from the literature and contributed to the writing and editing of the manuscript. Dr. Agid contributed to the writing and editing of the manuscript. Dr. Remington contributed to the writing and editing of the manuscript. All authors contributed to and have approved the final manuscript.

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