Symptom Recurrence Following Intermittent Treatment in First-Episode Schizophrenia Successfully Treated for 2 Years: A 3-Year Open-Label Clinical Study

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ABSTRACT

Objective: An unanswered question in the management of schizophrenia is how long antipsychotic treatment should be continued after a single psychotic episode. In this study, we assessed the rates of symptom recurrence with intermittent treatment in patients with a first episode of *DSM-IV*–defined schizophrenia or related illness after 2 years of successful continuous treatment. We also investigated antecedents of recurrence, as well as demographic and baseline clinical predictors of early recurrence, and we compared the psychopathology of the recurrence episode with that of the first episode.

Method: Outpatients in an academic psychiatric hospital setting (single site) who had responded well in an open-label study with risperidone long-acting injection were recruited for this intermittent treatment trial, and those who participated had their treatment tapered and discontinued over a period of up to 6 weeks, with follow-up for 3 years or until reemergence of symptoms. Open-label treatment with oral risperidone and risperidone long-acting injection was immediately reinstituted in the event of recurrence of symptoms. The study was conducted between February 2004 and March 2010. The primary outcome measure was symptom recurrence rate at 3 years.

Results: Participants (N = 33) had a mean age ± SD of 28 ± 7.9 years and a mean baseline Positive and Negative Syndrome Scale total score ± SD of 44.8 ± 7.4 at study entry. Symptom recurrence rates were 79% at 12 months, 94% at 24 months, and 97% at 36 months. Onset of recurrence symptoms was fairly abrupt, and symptom severity returned to levels close to those of the first episode. No significant predictors of early recurrence were identified.

Conclusions: Intermittent antipsychotic treatment, even after 2 years of successful treatment, may not be in the best interest of patients who have experienced a single psychotic episode.

Trial Registration: ClinicalTrials.gov identifier: NCT00378092

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While patients typically respond well to antipsychotic treatment for a first episode of schizophrenia,[1] an unanswered question is how long the treatment should be continued. Guidelines typically recommend 1 to 2 years for patients who achieve symptom stabilization (eg, see references 2–5), although it is not known whether a longer duration of treatment reduces the risk of recurrence.

The rationale for considering antipsychotic withdrawal is based on a supposition that a substantial portion (perhaps 10%–20%) of patients will never experience a recurrence after a single psychotic episode.[6] Unnecessary continuation of antipsychotic medication is undesirable due to the significant side-effect burden associated with these agents. An additional consideration is that clinicians may have difficulty in convincing patients that indefinite treatment is indicated. Medication discontinuation is common after the first episode, and the decision to discontinue medication is largely patient driven.[7]

The possible advantages of intermittent maintenance treatment need to be weighed against the consequences of recurrence of psychotic illness. There is a risk of such patients harming themselves or others, and relationships, education, or employment may be jeopardized. Also, it has been proposed that patients may not return to their previous level of functioning and that treatment resistance may emerge.[8,9]

While a targeted intermittent treatment strategy (ie, dose reduction and discontinuation if feasible, with immediate reintroduction of treatment if symptoms reemerge) reported similar symptom control to maintenance treatment,[10] it was later found that continuous medication was superior in preventing decompensations and hospitalizations and in the extent of employment at 2 years.[11] Intermittent maintenance treatment strategies have not been widely adopted, and the recently revised schizophrenia Patient Outcomes Research Team recommendations[12] advise against their routine use due to the increased risk of symptom worsening and relapse.

While studies of treatment discontinuation consistently report higher relapse rates than studies of maintenance treatment, results vary widely. In a comprehensive review, Gilbert et al[13] found a mean cumulative relapse rate of 52% (range, 0%–100%) over a mean follow-up period of 6.3 months (range, 0.5–24 months) for patients withdrawn from antipsychotics, versus 16% for those maintained on antipsychotic treatment. However, all but 2 of the 66 studies included in their review were conducted in chronic, multiepisode samples.

The following studies in first-episode samples have been reported: In a randomized, double-blind, placebo-controlled relapse prevention study (N = 28), Kane et al[14] reported a 41% relapse rate after 12 months of antipsychotic discontinuation, versus 0% for patients receiving maintenance treatment. In a multisite randomized controlled trial (N = 120), Crow et al[15] observed relapses over 2 years' time in 62% of patients whose treatment was discontinued, versus

Clinical Points

- After a single psychotic episode, most patients will experience symptom recurrence with reduction and discontinuation of treatment, even after 2 years of treatment.
- Clinicians should be aware that onset of relapse may be abrupt and early warning signs may be short-lived.
- At onset of relapse, symptom severity returns rapidly to levels close to those observed in the first psychotic episode.

46% in those who received maintenance treatment. Gitlin et al[16] investigated clinical course following antipsychotic discontinuation after at least 1 year of treatment in 53 patients with recent-onset schizophrenia and found that 78% experienced an exacerbation or relapse within 1 year and that 96% did so within 2 years. Wunderink et al[17] compared guided antipsychotic discontinuation with maintenance antipsychotic therapy in a randomized study among 131 patients with first-episode schizophrenia after 6 months of remission. Of 65 patients randomized to the discontinuation arm, 14 (21.5%) had no symptom recurrence, 16 (24.6%) relapsed, and 5 (7.7%) had mild symptom recurrence. In 30 subjects (46.2%) in the discontinuation arm, antipsychotics were not discontinued.[17] Finally, the results of 2 randomized controlled trials comparing treatment discontinuation with maintenance treatment have recently been reported. Gaebel et al[18] compared targeted intermittent treatment and maintenance treatment after 1 year of antipsychotic treatment among 44 patients with first-episode schizophrenia. Relapse rates and symptom worsening rates were significantly higher in the intermittent treatment group compared with the maintenance group (57% vs 4%, respectively). Chen et al[19] compared maintenance treatment using quetiapine 400 mg/d with intermittent treatment after 1 year of treatment among 178 remitted patients with first-episode psychosis. The risk of relapse at 12 months was 41% (95% CI, 29%–53%) for the quetiapine-treated patients and 79% (95% CI, 68%–90%) for the placebo group ($P < .001$).

The present study aimed to determine rates of symptom recurrence after introducing an intermittent treatment strategy in patients with first-episode schizophrenia who had received 2 years of continuous antipsychotic treatment and had responded well. We also investigated antecedents of symptom recurrence, severity of recurrence, and selected predictors of early symptom recurrence.

METHOD

Patient Disposition

Patients were considered for inclusion if they had successfully completed a previously reported 24-month, open-label study in which 50 patients with first-episode schizophrenia were treated with flexible doses of risperidone long-acting injection over 2 years.[20] This was a single-site study conducted in an academic psychiatric hospital setting. Inclusion criteria for the initial 24-month treatment study were a *DSM-IV* diagnosis (using the Structured Clinical Interview for *DSM-IV* Axis I Disorders[21]) of schizophrenia, schizophreniform disorder, or schizoaffective disorder for ≤ 12 months and cumulative exposure to antipsychotic medications of ≤ 12 weeks. Patients were excluded if they had another Axis I diagnosis, required mood stabilizers or antidepressants, or had significant medical illness. Patients were eligible to participate in the current study if they had completed the initial study and were judged to have responded well to treatment and to be clinically stable. Potential participants were excluded if they required mood stabilizers, were diagnosed with alcohol or drug dependence within a month prior to enrollment, or were at acute risk or had a history of suicide attempts.

Study Design

This study was an unblinded, noncomparative, single-site study (clinicaltrials.gov Identifier: NCT00378092). For patients taking higher than the minimum dose of risperidone long-acting injection (25 mg every 2 weeks), medication was tapered over a period of up to 6 weeks when necessary. Thereafter, any antipsychotics, mood stabilizers, or psychostimulants were not permitted. Lorazepam was allowed for sedation, as were antidepressants for depression or anxiety symptoms. The day of last dose of risperidone long-acting injection at pretapering levels was taken as baseline. The follow-up period was 3 years.

Precautions were taken as recommended for medication-free research in schizophrenia[22] to ensure that participants were freely consenting and competent and that risks were minimized. The study received ethical approval from the Human Research Ethics Committee of the University of Stellenbosch, Cape Town, South Africa. Patients and their families/caregivers were informed of the risks and benefits of the intermittent treatment strategy and were offered the alternative of ongoing maintenance treatment. Gradual antipsychotic discontinuation has been used to reduce the risk of relapse and was achieved in our study by using risperidone long-acting injection. Relapse rates after discontinuation of conventional depot antipsychotics with long washout periods are lower than with oral antipsychotic medication.[23] Similarly, pharmacokinetic studies of risperidone long-acting injection have shown that antipsychotic levels persist for weeks after the last dose.[24] Patients and caregivers were educated about early warning signs for which the patient should be monitored, and they were provided with a 24-hour mobile telephone number with instructions to contact the study coordinator in the event of concerns about possible recurrence of symptoms. Following treatment discontinuation, patients were formally assessed every 2 months during the first year and every 3 months thereafter. More frequent staff-patient contact was provided as needed. For patients considered at high risk for relapse, additional

telephone contact was maintained. In the event of recurrence of symptoms, open-label treatment with oral risperidone and risperidone long-acting injection was immediately reinstituted, and patients were followed up for a further 2 years. In the event of any clinical concerns in patients with symptom recurrence, hospitalization was arranged as a precautionary measure. The entire study was conducted between February 2004 and March 2010.

Assessments

Participants were assessed by means of the following instruments: the Positive and Negative Syndrome Scale (PANSS),[25] the Clinical Global Impressions-Severity of Illness (CGI-S) and -Change (CGI-C) scales,[26] the Calgary Depression Scale for Schizophrenia (CDSS),[27] the 12-item Short-Form Health Survey (SF-12),[28] the Social and Occupational Functioning Assessment Scale (SOFAS),[29] and the Patient Global Impression of Severity (PGI-S) and Patient Global Impression of Change (PGI-C) scales.[30] Assessments were performed by experienced investigators who underwent periodic rater training for the PANSS. Interrater reliability for the PANSS was between 0.86 and 0.93.

Outcome Measures

The clear-cut reemergence of psychotic symptoms was regarded as symptom recurrence. We used the following broad, operationalized criteria of Csernansky et al[31] to define relapse: significant clinical deterioration, defined as a CGI-C score of 6 (much worse); 25% increase in PANSS total score; hospitalization; significant suicidal or homicidal ideation; deliberate self-injury; and violent behavior. Recurrence was diagnosed by the investigator at the exit visit, and the time between first reemergence of any symptoms to that visit was estimated. Time to loss of remission status was evaluated for patients who were in remission at study entry. Remission was defined according to the Remission in Schizophrenia Working Group criteria.[32]

To explore for early warning signs at visits before symptom recurrence, we calculated scores on the various symptom severity scales (PANSS total and PANSS factor analysis–derived domain[33] scores, CDSS, and CGI) for the visits preceding symptom recurrence visits. With the recurrence visit as the starting point, we grouped patients according to the 3 most recent visits prior to the recurrence visit. The ability of patients to recognize early signs of recurrence was assessed at these same time points (by means of the PGI-C), as were patient functionality (SOFAS) and quality of life (SF-12 physical and mental components).

Finally, to compare the symptom profiles and severity of the recurrence episode with that of the first episode, we compared PANSS total and subscale scores at the recurrence visit with those from the baseline visit in the initial study[20] for the 32 patients who had experienced recurrence.

Data Analysis

All subjects were included in the data set. Demographics were evaluated with descriptive statistics. Score changes from baseline were tested using Wilcoxon signed rank test (ordinal/continuous data) and sign test (nominal data). Results are reported as mean ± standard deviation (SD). Differences were interpreted at the 5% significance level (2-tailed). Time to relapse and time to loss of remission status were estimated using Kaplan-Meier survival curves.

Table 1. Baseline Demographic and Clinical Characteristics (N = 33)

Characteristic	Data
Sex, n (%)	
Male	19 (57.6)
Female	14 (42.4)
Duration of untreated psychosis, mean ± SD, d	97 ± 112
Age, mean ± SD, y	28 ± 7.9
Ethnicity, n (%)	
White	4 (12.1)
Black	2 (6.1)
Mixed	27 (81.8)
Diagnosis, n (%)	
Schizophreniform disorder	17 (51.5)
Schizophrenia	16 (48.5)
Catatonic	1 (6.3)
Disorganized	1 (6.3)
Paranoid	6 (37.5)
Undifferentiated	8 (50.0)
Schizoaffective disorder	0 (0)
PANSS total score, mean ± SD	44.8 ± 7.4

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Predictors of Early Recurrence

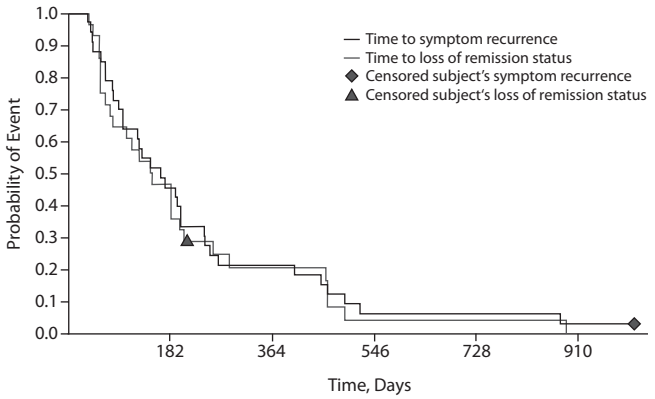
We divided the sample into those who experienced early symptom recurrence and those who experienced late symptom recurrence. We chose 12 months as the cut point on the basis of visual inspection of the survival curve. Step-wise logistic regression was conducted with the following variables entered into the model: age, sex, age at onset of illness, and baseline scores for PANSS total, PANSS factors, PANSS insight item, CGI-S, PGI-S, CDSS, SOFAS, and SF-12.

RESULTS

Thirty-three of 50 patients completed the 2-year treatment study with risperidone long-acting injection and were eligible to participate in the present study. All chose to take part and were subsequently enrolled. Baseline demographic and clinical details of the 33 participants are provided in Table 1. None had experienced a relapse in the preceding 2-year treatment period. At entry to this study, none of the participants were hospitalized, and 28 (84.8%) were in remission. Dosing for risperidone long-acting injection at the end of the previous study was 25 mg every 2 weeks for 20 patients (60.6%), 37.5 mg every 2 weeks for 10 patients (30.3%), and 50 mg every 2 weeks for 3 patients (9.1%).

Symptom recurrence rates were 79% at 12 months, 94% at 24 months, and 97% at 36 months. Mean ± SD time to recurrence was 207 ± 187 days. No participants completed the 36-month study period. One participant, who did not experience symptom recurrence, was withdrawn from the study after refusing to attend the final 36-month evaluation

Figure 1. Kaplan-Meier Plots of Time Until Loss of Remission Status and Time Until Symptom Recurrence[a]



[a]One subject was censored in the "time to symptom recurrence" analysis. This subject was lost to follow-up after month 33. In the "time to loss of remission status" analysis, 1 subject was censored. This subject experienced symptom recurrence after 210 days (defined by a Clinical Global Impressions score of 6) but, at the same time, continued to meet remission criteria.

Table 2. Mean Assessment Scale Scores for the Patients With Symptom Recurrence (N = 32) at Baseline, at the 3 Visits Preceding Symptom Recurrence, and at Symptom Recurrence

Assessment Scale Score	Baseline (n = 32), Mean	Visit 3 (n = 19), Mean	Visit 2 (n = 28), Mean	Visit 1[a] (n = 32), Mean	Symptom Recurrence Visit (n = 32), Mean
PANSS total	44.5	42.5	43.8	43.1	87.4
PANSS positive factor	11.6	11.0	11.3	11.2	27.5
PANSS negative factor	13.0	11.6	12.3	11.8	20.7
PANSS disorganized factor	11.8	11.4	11.7	11.7	22.0
PANSS excitement/hostility factor	4.1	4.1	4.1	4.3	8.7
PANSS depression/anxiety factor	4.1	4.3	4.4	4.1	8.7
PANSS lack-of-insight item	3.1	2.9	3.0	3.0	4.1
CGI-S	1.3	1.4	1.3	1.2	4.1
CDSS	0.4	0.0	0.4	0.4	2.3
CDSS suicidality item	0.0	0.0	0.0	0.0	0.1
SOFAS	66.5	67.6	66.4	68.3	40.8
PGI-S	1.2	1.1	1.1	1.3	2.6
SF-12 physical component	51.9	51.0	50.9	50.8	45.6
SF-12 mental component	48.1	53.1	49.0	50.7	40.7

[a]Mean days ± SD between visit 1 and symptom recurrence visit = 38.5 ± 22.5 days.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, PGI-S = Patient Global Impression of Severity scale, SF-12 = 12-item Short-Form Health Survey, SOFAS = Social and Occupational Functioning Assessment Scale.

visit. Mean time to loss of remission status ± SD for those patients who were in remission was 203 ± 194 days. Figure 1 presents the superimposed Kaplan-Meier plots of time until loss of remission status and time until symptom recurrence. The 2 curves closely follow each other, indicating that the interval between loss of remission status and onset of symptom recurrence is small.

Table 2 provides mean scores for the symptom severity scales at baseline, at the 3 visits prior to recurrence, and at the symptom recurrence visit. Results show that levels of psychopathology (psychotic and nonpsychotic), insight, suicidality, social and occupational functioning, and quality of life remained essentially unchanged from baseline for the visits preceding recurrence of psychosis. Post hoc inspection of the source notes indicated that families and caregivers estimated the time from onset of first noticeable symptoms to the recurrence visit to be a mean of 16.3 ± 10.9 days. Of the 32 patients (97%) who had symptom recurrence, 12 (38%) were hospitalized. Thirty-one of the 32 patients with symptom recurrence met predefined relapse criteria[31] at the exit visit. Twenty-six patients were classified as having early recurrence and 6 as having late recurrence. Logistic regression analysis indicated that none of the potential predictor variables were able to significantly predict early recurrence of symptoms (Table 3).

Mean PANSS scores ± SD at baseline in the initial study (first psychotic episode)[20] and those at the exit visit in the current study (symptom recurrence visit), respectively, for

Table 3. Results of the Step-Wise Regression Analysis for Potential Predictors of Early Symptom Recurrence[a]

Explanatory Variable	Odds Ratio (95% CI)	Wald χ^2	*P* Value
Age[b]	0.952 (0.859–1.055)	0.8752	.3495
Gender	0.469 (0.086–2.547)	0.7697	.3803
Age at onset of illness	0.952 (0.859–1.055)	0.8752	.3495
Duration of untreated psychosis	1.009 (0.990–1.028)	0.8525	.3559
PANSS negative subscale[b]	1.069 (0.890–1.283)	0.5041	.4777
PANSS general psychopathology subscale[b]	0.977 (0.764–1.249)	0.0349	.8517
PANSS total[b]	1.033 (0.912–1.170)	0.2604	.6098
PANSS Marder positive symptoms factor[b]	1.015 (0.708–1.456)	0.0067	.9350
PANSS Marder negative symptoms factor[b]	1.066 (0.880–1.292)	0.4310	.5115
PANSS Marder disorganized thoughts factor[b]	0.997 (0.660–1.508)	0.0002	.9898
PANSS insight item G12[b]	0.499 (0.166–1.500)	1.5325	.2157
Clinical Global Impressions-Severity of Illness[b]	1.929 (0.278–13.408)	0.4411	.5066
Patient Global Impression of Severity[b]	0.690 (0.139–3.414)	0.2073	.6489
Social and Occupational Functioning Assessment Scale[b]	0.905 (0.737–1.113)	0.8946	.3442
SF-12 physical component[b]	0.954 (0.826–1.103)	0.4002	.5270
SF-12 mental component[b]	0.964 (0.883–1.052)	0.6841	.4082

[a]Early symptom recurrence defined as symptom recurrence within 1 year.
[b]At entry into the initial treatment trial.
Abbreviations: PANSS = Positive and Negative Syndrome Scale, SF-12 = 12-item Short-Form Health Survey.

Table 4. Studies of Intermittent Treatment After a First Episode of Psychosis

Study	N	Treatment Duration	Symptom Recurrence Rate, %				Comparator Recurrence Rate, %
			12 Months	18 Months	24 Months	36 Months	
Kane et al (1982)[14]	28	Not specified	41				0
Crow et al (1986)[15]	120	Not specified			62		46
Gitlin et al (2001)[16]	53	3 months in remission	78		96		NA
Wunderink et al (2007)[17]	131	6 months in remission		43			21
Gaebel et al (2010)[18]	44	12 months	57				4
Chen et al (2010)[19]	178	12 months+	79				41
Emsley et al (current study)	33	24 months	79		94	97	NA

Abbreviation: NA = not applicable.

the 32 patients who experienced symptom recurrence were as follows: PANSS total, 92.7 ± 14.4 and 87.4 ± 15.2 ($P = .05$); PANSS positive subscale, 25.4 ± 3.9 and 21.2 ± 4.8 ($P = .0001$); PANSS negative subscale, 25.5 ± 8.7 and 24.2 ± 6.4 ($P = .2$); and PANSS general psychopathology subscale, 41.8 ± 6.9 and 42.1 ± 8.0 ($P = .7$).

DISCUSSION

There were 3 main findings in our study. First, there was a very high symptom recurrence rate. Second, symptoms returned relatively abruptly, and early warning signs were not evident at the preceding visits. Third, despite the much shorter duration of active illness for the recurrence episode, symptoms returned to levels close to those observed in the first psychotic episode.

Our results, together with those of other published studies, suggest that even after a single psychotic episode most patients will experience symptom recurrence with intermittent treatment if followed for a sufficient period of time. Table 4 depicts studies to date that have investigated rates of recurrence after treatment reduction/discontinuation in first-episode samples and shows that there is no clear relationship between prior duration of treatment and recurrence rates. The 2-year treatment duration of our initial study was longer than in the other studies and did not reduce risk of recurrence. The follow-up period in our study was also longer than in the other studies, and, as would be anticipated, recurrence rates are related to the duration of follow-up after treatment discontinuation. Our 12-month recurrence rate of 79% is similar to the rates reported by Gitlin et al[16] (78%) and Chen et al[19] (79%), but it is considerably higher than the rates reported by Kane et al[14] (41%) and Gaebel et al[18] (57%). Our 24-month recurrence rate of 94% was similar to that of Gitlin et al[16] (96%) but higher than that of Crow et al[15] (62%). Differences in patient samples and study methodologies may explain some of these disparities. Together with the results of the Gitlin et al[16] study, our findings suggest that, if patients are followed up for long enough, the majority will relapse after treatment discontinuation.

While the present study was not specifically designed to detect early warning signs, 3 aspects of our findings suggest that transition from remission to relapse occurs relatively abruptly in many patients. First, the low levels of symptomatology at study entry remained that way up until and including the visit immediately prior to recurrence. Second, the superimposed survival curves indicate that remission status was retained until shortly before relapse. Third, the

retrospective estimates of family members and caregivers indicated a duration of days to weeks between the onset of the first recognizable symptoms and clear-cut symptom recurrence. These findings need to be interpreted with caution, as formal assessments were conducted only at 2-month (and later 3-month) intervals and it is quite possible that more frequent assessments by a trained clinician would have picked up more subtle changes prior to relapse. Indeed, some studies[34–36] suggest that relapse is a more gradual process and that early warning signs may be useful in predicting relapse. Other studies[37,38] indicate that, while early warning signs may be present, they are frequently of brief duration—days or at best weeks. Our results are consistent with several other studies[39–42] that found early warning signs to be unreliable predictors of relapse. It is important to note that several factors may confound the comparison of precursor symptoms of a first psychotic episode with those of a subsequent relapse. For example, residual symptoms may be difficult to distinguish from prodromal symptoms, and medication is likely to be started earlier with relapses compared with first psychotic episodes. Nonetheless, evidence suggests that the precursors of a psychotic relapse are different from those of a first episode of psychosis. In the latter (ie, first episode), prodromal symptoms are the rule and appear gradually, frequently preceding the onset of psychosis by months or even up to several years.[43] For recurrence episodes, it seems that early warning signs appear days, and at best weeks, before the onset of florid psychotic symptoms in most cases and that symptom severity returns to levels similar to those observed in the first episode.

Besides the unreliability of early warning signs, an added difficulty for clinicians is our inability to predict which patients will require continuous treatment to prevent relapse.[44] Our failure to identify any significant demographic or clinical predictors of early symptom recurrence was therefore not unexpected and was consistent with previous reports,[45] although poor premorbid functioning has been described by some as a risk factor for relapse.[46,47] Several recurrences occurred within a few weeks of baseline, suggesting that these recurrences may have happened in the presence of substantial antipsychotic occupancy of D2 receptors, given the persistence of steady-state blood levels for several weeks after the last dose of risperidone long-acting injection.[24]

There are several limitations to this study, including small sample size, absence of a control group, relative infrequency of formal assessment visits, and lack of a scale to specifically detect prodromal symptoms. Further, the fact that treatment discontinuation was open is a potential weakness in that patients, their families, and clinicians were all aware that no treatment was being administered. Also, selection bias limits the generalizability of the results. On the one hand, this study specifically targeted patients who were likely to have a better outcome; our results may therefore differ from results among a less responsive population (while the relapse rates could not increase, the course after symptom recurrence could be worse). On the other hand, very mildly ill patients may not have been recruited because of doubts about the need for 2 years of treatment with risperidone long-acting injection. Strengths of the study include the use of validated operationalized criteria for diagnosis of schizophrenia and for remission and relapse, the relatively long treatment and follow-up periods, the standardized treatment regimen, and the elimination of covert nonadherence as a potential confounder by using a long-acting injectable antipsychotic.

CONCLUSIONS

This study confirms high recurrence rates with intermittent treatment following a first episode of psychosis. Our results extend previous findings by suggesting that (1) a longer treatment period does not reduce the risk of relapse; (2) if patients are followed up long enough, the majority are likely to relapse; and (3) when recurrences do occur, there is a rapid return of symptoms to severity levels similar to the first episode.

Drug names: lorazepam (Ativan and others), quetiapine (Seroquel), risperidone (Risperdal and others).

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