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ORIGINAL ARTICLE

Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multi-follow-up study

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Background. This research assesses whether multi-year treatment with antipsychotic medications reduces or eliminates psychosis in schizophrenia. It provides 20 years of longitudinal data on the frequency and severity of psychotic activity in samples of schizophrenia patients (SZ) treated *versus* those not treated with antipsychotic medications.

Method. A total of 139 early young schizophrenia and mood-disordered patients were assessed at index hospitalization and then reassessed six times over 20 years for psychosis and other major variables.

Results. At each follow-up assessment over the 20 years, a surprisingly high percentage of SZ treated with antipsychotics longitudinally had psychotic activity. More than 70% of SZ continuously prescribed antipsychotics experienced psychotic activity at four or more of six follow-up assessments over 20 years. Longitudinally, SZ not prescribed antipsychotics showed significantly less psychotic activity than those prescribed antipsychotics ($p<0.05$).

Conclusions. The 20-year data indicate that, longitudinally, after the first few years, antipsychotic medications do not eliminate or reduce the frequency of psychosis in schizophrenia, or reduce the severity of post-acute psychosis, although it is difficult to reach unambiguous conclusions about the efficacy of treatment in purely naturalistic or observational research. Longitudinally, on the basis of their psychotic activity and the disruption of functioning, the condition of the majority of SZ prescribed antipsychotics for multiple years would raise questions as to how many of them are truly in remission.

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Key words: Antipsychotic medications, longitudinal, psychosis, schizophrenia, treatment.

Introduction

Does continuous multi-year treatment with antipsychotic medications reduce or eliminate psychosis and are the results superior to a non-medicated sample? Despite these medications being viewed as 'antipsychotics', their long-term effectiveness in eliminating psychosis in schizophrenia patients (SZ) is still unknown. Antipsychotic medications are seen as the cornerstone for the short- and long-term treatment of SZ, based on their action reducing the period of intense psychosis during acute hospitalization, and on the numerous 6-month to 2-year double-blind studies of schizophrenia out-patients (Gilbert *et al.* 1995; Davis *et al.* 2003; Buchanan *et al.* 2010). American Psychiatric Association (APA) guidelines (Lehman *et al.* 2004) indicate clinicians should consider discontinuing antipsychotics for SZ who are symptom free for a year or longer. However, many clinicians assume that antipsychotics are important for continued stability and keep SZ on antipsychotics indefinitely.

A major issue is the lack of evidence of long-term (>3 years) treatment with antipsychotic medications and whether, as 'antipsychotics', they reduce or eliminate psychosis. Optimistic views by the World Psychiatric Association (WPA) Pharmacopsychiatry Section note that: 'Antipsychotic treatment has a significant impact on the long-term course of schizophrenic illness and can significantly facilitate recovery' (Tandon *et al.* 2008, p. 31). However, in a comprehensive review of the very many double-blind studies, Leucht *et al.* (2012) noted that 'nothing is known about the effects of antipsychotic drugs compared to placebo after three years'.

Research by us and other investigators has begun to question the long-term effectiveness of antipsychotics. This research has produced clear evidence of subsamples of SZ who, on a long-term basis, show favorable outcomes without prolonged antipsychotic treatment (Bleuler, 1978; Fenton & McGlashan, 1987; Harding *et al.* 1987; Harrow *et al.* 2005, 2012; Harrow & Jobe, 2007, 2013; Jablensky & Sartorius, 2008).

The current multi-follow-up research used 20-year longitudinal data, collected prospectively, at multiple

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times, at systematic intervals for treated and untreated SZ, and focused on psychosis, assessing: (1) How frequently over a 20-year period do SZ treated with antipsychotics experience psychosis? (2) For those SZ experiencing psychosis while being treated with antipsychotics, how severe are the psychotic symptoms? (3) Is the psychosis less severe than that of SZ not in treatment? (4) How effective is antipsychotic treatment over time for mood-disordered patients who were psychotic at the acute phase?

Method

Sample and 20-year follow-up schedule

At a relatively early phase in their disorder, 139 young patients were assessed prospectively at the acute phase of hospitalization as part of the Chicago Follow-up Study, a prospectively designed, longitudinal, multi-follow-up research program (Harrow *et al.* 1990, 1994, 2005, 2012; Harrow & Jobe, 2010, 2013; Jobe & Harrow, 2010). These patients were then reassessed at five or six subsequent follow-ups over the next 20-year period by trained interviewers who were not informed of their diagnosis or of the results of previous follow-ups. The assessments, which included structured research interviews [the Schedule for Affective Disorders and Schizophrenia (SADS); Endicott & Spitzer, 1978] and a functioning interview, occurred at index hospitalization, and at 2, 4.5, 7.5, 10, 15 and 20 years post-index hospitalization.

The sample of 139 DSM-III-diagnosed patients included 70 patients with schizophrenia spectrum disorders (61 SZ and nine schizo-affective patients). After structured research interviews at index hospitalization, satisfactory inter-rater reliability for diagnosis was obtained for the SZ sample (k=0.88). We also assessed a control sample of 69 patients with mood disorders, all of whom were psychotic at index hospitalization. All SZ met the 6-month duration of illness criteria (none were schizophreniform patients). From among the 70 SZ, 59 were assessed at the 20-year follow-ups. The other 11 SZ were assessed at all of the first five follow-ups, including the 15-year follow-ups. The 69 non-schizophrenia patients included 38 psychotic bipolar patients and 31 psychotic unipolar depressives. Within the limits of studying relatively young patients (mean age at index hospitalization was 23 years), the sample comprised consecutive admissions to two Chicago hospitals (a private hospital and a state hospital). At index hospitalization, 41% of the patients were first admissions and another 25% had only one previous hospitalization. The median level of education at index hospitalization was 13 years. Fifty-one per cent of the sample were males. Using the Hollingshead–Redlich scale (1958) for socio-economic status (SES), 53% were from households with SES of 1–3 (higher SES) and 47% were from households with SES of 4–5 (lower SES). The research received Institutional Review Board approval from the University of Illinois at Chicago, and informed consent was obtained from all participants.

Table 1. *Schizophrenia patients (SZ) prescribed antipsychotic medications at each follow-up over the 20 years of assessments*

Follow-up Year	Antipsychotic medications with or without other medications (%)	Other psychiatric medications (%)	No psychiatric medications prescribed (%)
2	67	5	28
4.5	66	9	25
7.5	63	14	23
10	62	10	28
15	66	3	31
20	62	9	29

Antipsychotic medications

Table 1 presents data on the percentage of SZ prescribed antipsychotics and those not prescribed medications at each follow-up assessment. Typically, as occurs in the natural course of psychotic patients, there was no single uniform treatment plan that applied to all patients.

At the 20-year assessments, 62% of SZ were prescribed antipsychotics with or without other medications and another 9% were prescribed other medications. For those SZ prescribed antipsychotics, the median dose prescribed at the 10-year follow-ups was 575 chlorpromazine (CPZ) equivalent units, and at the 15-year follow-ups 500 CPS equivalent units for first- and second-generation antipsychotics (Gardner *et al.* 2010), which is consistent with the Schizophrenia Patient Outcomes Research Team (PORT) guidelines (Buchanan *et al.* 2010). At the 20-year assessments, 28% of the mood-disordered patients were prescribed antipsychotics and 37% were prescribed other medications but not antipsychotics.

In addition, 25 of the SZ were prescribed antipsychotic medications at every one of the follow-up assessments (group 1), and another 24 SZ were prescribed antipsychotic medications at some, but not all, follow-ups (group 2). Another 15 SZ were not on antipsychotics at any of the follow-up assessments (starting at the 2-year follow-ups) over the 20 years (group 3). Six other SZ had a 20-year follow-up but had less

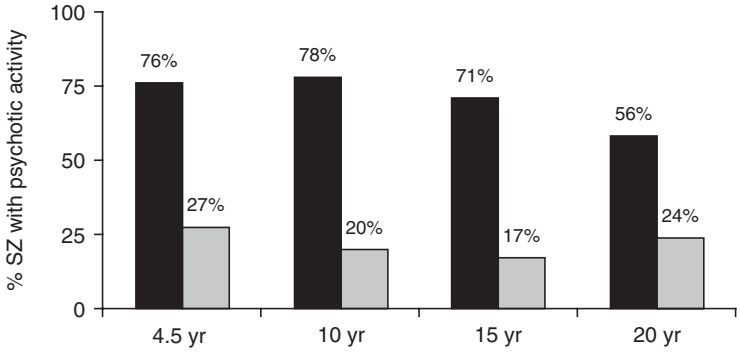

Fig. 1. Longitudinal comparisons of psychosis in medicated (■) and unmedicated (▨) schizophrenia patients (SZ).

than four follow-up assessments where definitive data on psychosis could be obtained. Their data on medications and psychosis were not included in comparisons of groups 1 and 3, but were included in other comparisons of psychosis at individual follow-up assessments for which they had definitive data. At assessments, interviewers focused on longitudinal issues and interviewers were not aware that the data would be used for issues involving antipsychotic efficacy.

Longitudinal data, comparing groups 1 and 3 on psychosis, analyzing whether SZ continuously prescribed antipsychotics manifest less psychotic symptoms have not been available previously to the field.

Assessment of psychosis and disorganization/formal thought disorder

Each patient was rated at each follow-up assessment on a standardized structured interview, the SADS (Endicott & Spitzer, 1978), for a range of different symptoms. These included ratings of 16 individual types of delusions and four different types of hallucinations (auditory, visual, olfactory and somatic-tactile). Delusions were rated on three-point scales: 1=delusion absent, 2=weak or equivocal, 3=full delusion present (Harrow & Jobe, 2010). Hallucinations were also rated on a similar three-point scale for each type of hallucination (Goghari *et al.* 2013). As patients are viewed as delusional regardless of whether they show one or several different types of delusions, a single composite rating of delusions and similarly of hallucinations was based on the highest score for each patient at each follow-up. Similarly, patients received an overall score for psychosis based on the presence of delusions and/or hallucinations.

Disorganization/formal thought disorder was assessed at each follow-up with an evaluation system previously used by our group and other investigators (Harrow & Quinlan, 1985; Holinger *et al.* 1999; Harrow *et al.* 2004; Subotnik *et al.* 2006).

Severity of psychosis

Assessment of severity of psychotic symptoms for those SZ who showed psychotic activity was evaluated using two different measures. One measure of severity involved specific ratings of the degree of disruption by their psychotic symptoms of the patients' social and instrumental functioning (a five-point rating scale). The other measure involved a general evaluation of the severity of their psychosis (a four-point rating scale). These two scales were rated for each patient at each follow-up assessment.

Assessment of prognostic factors

Diagnosis is one factor that may influence vulnerability to psychosis over time. To assess and control additional influences on psychosis over time for SZ, we assessed two important prognostic scales, both administered at index hospitalization prior to any follow-up assessments. One scale, from the research of Vaillant (1978) and Stephens *et al.* (1997), assesses the influence of prognostic factors. The other scale, developed by Zigler & Glick (2001), was used to assess the influence on psychosis of pre-morbid developmental achievements.

Results

Psychotic activity and disorganization/formal thought disorder in SZ prescribed antipsychotic medications

Figure 1 presents longitudinal data, comparing SZ prescribed antipsychotics to SZ not prescribed medications. These longitudinal data show that, at each follow-up, a surprisingly high percentage of SZ prescribed antipsychotic medications experienced either mild or more severe psychotic activity. The differences in percentages of SZ with psychotic activity were not significant at the 2-year follow-ups, but at each of the next five assessments over the 20 years, significantly

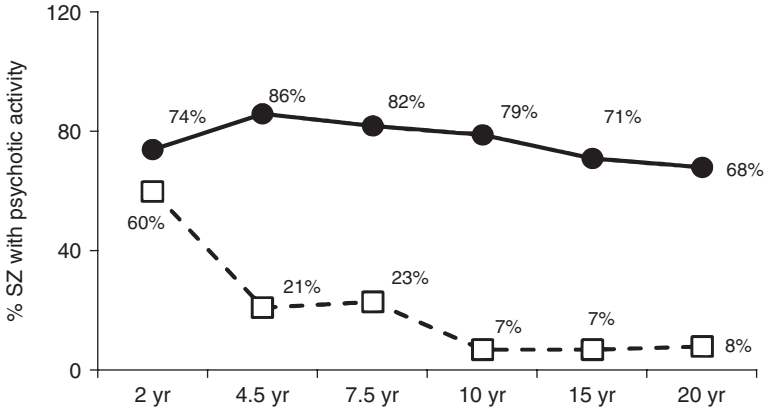

Fig. 2. Twenty-year longitudinal assessment of psychosis in schizophrenia patients (SZ): ●, always prescribed antipsychotic medications; □, not prescribed psychiatric medications at any assessment.

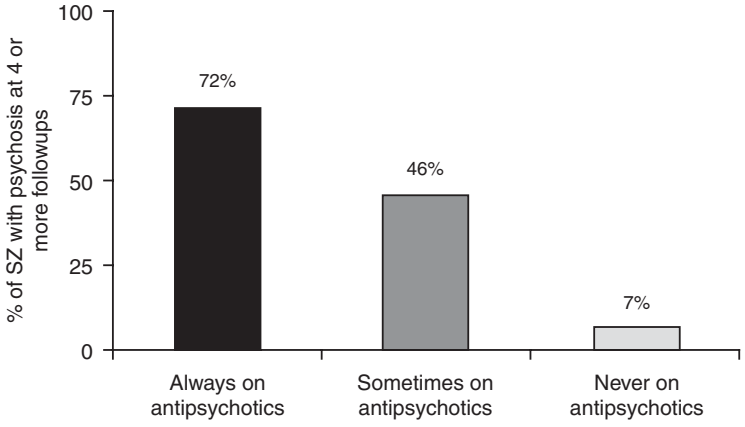

Fig. 3. Schizophrenia patients (SZ) with psychotic activity at ⩾4 follow-ups.

more SZ prescribed antipsychotics had psychotic activity than SZ not on medications. The χ^2 values for the last five follow-up assessments, with 1 degree of freedom (df), range from 5.3 to 15.39 ($p<0.05$). At five of the six assessments, at least 70% of SZ prescribed antipsychotics showed at least some psychotic activity.

Figure 2 presents longitudinal data over 20 years on the percentage of SZ who experienced psychotic activity, considering separately: (*a*) only SZ prescribed antipsychotic medications at all follow-ups (group 1) and (*b*) only SZ not on antipsychotics at all follow-ups (group 3). After the 2-year follow-ups, the SZ continuously prescribed antipsychotics showed significantly more psychosis at the next five follow-ups (t values ranged from 3.71 to 5.72, $p<0.001$). Separate Cohen's d values also indicated large effect sizes: $d=2.14$ at the 10-year follow-ups and $d=1.40$ at the 20-year follow-ups. A two-way repeated-measures ANOVA (medication groups × follow-up assessments) comparing the two medication groups over the six follow-ups was significant ($F=12.01$, df=1,12, $p<0.01$).

All 25 SZ continuously prescribed antipsychotic medications experienced at least mild levels of psychosis during 1 or more follow-up years over the 20 years. As shown in Fig. 3, 72% of the always-prescribed SZ group (18 of the 25 SZ) experienced mild or moderate-severe psychosis during at least four of the six follow-ups over the 20 years.

Although the consistent significant differences in psychotic activity over a prolonged period between the two groups (groups 1 and 3) are influenced by the high percentage of psychosis in SZ prescribed antipsychotics, they were also influenced by the low percentage of SZ not on antipsychotics (group 3) who experienced psychosis.

The SZ never on antipsychotics had significantly less disorganization/formal thought disorder than the SZ always prescribed antipsychotics at the 10-year follow-ups ($t=2.48$, df=25, $p=0.02$) and at the 20-year follow-ups ($t=2.58$, df=22, $p<0.02$).

Longitudinal data on patterns of psychotic activity

Analysis of the individual patterns of psychotic activity provide further estimates of psychotic activity and its association with antipsychotics.

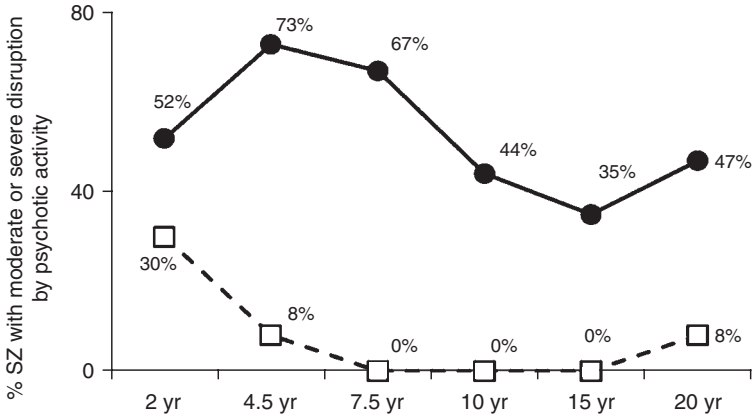

Fig. 4. Severity of psychotic activity: disruption of functioning by psychosis for schizophrenia patients (SZ) continuously prescribed antipsychotic medications (●, always prescribed antipsychotic medications; □, not prescribed psychiatric medications at any assessment).

SZ continuously prescribed antipsychotics showed significantly more psychotic activity, with 44% showing continual psychotic activity. However, although many showed frequent psychotic activity, others (28%) showed psychotic activity only a few times (only at one or two of the 5–6 assessments).

In the overall sample, only 12 SZ were psychosis free at all assessments. Seven of these SZ were from the group not on medications at all assessments. Two of these seven SZ were in complete recovery at all assessments (complete recovery during the assessment year defined as no positive or negative symptoms, no rehospitalization, some social contacts, and working at least half time). The other five SZ who were psychosis free at all assessments were from the group prescribed antipsychotics at some, but not all, assessments. None of the patients who were psychosis free at all assessments were from the 25 SZ continuously prescribed antipsychotics.

However, more than half of the SZ continuously prescribed antipsychotic medications had one or more periods in which they were non-psychotic, including six SZ who were not psychotic at the first 2-year follow-ups. These SZ then continued to have newly recurring psychotic activity while still being prescribed antipsychotics.

Although only two SZ were in complete recovery at all assessments, 40% of the entire sample of SZ were in complete recovery during at least one of their 5–6 assessments over the 20-year period. This could indicate their potential for better functioning under some circumstances.

Severity of psychotic symptoms

Data on severity of psychosis involving the degree of disruption by their psychotic symptoms of social and instrumental functioning are reported in Fig. 4. Significantly more SZ continuously prescribed antipsychotics than continuously unmedicated SZ had moderate or severe disruption. χ^2 values comparing these two groups on the percentage with moderate or severe disruption were significant at five of the six assessments. These five χ^2, with 1 df, ranged from 5.66 to 14.73 ($p<0.02$). Looked at individually, at the six 20-year assessments, 32% of SZ continuously prescribed antipsychotics were not psychotic, 21% were psychotic but showed no or only very mild disruption, and 47% were psychotic and experienced moderate or severe disruption.

The other scale for severity of psychotic symptoms showed similar results. More psychotic SZ continuously prescribed antipsychotics (group 1) showed moderate or severe psychotic symptoms than mild symptoms at all six follow-ups.

In addition, the SZ continuously prescribed antipsychotics did not show significant improvement over time in terms of less severe or milder psychosis at the 20-year assessments than at the 2-year assessments.

Delusions and hallucinations

At each of the six follow-up assessments, the majority of SZ with any psychotic activity had both delusions and hallucinations (e.g. at the 20-year follow-ups, 66% of SZ with psychotic activity had both delusions and hallucinations, 21% had only delusions and 14% had only hallucinations).

Influence of prognostic factors

We also analyzed prognostic factors that may influence SZ outcome, controlling for prognostic factors (Vaillant, 1978) and pre-morbid developmental achievements (Zigler & Glick, 2001). SZ continuously prescribed antipsychotics had significantly poorer

developmental scores on the Zigler scale (t=2.09, df=36, p<0.05). However, when controlling for this by comparing SZ from each group who had poor prognosis scores on both prognostic indices, SZ continually prescribed antipsychotics had significantly more frequent periods of psychotic activity than SZ continuously not on antipsychotics (χ^2=4.11, df=1, p<0.05). These data, and data from many other investigators, indicate that multiple factors influence psychosis and outcome, including biological vulnerability to psychosis, prognostic and developmental factors, treatment, age of patient, personality factors, other developmental factors and stressful life events (Harrow & Jobe, 2007; Murray *et al.* 2008; Silverstein & Bellack, 2008; Docherty *et al.* 2009; Jobe & Harrow, 2010; Cornblatt *et al.* 2012).

Post-hospital psychotic symptoms in mood-disordered psychotic patients

The mood-disordered patients showed significantly less psychotic activity than the SZ at five of the six follow-up assessments over the 20 years. Unlike the SZ, only a small percentage of mood-disordered patients had psychotic activity at four or more assessments (only 12%).

Data comparing the initially psychotic (at index) mood-disordered patients indicate that significantly more of the mood-disordered patients treated with antipsychotic medications were psychotic than patients not on antipsychotics at two follow-up assessments over the 20 years [significant at the 7.5-year follow-ups (χ^2=3.76, df=1, p=0.05) and the 10-year follow-ups (χ^2=8.17, df=1, p<0.01)].

Rehospitalization

Assessing rehospitalization, at four of the six assessments at least 50% of SZ with moderately severe or very severe psychotic symptoms were rehospitalized. SZ continuously prescribed antipsychotics were rehospitalized significantly more frequently than SZ not prescribed antipsychotics at any follow-ups (t=5.56, df=38, p<0.001). For SZ, there was a correlation at the 20-year assessment between severity of psychosis and rehospitalization at some point during the year (r=0.44, df=49, p<0.001). Some SZ who were not psychotic were also rehospitalized, but for most SZ the data suggest that psychosis was an important factor in rehospitalization.

Discussion

Data from previous reports and from our longitudinal sample indicate that not all SZ need long-term antipsychotic treatment (Bleuler, 1978; Fenton & McGlashan, 1987; Harding *et al.* 1987; Harrow & Jobe, 2007; Jablensky & Sartorius, 2008; Harrow *et al.* 2012; Wunderink *et al.* 2013). Major questions concerning antipsychotic treatment have been raised by several authors (Tranter & Healy, 1998; Healy, 2002; Moncrieff, 2009*a*,*b*; Whitaker, 2011; Morrison *et al.* 2012). These questions concern risk–benefit ratios and potentially serious side-effects (ADA, 2004; Ho *et al.* 2011; Zipursky *et al.* 2013). In addition, some clinical research has suggested positive results with reduced use of antipsychotics on acute-phase patients (Ciompi & Hoffmann, 2004; Bola *et al.* 2009; Seikkula *et al.* 2011).

Looking at a related but somewhat different and more theoretical issue, Kendler & Schaffner (2011) have summarized a large amount of research designed to evaluate the dopamine hypothesis of schizophrenia (DHS). They point out, using a Bayesian approach, that the empirical evidence attempting to confirm the DHS has produced very few positive findings. However, the empirical evidence on the validity of the dopamine hypothesis of antipsychotic drug action (DHAPDA) is very strong, based on studies of duration 6 months to 2 years. Our negative results do not apply to the short-term pharmacological evidence on the DHAPDA but do suggest that, when assessing long-term outcome, these medications may cease to have positive effects for many patients.

The current research focused on whether long-term use of antipsychotics reduces or eliminates psychosis in schizophrenia. Not available to the field before have been multi-assessment long-term data on psychotic activity in SZ treated with antipsychotic medications for a 20-year period, systemically studying the relationship between antipsychotic medications, the frequency and severity of psychotic symptoms and changes over a multi-year period in psychotic symptoms. Does the short-term efficacy of antipsychotics (first 2–3 years) continue with long-term use of these medications? Analysis of some non-psychiatric medications indicates that their short-term efficacy persists for many years afterwards, whereas for other medications (e.g. use of adrenergic agents in chronic asthma), the body eventually readjusts and they become ineffective.

Surprisingly, the data on frequency over a 20-year period indicate that a high percentage of SZ continuously prescribed antipsychotics showed psychotic activity at most follow-up years, suggesting that, for some or many SZ, prolonged use may impede the possibility of recovery. A significant minority of SZ showed more favorable outcomes without prolonged use of antipsychotics.

The current research involved a naturalistic or observational study, within a longitudinal framework.

Research using a randomized assignment of patients to the experimental variables under study can provide more definitive results, although randomized studies are difficult to conduct when investigating results over 10 years. However, Wunderink *et al.* (2007, 2013) used a randomized design to study long-term antipsychotic use. They studied a first-episode SZ sample hospitalized at a similar age as our sample and used a dose-reduction/discontinuation scheme extending the assessments of patients to a 7-year period. Their study, involving a randomized design, and ours, using a 20-year naturalistic design, found similar results indicating poorer outcome for SZ prescribed antipsychotics over a prolonged period. Both studies found a significantly better outcome for unmedicated SZ, including similar time points (after 2 years), when significant differences in favor of unmedicated SZ emerged (see Figs 2 and 4). Other recent studies have emphasized the importance of psychosocial programs and other approaches to treatment for SZ (McGorry *et al.* 2013; McGurk *et al.* 2013; Mueser *et al.* 2013).

Longitudinal evidence suggests that long-term outcome for schizophrenia in the modern era has not improved much from the pre-antipsychotic era (Hegarty *et al.* 1994; Jääskeläinen *et al.* 2013).

In the current sample, none of the 25 SZ prescribed antipsychotics continuously were completely psychosis free throughout the 20-year period. By contrast, there was a low frequency of psychotic symptoms for most SZ continuously not on antipsychotics (group 3). Several of them had left treatment.

Lack of adherence to prescribed medications reduces the effectiveness of antipsychotics for patients. In research on medication adherence for psychiatric patients with psychosis, the mean rate of adherence was estimated at 58% (Cramer & Rosenheck, 1998; Osterberg & Blaschke, 2005). Lack of adherence contributes to the very poor outcome in some patients in treatment. However, the very large significant differences, in the opposite direction from that expected, found in rates of psychosis and rehospitalization when comparing unmedicated SZ to those prescribed antipsychotics is so striking and the timing consistent with other reports about antipsychotic effects diminishing or even reversing after the 2–3-year period (Harrow *et al.* 2005, 2012; Harrow & Jobe, 2007; Wunderink *et al.* 2013) that it suggests adherence is not the main factor contributing to poor outcome.

In addition, lack of adherence does not contribute to the relatively favorable outcomes of many SZ who were unmedicated for many years. Often, these unmedicated SZ are not taken into account in estimates of outcome in schizophrenia. The field knows very little about this type of SZ. Cohen & Cohen (1984) have noted the bias that can arise from our more frequent clinical contact with chronic poor outcome patients.

The data also have bearing on the issue of whether SZ prescribed antipsychotics became non-psychotic and then afterwards stopped taking medications and remained psychosis free. This is unlikely because analysis of the 12 SZ with complete data at the first two follow-ups who were not on antipsychotics at both follow-ups indicates that, among those SZ who had psychotic activity at the first 2-year follow-up, 57% had improved and were not psychotic at the second 4.5-year follow-up.

By contrast, there were 29 SZ who were on antipsychotics at both of the first two follow-ups, and 21 of them had psychotic activity at the first follow-up. Only two of these 21 SZ (10%) were not psychotic at the second follow-up. After the acute phase, these medications are viewed as antipsychotics, but the high number of treated SZ with psychotic activity provides strong evidence that, for most SZ, long-term antipsychotic treatment does not eliminate or reduce psychosis.

The psychosis of some SZ diminished after they were continuously off antipsychotics, only to return later, while others stayed psychosis free for much of the remaining 15–18 years.

In addition, the 20-year data for SZ continually prescribed antipsychotics did not show reductions in severity over time in terms of 'milder' psychosis at the 20-year follow-ups than at the 2-year follow-ups, although they also did not show an increase in severity over time.

Would these SZ be psychotic more frequently if they were not being treated with antipsychotics?

The SZ continuously prescribed antipsychotics over the 20-year period showed a surprisingly frequent presence of psychotic activity (psychosis at four or more of the five or six follow-ups). These results suggest that, longitudinally, the antipsychotics are not effective in eliminating or reducing psychosis for the great majority of SZ, and may impede the recovery of some SZ.

Analyzing severity: would the SZ psychotic activity be more severe if they were not treated with antipsychotics?

During the acute phase, when hospitalized, a large number of SZ have florid psychosis, and the use of antipsychotics reduces the severity of psychosis for many SZ. Most theorists view this as a direct antipsychotic effect, but some theorists (Moncrieff, 2009*b*) have instead attributed this to antipsychotics leading

to emotional indifference, with dulling of all thoughts, including both realistic and psychotic thoughts.

The data rating the severity of psychosis indicate that the psychosis of the majority of SZ prescribed antipsychotics throughout were at least of moderate intensity, with some disruption, rather than very mild or not disruptive at all. With moderate or greater intensity of psychosis and moderate or severe disruption of functioning, they would not fit modern definitions of 'remission' (Andreasen *et al.* 2005).

With regard to severity of psychosis, 20 of the 25 SZ continuously prescribed antipsychotics were rehospitalized during at least two of the different follow-up years they were assessed.

Does long-term administration of antipsychotic medications increase the probability of frequent psychotic activity in SZ?

We found that 72% of SZ prescribed antipsychotics continuously experienced psychotic activity at four or more of the 5–6 follow-ups (Fig. 3). Is the frequent psychotic activity of these SZ just due to their high vulnerability to frequent psychosis, or after prolonged treatment, does antipsychotic use increase the prospects of low-moderate psychosis? The SZ not in treatment do not show this frequent psychosis.

Many SZ continuously prescribed antipsychotics were poor prognosis SZ, and the SZ who stopped taking antipsychotics may have had a milder illness. The poorer prognostic features probably contributed to their experiencing psychotic symptoms. However, the very large significant differences in the opposite direction from that expected of medicated patients, with their very high frequency of psychotic activity, makes it unlikely that milder illness in some unmedicated SZ accounts completely for these differences. As noted earlier, psychosis is probably a consequence of a combination of different factors co-occurring, rather than only one factor. In addition, when SZ with poor prognostic features who were not prescribed antipsychotics were compared to SZ continuously prescribed antipsychotics, SZ prescribed antipsychotics showed more frequent psychosis over time.

Psychosis in mood-disordered patients

Not surprisingly, at five of the six follow-up assessments over the 20-year period, initially psychotic mood-disordered patients were significantly less psychotic than the SZ. These data fit models in which bipolar patients and unipolar depressives who were psychotic at index hospitalization, while still vulnerable to psychosis (all were psychotic at the acute phase), are considerably less vulnerable to psychosis than SZ.

The data on SZ and mood-disordered patients who were psychotic at index hospitalization could be interpreted as indicating that, for SZ (who are more vulnerable to psychosis), the antipsychotics, on a long-term basis, may increase their chances of psychosis. However, the less vulnerable (to psychosis) mood-disordered patients still showed some limited vulnerability to psychosis over time and have a greater vulnerability than initially non-psychotic depressives (Sands & Harrow, 1994), but do not have as frequent psychotic activity because of their lower vulnerability, as compared to SZ.

Conclusions

The surprisingly frequent psychotic activity for most SZ continuously prescribed antipsychotics was in contrast to the significantly less psychosis for unmedicated SZ. The relatively high percentage of continuously prescribed SZ with moderate levels of psychosis at many follow-ups could be influenced by a combination of factors. The most important factor is the high vulnerability to psychosis of many SZ, which leads to a high risk of psychosis. Another factor could be prolonged treatment with partial dopamine blockers or antipsychotics, which may produce a medication-generated build-up of supersensitive dopamine receptors or excess dopamine receptors for some or many SZ. Evidence for this has been found in important animal research (e.g. Seeman *et al.* 2006; Seeman & Seeman, 2014) and in human research (Chouinard & Jones, 1980; Fallon *et al.* 2012) studying relapse in treatment-compliant patients, and in other research (Kurita *et al.* 2012). The combination of these two high-risk factors, acting together, could dramatically increase the possibility of psychotic symptoms. If multi-year use of antipsychotics increases the possibility of psychosis, as the data suggest, does it increase it for some or all SZ? Further research is needed in this area (Tranter & Healy, 1998).

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Declaration of Interest

None.

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