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Clinical Outcome After Antipsychotic Treatment Discontinuation in Functionally Recovered First-Episode Nonaffective Psychosis Individuals:

A 3-Year Naturalistic Follow-Up Study

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ABSTRACT

Objective: The timing of antipsychotic discontinuation in patients who have fully recovered from their initial episode of psychosis is still open to discussion. We aimed to evaluate the risk of symptom recurrence during the 3 years after antipsychotic discontinuation in a sample of functionally recovered first-episode nonaffective psychosis (FEP) patients (*DSM-IV* criteria) with schizophrenia spectrum disorder.

Method: Participants in this open-label, nonrandomized, prospective study were drawn from an ongoing longitudinal intervention program of FEP from a university hospital setting in Spain. From July 2004 to February 2011, functionally recovered FEP individuals were eligible if they met the inclusion criteria of (1) a minimum of 18 months on antipsychotic treatment, (2) clinical remission for at least 12 months, (3) functional recovery for at least 6 months, and (4) stabilization at the lowest effective doses for at least 3 months. Forty-six individuals who were willing to discontinue medication were included in the discontinuation group (target group). Twenty-two individuals opted to stay on the prescribed antipsychotic medication and therefore were included in the maintenance group (control group). Primary outcome measures were relapse rate at 18 and 36 months and time to relapse.

Results: The rates of relapse over the 3-year period were 67.4% (31 of 46) in the discontinuation group and 31.8% (7 of 22) in the maintenance group. The mean time to relapse was 209 (median = 122) days and 608 (median = 607) days, respectively (log rank = 10.106, $P = .001$). The resumption of antipsychotic medication after the relapse occurred was associated with clinical stability and lack of further relapses. When the overall group of relapsed individuals from the 2 conditions (N = 38) was compared to those who remained asymptomatic after 3 years (N = 30), there were significant differences ($P < .05$) in total scores on the Scale for the Assessment of Negative Symptoms, the Clinical Global Impressions scale, and the Disability Assessment Schedule.

Conclusions: Antipsychotic treatment discontinuation in individuals who had accomplished a functional recovery after a single psychotic episode was associated with a high risk of symptom recurrence. Relapsed individuals had a greater severity of symptoms and lower functional status after 3 years.

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In clinical practice, physicians very often face the dilemma of maintaining their patients' antipsychotics, thereby increasing the risk of side effects, or discontinuing them, risking relapse in those patients who have fully recovered from their initial episode of psychosis. Antipsychotics play a crucial role in diminishing "bloom" psychotic symptoms in the acute phase[1,2] and also in preventing relapses during the maintenance phase.[3,4] Nonetheless, maintenance prophylactic antipsychotic medication also has metabolic, motor, and cognitive disadvantages, and the lowest effective-dose regimen is highly recommended.[5] A lack of insight into the prophylactic effects of medicine, emergence of disturbing side effects, and concerns over the long-term harm associated with antipsychotics are key factors that make patients discontinue treatment once their acute symptoms have subsided.

The timing of medication discontinuation for individuals with a single psychotic episode remains unclear. Most of the published guidelines and algorithms do not argue against withdrawing antipsychotics after minimums of 1 year or 2 years of medication.[6] The treatment period was restricted to 2 years because of the paucity of longer randomized (maintenance treatment or placebo) studies of relapse prevention after a first episode.[7] Zipursky,[8] after systematically reviewing the literature, concluded that a trial off of antipsychotic medication should not be recommended. The Canadian clinical practice guidelines propose that patients who have been on medication for at least 1 to 2 years and who have achieved clinical remission and functional recovery may be considered candidates for a trial off of antipsychotic medication.[9] Wunderink and colleagues[10] concluded that in remitted first-episode nonaffective psychosis (FEP) patients, dose reduction or discontinuation of antipsychotics during early phases may have a

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better long-term functional outcome. The profile of patients who would benefit from treatment discontinuation and the optimal duration of prophylactic antipsychotic medication remain unclear.

We aimed to investigate the rate of long-term relapse after antipsychotic treatment discontinuation in functionally recovered first-episode nonaffective psychosis individuals in real-world clinical practice. We hypothesized that functionally recovered patients who stop antipsychotic medication might not have a greater risk of relapse compared to those patients who maintain medication. It was also of interest to investigate potential differences between the 2 groups (discontinuation vs maintenance) in functional outcome and whether those recovered patients who discontinue antipsychotic treatment may have a better long-term functional outcome.

Clinical Points

- In clinical practice, physicians very often face the dilemma of maintaining or discontinuing antipsychotics in those patients who have fully recovered from their initial episode of psychosis. The timing of medication discontinuation for individuals with a single psychotic episode remains unclear.
- Antipsychotic treatment discontinuation is associated with a high rate of relapse even in first-episode nonaffective psychosis patients with a good outcome.
- In those individuals who are willing to discontinue medication, a planned medication withdrawal strategy with a systematic follow-up should be established to prevent unrestrained treatment disengagement.
- Clinicians should provide accurate information to patients and relatives concerning the risks and benefits of withdrawing medication.

METHOD

Study Setting

The participants in this study were drawn from an ongoing longitudinal intervention program of first-episode psychosis, Programa Asistencial de Fases Iniciales de Psicosis (PAFIP), University Hospital Marques de Valdecilla, Santander, Cantabria, Spain (ClinicalTrials.gov: NCT02220504).[11] In conformance with international standards for research ethics, the local institutional review board approved this program. Patients meeting inclusion criteria, and their families, provided written informed consent for the patients to be included in the PAFIP. The full inclusion and exclusion criteria of the PAFIP have been presented elsewhere.[12]

Study Design and Participants

This was an open-label, nonrandomized, prospective clinical study evaluating the outcome at 18 months and 36 months of antipsychotic discontinuation in functionally recovered first-episode nonaffective psychosis individuals (*DSM-IV* criteria) with schizophrenia spectrum disorder. The entry criteria required all subjects to have had a single psychotic episode, to have been stabilized at the lowest effective dose of an antipsychotic regimen, and to have achieved clinical remission and functional recovery. The specific inclusion criteria prior to study entry were: (1) a minimum of 18 months on antipsychotic treatment, (2) meeting clinical remission criteria for at least 12 months, (3) meeting functional recovery criteria for at least 6 months, and (4) being stabilized at the lowest effective dose for at least 3 months. From July 2004 to February 2011, all PAFIP individuals who met the inclusion criteria were invited to participate in the study. Patients were advised of the potential risk of relapse after treatment discontinuation and voluntarily chose discontinuation or maintenance treatment. Sixty-eight first-episode subjects were eligible and agreed to participate in the study. No patients who met the inclusion criteria refused to participate in the study. Patients who were willing to discontinue antipsychotic medication were included in the treatment discontinuation group (target group, n = 46). Twenty-two individuals meeting the inclusion criteria opted to stay on the prescribed antipsychotic medication and therefore were included in the maintenance treatment group (control group). All included patients were clinically and functionally assessed during the 3-year follow-up period.

Treatment Stabilization Prior to Study Entry

Antipsychotic medication was slowly tapered from maximum doses until reaching the lowest effective doses (half or less of the maximum doses) according to the treating psychiatrist's clinical judgment. There was no protocol for tapering the antipsychotic dose from the maximum dose prescribed; however, clinicians were encouraged to slowly taper drugs to achieve the lowest effective dose and to avoid withdrawal or rebound of target symptoms. At the time of treatment discontinuation, patients had been stabilized on the lowest effective doses for at least 3 months. The amount and type of medications being prescribed prior to study entry and during the follow-up period were thoroughly recorded as chlorpromazine equivalent doses.

Definitions of Clinical Remission, Relapse, and Functional Recovery

Remission was defined according to Andreasen's criteria[13] covering the Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS) scores.

Relapse was defined as the occurrence of any of these criteria during follow-up: (1) a rating of 5 or above on any key BPRS[14] symptom items, (2) a Clinical Global Impressions (CGI) scale[15] rating of ≥ 6 and a CGI change score of "much worse" or "very much worse," (3) hospitalization for psychotic psychopathology, or (4) completed suicide. The key BPRS symptoms were unusual thought content, hallucinations, suspiciousness, conceptual disorganization, and bizarre behavior. Exacerbation was defined as any 2-point increase of any of the key BPRS symptoms, excluding changes in which the rating remained at the nonpsychotic level (ie, < 3). Patients were considered to have had a relapse/exacerbation if the reemerged symptoms lasted for at least 1 week.[4,16] The

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reintroduction of antipsychotic treatment was enabled at the treating psychiatrist's discretion once the recurrence of psychotic symptoms was evident. The presence of 3 factors related to the emergence of the relapse/exacerbation were recorded: (1) patient-reported nonadherence to antipsychotic treatment (in the maintenance treatment group only), (2) the use of illicit drugs, and (3) life-related, stressful situations.

Functional status was determined by gathering information from multiple sources about self-care; living; vocational role; and family, partner, and peer relationships. Ratings were based on the information obtained from the patient, relatives, case notes, and observations of the patient during the previous 6 months. The patient and his or her relatives were independently assessed by a psychiatrist and a social worker. In addition, for rating social disability, we used the global disability item from the Spanish version of the Disability Assessment Schedule (DAS).[17] The global disability item has a score range of 0 (no disability) to 5 (gross disability).[17] By combining the above criteria, we dichotomized the functional status as "functional recovery" and "functional deficits." The "functional recovery" status indicated that (1) the patient was currently participating in part-time (paid and fewer than 35 hours per week) or full-time work or study with the same or better level of performance as before the psychotic episode and (2) had no functional disability (score of 0 in the DAS).

Follow-Up Protocol

The discontinuation-treatment patients (target group) were screened every month for the first 6 months and every 2 months from the 7th to 18th month. The frequency of clinical visits was increased if needed because of clinical changes. From the 19th month to the final assessment (36 months), the patients were interviewed for clinical evaluation and assessment according to the treating psychiatrist's clinical criteria. Individuals in the maintenance-treatment group (control group) were regularly seen based on the judgment of the treating psychiatrist during the 3-year follow-up. The BPRS and the CGI ratings were acquired for any clinical interview in which symptomatology changes needed to be assessed to decide the existence of relapse or clinical exacerbation.

Patients were removed from the discontinuation treatment arm and resumed antipsychotic treatment if any of the following conditions were met: (1) psychotic relapse/exacerbation according to previous definitions or (2) clinical worsening that did not meet the relapse criteria but that warranted a change in the treatment regimen. Once it became clear that the patient had clinically significant reemergence of psychotic symptoms, our purpose was to intervene as soon as possible to avoid, if possible, a florid psychotic episode.

In the maintenance-treatment group (control group), individuals continued with the standard regimen of clinical interviews and lowest effective-dose treatment as established by the treating psychiatrist based on patients' clinical status and requirements.

No other psychological interventions were systematically conducted during the 3 years of follow-up in either of the 2 groups. At the treating physician's discretion, lormetazepam, lorazepam, or clonazepam were permitted for clinical reasons. Antidepressants were permitted if they were clinically needed.

Assessments

The severity scores on all scales, the CGI scale,[15] the BPRS (expanded version of 24 items),[14] the Scale for the Assessment of Positive Symptoms (SAPS),[18] and the SANS,[19] were used to evaluate clinical symptomatology according to the follow-up protocol. The presence of early warning signs of relapse in psychosis were assessed by the Early Signs Scale (ESS)[20] at all interviews in the discontinuation group during the first 18 months.

Adherence to antipsychotic drugs was assessed from information obtained from patients and close relatives by the staff (nurse, social worker, and psychiatrists) involved in the clinical follow-up. Patients were consensually defined as having a good adherence if they regularly took at least 90% of the prescribed medication.

Outcome Measures

Primary outcome measures included relapse rate and time-to-relapse. The main outcome was the percentage of relapse/exacerbation in the 2 groups of patients (discontinuation and maintenance) and mean time to relapse.

Secondary outcome measures included severity of clinical psychopathology and functional status at 3 years.

Clinical psychopathology differences between groups were evaluated by the mean change from study intake to 3 years for the CGI, BPRS, SAPS, and SANS total scores. In addition, the number of functional recovery individuals at 3 years was assessed.

Calculation of the Mean Daily Dose of Antipsychotic Medications and the Timeline of Dosing

To compare antipsychotic use, prescribed medications were converted to chlorpromazine equivalents. Chlorpromazine equivalent daily doses were calculated based on published data.[21,22] Data on doses were thoroughly recorded at baseline and every 3 months during the follow-up period.

Statistical Analyses

Statistical analyses were performed using the SPSS software version 19.0 (IBM Corp, Armonk, New York). All data were tested for normal distribution using the Kolmogorov-Smirnov test. When continuous variables were compared between groups, one-way analysis of variance (ANOVA) was used for normally distributed data, and the Mann-Whitney *U* test was used for non-normally distributed data. Categorical data were analyzed using χ^2 test. All of the hypotheses were tested by using a 2-sided significance level of .05. No adjustments were made for multiple comparisons.

The primary aim of this study was to test the hypothesis that discontinuation or maintenance of lowest effective dose

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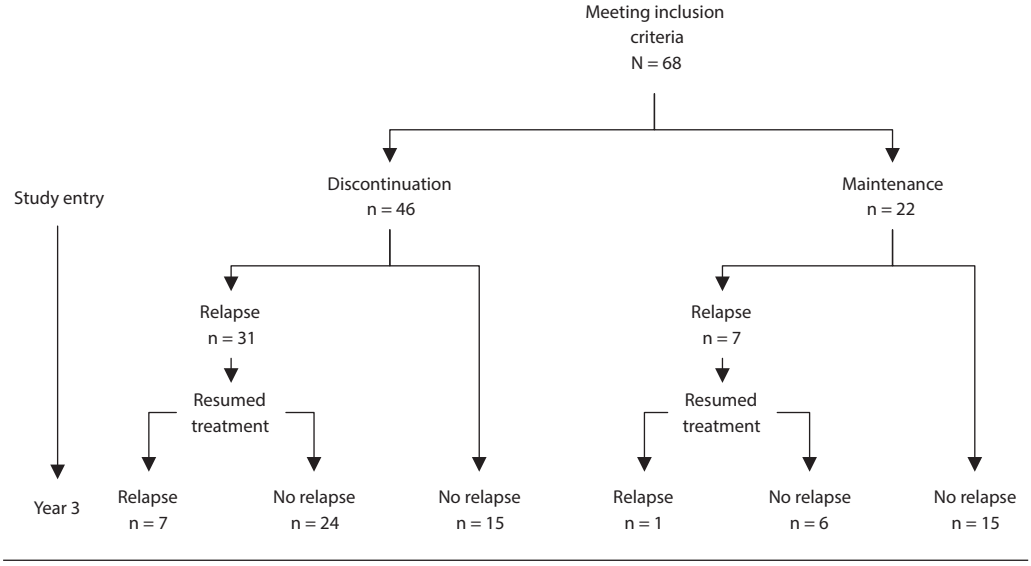
Figure 1. Flow Diagram of Subjects Through the Phases of the Randomized Trial



would result in different relapse rates. Kaplan-Meier survival curves and a log rank test were used to assess time-to-relapse. Analysis of variance or the Mann-Whitney *U* test was used to compare clinical symptoms and functionality after 3 years between groups. The percentages of relapse rates between groups were examined by χ^2 tests.

The secondary aim of this study was to identify predictors of relapse after treatment discontinuation. A dichotomous variable was created that was assigned a value of 1 once a patient experienced a relapse. One-way ANOVA and the Mann-Whitney *U* test were used to compare characteristics (sociodemographic, premorbid, clinical, and drug-consumption variables) of patients between the 2 groups. Following this, logistic regression ("Enter Method") was used to examine a multivariate prediction model that included all potentially useful variables. The significant variables with predictive power ($P < .15$) resulting from the primary analyses comparing relapse and nonrelapse patients were entered into binary logistic regression analyses for discriminating in the discontinuation strategy those patients who relapsed (relapse as dependent variable).

RESULTS

Description of Study Cohort

Figure 1 shows the trial profile. The demographic and clinical characteristics of patients in the 2 groups (discontinuation [n = 46] and maintenance [n = 22]) are shown in Table 1. Compared with the rest of the patients enrolled in the PAFIP (N = 329), the study sample had a lower frequency of schizophrenia diagnosis, a later age at illness onset, and a higher education level (see Supplementary eTable 1 at PSYCHIATRIST.COM). Patients in the maintenance group had a greater baseline CGI score than those in the discontinuation group (Table 1) (maintenance = 6.5 ± 0.7, discontinuation = 6.1 ± 0.6; $P = .004$) and a longer duration of treatment until discontinuation (maintenance = 745 ± 37 days, discontinuation = 937 ± 226 days; $U = 231.5$, $P < .001$). All of the subjects who met the inclusion criteria for the present study presented good treatment adherence (according to stated criteria).

Implementation of the Treatment Strategies

At the time of study entry, patients were on the lowest effective doses as follows: amisulpride (n = 1), mean dose 200 mg/d; aripiprazole (n = 9), mean dose 8.9 ± 2.2 mg/d; haloperidol (n = 6), mean dose 1.5 ± 0.6 mg/d; olanzapine (n = 19), mean dose 5.4 ± 1.3 mg/d; quetiapine (n = 8), mean dose 206.3 ± 62.3 mg/d; risperidone (n = 20), mean dose 1.5 ± 0.6 mg/d; ziprasidone (n = 5), mean dose 68.0 ± 11.0 mg/d. The mean length of time on these doses was as follows: amisulpride, 8 months; aripiprazole, 12.7 ± 7.9 months; haloperidol, 11.8 ± 2.7 months; olanzapine, 7.6 ± 4.3 months; quetiapine, 12.3 ± 7.6 months; risperidone, 10.7 ± 7.6 months; and ziprasidone, 16 ± 3.4 months. The mean length between initiation of medication tapering from the maximum dose until the lowest effective dose (according to treating psychiatrist's criteria) was 16.0 ± 9.8 months.

The mean duration of treatment prior to study entry was different between the groups (discontinuation, 31.0 months; maintenance, 24.6 months; $P < .001$). The mean maximum chlorpromazine equivalent doses were 345.5 ± 187.0 mg/d in the discontinuation group and 316.7 ± 147.6 mg/d in the maintenance group ($U = 465.5$, $P = .591$). There was a significant difference between groups in the mean chlorpromazine equivalent dose at study entry (discontinuation, 106.8 mg/d; maintenance, 138.3 mg/d; $U = 338.0$; $P = .023$) (Table 2).

Relapse Rate and Time to Relapse

In the discontinuation group, 31 patients (27 relapses and 4 exacerbations; 67.4%) relapsed over the 3-year period

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Table 1. Demographic and Clinical Characteristics of 68 Drug-Naïve Patients With a First Episode of Psychosis

Characteristic	Total (N = 68)		Maintenance (n = 22)		Discontinuation (n = 46)		Statistic	*P*
			Mean	SD	Mean	SD		
Age at PAFIP admission, y	30.7	8.2	31.1	8.3	30.5	8.2	$F = 0.075$	.785
Age at psychosis onset, y	30.0	8.0	30.3	8.3	29.8	8.0	$F = 0.055$	.816
Duration of illness, mo	19.2	23.9	22.1	30.8	17.8	20.1	$U = 425.5$	.290
Duration of psychosis, mo	8.4	14.3	9.2	11.7	8.0	15.5	$U = 502.0$	.958
Duration of treatment until discontinuation, d	876.8	209.4	745.5	37.5	937.3	226.6	$U = 231.5$	< .001
Initial SAPS total score	13.8	4.5	14.3	5.5	13.5	4.0	$F = 0.429$	.515
Initial SANS total score	6.4	5.8	7.6	6.6	5.9	5.4	$U = 432.5$	.333
Initial BPRS total score	61.6	12.9	64.6	14.3	60.1	12.1	$F = 1.827$	.181
Initial CGI score	6.2	0.7	6.5	0.7	6.1	0.6	$U = 308.0$	.004
Initial positive dimension	7.2	2.3	7.4	2.5	7.0	2.2	$U = 475.5$	.668
Initial negative dimension	4.3	5.2	4.9	5.5	4.0	5.1	$U = 440.0$	.372
Initial disorganized dimension	6.6	3.7	6.9	4.0	6.5	3.5	$F = 0.181$	.672
	n	%	n	%	n	%	χ^2_1	*P*
Diagnosis (*DSM-IV* criteria)								
Schizophrenia	27	39.7	11	50.0	16	34.8	1.440	.230
Other diagnoses	41	60.3	11	50.0	30	65.2		
Brief psychotic disorder	5	7.4	0	0.0	5	10.9		
Unspecified psychotic disorder	4	5.9	0	0.0	4	8.7		
Schizophreniform disorder	30	44.1	10	45.5	20	43.5		
Schizoaffective disorder	2	2.9	1	4.5	1	2.2		
Male	32	47.1	9	40.9	23	50.0	0.494	.482
Race (white)	67	98.5	21	95.5	46	100.0	2.122	.145
Education level (elementary)	23	33.8	7	31.8	16	34.8	0.058	.809
Socioeconomic status of parents (not/low qualified worker)	37	54.4	12	54.5	25	54.3	0.000	.988
Living in urban area (yes)	45	66.2	15	68.2	30	65.2	0.058	.809
Living with family (yes)	37	54.4	12	54.5	25	54.3	0.000	.988
Student (yes)	15	22.1	4	18.2	11	23.9	0.284	.594
Single (yes)	50	73.5	18	81.8	32	69.6	1.148	.284
Unemployed (yes)	23	33.8	6	27.3	17	37.0	0.624	.430
Family history of psychosis (yes)	15	22.1	6	27.3	9	19.6	0.514	.473
Hospitalization at intake (yes)	42	61.8	14	63.6	28	60.9	0.048	.826
Tobacco use (yes)	42	61.8	14	63.6	28	60.9	0.048	.826
Cannabis use (yes)	28	41.2	10	45.5	18	39.1	0.246	.620
Alcohol use (yes)	38	56.7	12	54.5	26	57.8	0.063	.802
Other drug use (yes)	12	17.6	4	18.2	8	17.4	0.006	.936

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions scale, PAFIP = Programa Asistencial de Fases Iniciales de Psicosis, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.

Table 2. Treatment Doses and Relapse Rate in the 2 Groups of Patients

Treatment and Relapse	Treatment Maintenance, n = 22			Treatment Discontinuation, n = 46			Statistic	*P*
	Mean	(Median)	SD	Mean	(Median)	SD		
Chlorpromazine equivalent doses, mg/d								
Maximum dose	316.7	(283.3)	147.6	345.5	(300.0)	187.0	$U = 465.5$	.591
Dose at study entry	138.3	(133.3)	80.7	106.8	(100.0)	64.6	$U = 338.0$	.023
Dose at 3 y at final assessment[a]	137.1	(133.3)	60.7	124.5	(100.0)	60.1	$F = 0.537$	.467
Time to relapse, d	608.0	(607.0)	179.6	209.2	(122.5)	230.3	$F = 18.322$	< .001
		n	%		n	%	χ^2_2	*P*
Relapse/exacerbation rate		7	31.8		31	67.4	7.639	.006

[a]n = 32 treatment discontinuation group; n = 20 treatment maintenance group.

(Table 2). The rates for the first relapse at 12 and 18 months were 56.5% and 58.7%, respectively. The mean time to relapse was 209.2 days (95% CI, 124.7–293.6; median = 122; range, 12–911) (Figure 2). Of the 31 patients who relapsed in the discontinuation group, 3 (9.7%) admitted the use of illicit drugs, 7 (22.6%) reported to have lived stressful situations shortly prior to clinical exacerbation, and 4 (12.9%) reported the 2 factors (illicit drugs and stressful situations) that could have triggered the emergence of the relapse. There was a significant difference in the mean time to relapse between factors related to the emergence of the relapse/exacerbation ($F_3 = 4.906$, $P = .008$). The mean time to relapse in those cases reportedly associated to stressful situations was 454.6 ± 345.8 days (median = 567 days; range, 14–911 days). The mean

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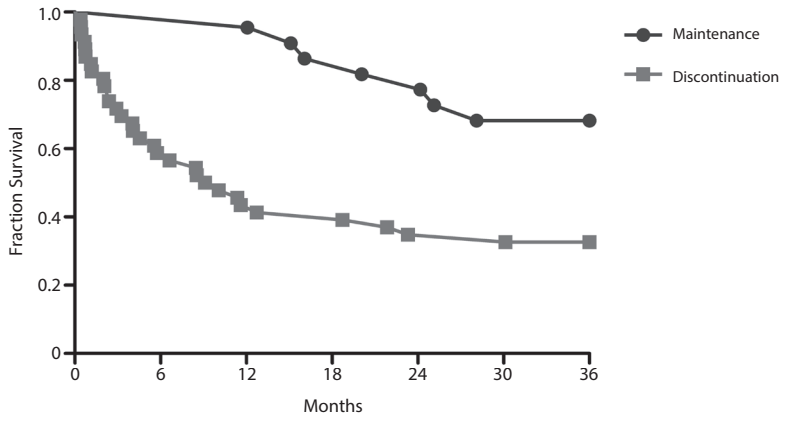
Figure 2. Kaplan-Meier Survival Curves for Time to Relapse



	0		6 m		12 m		18 m		24 m		30 m		36 m	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Maintenance	22	100.0	22	100.0	22	100.0	19	86.4	18	81.8	15	68.2	15	68.2
Discontinuation	46	100.0	27	58.7	20	43.5	19	41.3	16	34.8	16	34.8	15	32.6

time to relapse in those cases seemingly related to the use of illicit drugs was 200.0 ± 50.3 days (median = 174 days; range, 168–258 days). The mean time to relapse in those cases with 2 factors (illicit drugs and stressful situations) reported was 102.0 ± 80.1 days (median = 97.5 days; range, 12–201 days). The mean time to relapse in the remaining cases (n = 17) was 134.9 ± 134.2 days (median = 72 days; range, 13–385 days).

Of the 22 patients in the maintenance group, 7 individuals (5 relapses and 2 exacerbations; 31.8%) relapsed at least once over the 3-year period. None of the patients in the maintenance group relapsed at 12 months, and 14% (n = 3) relapsed at 18 months. The mean time to relapse was 608 days (95% CI, 441.9–774.1; median = 607; range, 365–850) (Figure 2). When analyzing likely causes associated with relapse in the maintenance treatment group, 5 individuals acknowledged having stopped medication prior to relapse, and noticeable stressful situations and dose tapering were identified in the other 2 cases. Thus, the relapse/exacerbation rate among those individuals in the maintenance group who did not acknowledge stopping medication during follow-up (n = 17) was very low at 11.8% (2 of 17).

There was a significant difference between the discontinuation and the maintenance groups in the time to relapse (log rank = 10.106, $P = .001$) (see Figure 2).

It is of note that most (30 of 38) of the relapsed individuals experienced no additional relapse/exacerbation during the remaining observational period after resuming antipsychotic treatment. Overall, relapsed patients responded promptly to resuming antipsychotics or increasing doses, with the mean time of duration of psychotic symptoms 7.9 weeks; range, 1–32; SD = 6.53 (discontinuation group: 6.9 weeks; range, 1–32; SD = 5.9; maintenance group: 12.2 weeks; range, 1.4–27; SD = 7.7). Only 11 of 38 (28.9%) relapsed patients needed to be hospitalized (discontinuation group: n = 10/31, 32.3%; maintenance group: n = 1/7, 14.3%). The onset of relapse was abrupt (psychotic symptoms reemerged in less than 1 month) and no significant changes in the presence of early signs within the preceding month to relapse were observed (using ESS) in 85% of relapses.

Clinical Symptomatology and Functionality After 3 Years

There were no significant differences in the severity of symptoms and functional status at 3 years from study entry between the discontinuation and maintenance groups (Supplementary eTable 2). When relapsed and nonrelapsed patients in the discontinuation group were compared, only a difference in the severity of negative symptoms was observed ($P = .049$). Nonetheless, when the overall group of relapsed individuals, including individuals from the 2 conditions (maintenance and discontinuation, n = 38), was compared to nonrelapsed individuals (n = 30), there were significant differences in mean total scores on the SANS (nonrelapsed = 0.0 ± 0.0, n = 30; relapsed = 1.6 ± 3.9, n = 38; $P = .005$), CGI (nonrelapsed = 1.1 ± 0.4, n = 30; relapsed = 1.7 ± 1.4, n = 38; $P = .027$), and good (score 0) DAS (nonrelapsed = 96.7% [29 of 30]; relapsed = 78.9% [30 of 38]; $P = .032$). Relapsed patients showed a more severe symptomatology and poorer functional status at 3 years (Supplementary eTable 3).

Predictors of Relapse in the Discontinuation Group

There were no differences in premorbid, sociodemographic, and clinical (at PAFIP entry) variables between relapsed and nonrelapsed individuals who had discontinued the antipsychotic treatment (Supplementary eTable 4). The significant variables with predictive power ($P < .15$) resulting from the primary analyses comparing relapse (n = 31) and nonrelapse (n = 15) patients were entered into binary logistic regression analyses. Overall, the model,

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Table 3. Binary Logistic Regression of Variables Significantly Differentiating Relapsed Patients in the Discontinuation Group

Variable	B	SE	Wald χ^2	*P*	Exp(B)	95% CI for Exp(B) Lower	Upper
Duration of untreated psychosis	−0.036	0.024	2.214	.137	0.964	0.919	1.012
Initial positive symptoms dimension[a]	0.255	0.177	2.093	.148	1.291	0.913	1.825
Living with family	−2.085	1.222	2.912	.088	0.124	0.011	1.363
Family history of psychosis	−1.468	0.872	2.838	.092	0.230	0.042	1.271
Constant	1.399	1.659	0.712	.399	4.052		

[a]Based on the Scale for the Assessment of Positive Symptoms.

including duration of untreated psychosis ($P = .071$), positive symptoms dimensions ($P = .075$), family history of psychosis ($P = .102$), and living with family ($P = .085$), was retained. This model had good powers of discrimination and explained a significant proportion of the variance ($\chi^2_4 = 10.346$, $P = .035$, Nagelkerke $R^2 = 0.281$). Each of the selected predictors was force-entered into a logistic regression model. Although duration of untreated psychosis (OR = 0.96; 95% CI, 0.919–1.012; $P = .137$), positive symptoms dimensions (OR = 1.29; 95% CI, 0.913–1.825; $P = .148$), family history of psychosis (OR = 0.23; 95% CI, 0.42–1.271; $P = .092$), and living with family (OR = 0.12; 95% CI, 0.011–1.363; $P = .088$) did not reach statistical significance, the model predicted relapse with 73.9% accuracy, classifying correctly 40% of nonrelapse patients and 90% of relapse patients. (Table 3).

DISCUSSION

This open-label, nonrandomized study revealed that the rate of symptom recurrence in functionally recovered FEP patients following the self-elected discontinuation of antipsychotic treatment is extremely high. Although the risk of relapse after treatment discontinuation was greater during the first 12 months, it persisted beyond this period, and life-related stressful situations appeared to trigger the recurrence of symptoms at these later stages. Relapsed individuals had a greater severity of symptoms and lower functionality in those 3 years compared to those patients who did not relapse during the follow-up.

The elevated rate of relapse in our medication discontinuation group was somewhat unexpected because the stringent criteria of inclusion were aimed at a subset of individuals with a remarkably good outcome after the first psychotic break. The time to relapse after treatment discontinuation was variable. Nonetheless, we observed that the highest frequency of relapse occurred during the first months after treatment discontinuation. In our study, the mean time to recurrence of psychotic symptoms after treatment discontinuation was 209 days, and more than 40% of relapses occurred before the sixth month after discontinuation. The recommencement of antipsychotic treatment was associated with clinical remission and lack of further relapses during the remaining follow-up. We observed a low rate of hospitalizations and a rapid return to baseline shortly after recurrence of psychotic symptoms. It has been proposed that an enhanced sensitivity of mesolimbic dopamine D_2 receptors as a consequence of long-term D_2 blockade may lead to "antipsychotic-induced supersensitivity psychosis" associated with antipsychotic withdrawal.[23] An abrupt discontinuation of medication may lead to a higher risk of recurrence of psychotic symptoms.[24] Thus, a gradual downward titration was conducted in our study to prevent unwanted side effects of dopamine supersensitivity. The acute-phase maximum dose (345.5 mg/d) was slowly tapered until reaching the lowest effective dose (106.8 mg/d), and this dose was maintained for a mean time of 9 months before treatment discontinuation. It has been described that the treatment response after a second episode is variable,[25] and a subset of first-episode schizophrenia patients (15%–20%) will clearly fail to remit after symptom recurrence.[26,27] In only 14 cases (45.2%) did the use of illicit drugs and/or life-related stressful situations appear to elicit the relapse. No explicit changes in the style of living or toxic habits were observed in the rest of the relapsed individuals.

In our study, the transition from recovery to relapse was abrupt in most cases, and early warning signs of relapse were somewhat unreliable predictors of relapse. The identification of prodromal symptoms of an impending relapse episode in individuals at risk is difficult.[28–32]

The estimates of relapses at 1 year and 3 years in the maintenance treatment group were 0% and 32%, respectively. Previous review and meta-analysis studies[1,8] exploring the 1-year risk of symptom recurrence with maintenance medications revealed a wide range of relapses (from 3% up to 27%). It is of note that despite having decided to maintain the established antipsychotic doses, 5 of the 7 individuals who relapsed among the maintenance treatment individuals admitted having abruptly withdrawn medication prior to suffering the clinical relapse. In the other 2 cases, relapses were associated with stressful situations and dose tapering. These findings highlight the fact that in clinical practice, it is unlikely that patients accept an indefinite treatment after a single episode of psychosis.

A systematic review of studies exploring the recurrence of psychotic symptoms with antipsychotic discontinuation in first-episode nonaffective psychosis reported a weighted mean recurrence rate of 77% during the first year and more than 90% at 2 years.[33] In contrast, the 1-year risk of recurrence within the medication continuation group was estimated at 3%. These estimates differed considerably from the 1-year rates of relapse in FEP patients of 61% in the discontinuation group and 26% in the continuation medication group reported by Leucht and colleagues.[1] Methodological discrepancies in the study design;

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inclusion criteria, and duration of follow-up, diagnosis, and hospitalization rates make comparability between studies problematic.[33] Wunderink and colleagues,[34] exploring remitted psychotic patients, observed that relapse rates were 2 times higher in individuals who gradually tapered or discontinued medication, and that only 20% of patients could be successfully discontinued. Strikingly, those patients with an earlier reduction or discontinuation treatment strategy appear to have long-term functional gains compared with individuals who maintained treatment.[35] Stopping antipsychotic medication has been repeatedly demonstrated as the biggest predictor of relapse in schizophrenia.[3–5,36] It is of note that, despite most relapsed patients' responding promptly to resuming antipsychotics, our data herein indicate that patients who suffered a relapse had a decreased functional status and a greater severity of symptomatology at 3 years compared with those patients who did not relapse.

The lack of a randomized study design, the relatively small sample size, and the fact that assessors were not blind to medication status are major limitations that must be taken into account in the interpretation of the current investigation. These caveats reflect the great difficulty in the design and performance of this type of investigation, which aimed to address a crucial and unsolved dilemma in real-world clinical practice.

CONCLUSIONS

We found that for individuals, after having a single psychotic episode and having accomplished a functional recovery, antipsychotic treatment maintenance is associated with a lower risk of symptom recurrence. Clinicians should accurately inform patients and their relatives that, even if patients have been symptom-free and functionally recovered on antipsychotic treatment, the risk of relapse is likely to be high if antipsychotics are discontinued. Despite this risk, numerous individuals may still be disposed to discontinue medication after recovering from their single episode of psychosis; therefore, a planned medication withdrawal strategy with a systematic follow-up should be established in first-episode programs to prevent unrestrained treatment disengagement.

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Drug names: aripiprazole (Abilify), clonazepam (Klonopin and others), lorazepam (Ativan and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Author contributions: Drs Mayoral-van Son, Parrilla-Escobar, and Moreno collected clinical data. Dr Mayoral-van Son interpreted the results and drafted the manuscript. Mr Ortiz-Garcia de la Foz performed the statistical analyses and drafted the manuscript. Dr Crespo-Facorro interpreted the results and reviewed the manuscript. Drs Valdizan and Martinez-Garcia helped in the interpretation of clinical data and reviewed the manuscript. The corresponding author had access to all study data. All authors approved the final version of the manuscript.

Potential conflicts of interest: **Dr Crespo-Facorro** has received honoraria for his participation as a speaker at educational events from Otsuka, Lundbeck, and Johnson & Johnson. **Drs Mayoral-van Son**, **Valdizan**, **Parrilla**, **Moreno**, and **Martinez-Garcia** and **Mr Ortiz-Garcia de la Foz** report no additional financial or other relationship relevant to the subject of this article.

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Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Clinical Outcome After Antipsychotic Treatment Discontinuation in Functionally Recovered First-Episode Nonaffective Psychosis Individuals: A 3-Year Naturalistic Follow-Up Study

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List of Supplementary Material for the article

1. **eTable 1** Comparison of sociodemographic, premorbid and clinical characteristic at intake between study sample (N = 68) and the rest of PAFIP sample (N = 329) patients
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Supplementary Table 1. Comparison of sociodemographic, premorbid and clinical characteristic at intake between study sample (N = 68) and the rest of PAFIP sample (N = 329) patients.

	Study Sample (N=68)		PAFIP (N=329)			
Characteristics	**Mean**	**SD**	**Mean**	**SD**		**p**
Age at admission, y	30.7	8.2	29.7	9.7	U=9879.0	0.129
Age at psychosis onset, y	30.0	8.0	28.4	9.2	U=9383.5	0.036
Duration of illness, mo	19.2	23.9	27.3	45.5	U=10520.5	0.668
Duration of psychosis, mo	8.4	14.3	15.9	36.4	U=10017.0	0.174
Initial SAPS total score	13.8	4.5	13.4	4.3	U=10867.5	0.711
Initial SANS total score	6.4	5.8	7.2	6.3	U=10503.5	0.427
Initial BPRS total score	61.6	12.9	62.6	12.5	F=0.347	0.556
Initial CGI score	6.2	0.7	6.3	0.7	U=10096.5	0.165
Initial positive dimension	7.2	2.3	7.5	2.4	U=10308.0	0.279
Initial negative dimension	4.3	5.2	5.5	5.8	U=9791.0	0.100
Initial disorganized dimension	6.6	3.7	6.0	3.4	U=10335.0	0.318
	N	**%**	**N**	**%**	**χ^2 (df=1)**	**p**
Diagnosis						
Schizophrenia	27	39.7	200	60.8	10.232	0.001
Other diagnoses	41	60.3	129	39.2		
Brief psychotic disorder	5	7.4	37	11.2		
Unspecified psychotic disorder	4	5.9	23	7.0		
Schizophreniform psychosis	30	44.1	66	20.1		
Schizoaffective disorder	2	2.9	3	0.9		
Sex(male)	32	47.1	194	59.0	3.259	0.071
Race(causasian)	67	98.5	319	97.0	0.515	0.473
Education level (elementary)	23	33.8	170	51.8	7.309	0.007
Socioeconomic status of parents (Not/Low qualified worker)	37	54.4	170	52.5	0.085	0.770
Urban area (yes)	45	33.8	249	24.1	2.793	0.095
Living with family (yes)	49	72.1	239	72.9	0.018	0.892
Student (yes)	15	22.1	61	18.6	0.435	0.509
Single (yes)	50	73.5	246	75.0	0.065	0.799
Unemployed (yes)	23	33.8	153	46.6	3.751	0.053
Family psychiatric history (yes)	15	22.1	73	22.3	0.001	0.972
Hospital status inpatient (yes)	42	61.8	214	65.0	0.265	0.607
Tobacco (yes)	42	61.8	191	58.1	0.320	0.572
Cannabis (yes)	28	41.2	143	43.5	0.120	0.729
Alcohol (yes)	38	56.7	177	53.8	0.191	0.662
Other drugs (yes)	12	17.6	80	24.4	1.436	0.231

Abbreviations: BPRS: Brief Psychiatric rating Scale; CGI: Clinical Global Impression; SANS: Scale Assessment of Negative Symptoms. SAPS: Scale Assessment of Positive Symptoms

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Supplementary Table 2. Comparison of clinical characteristic at 3 years between maintenance (N = 22) and discontinuation (N = 46) groups.

	Total (N=68)		Maintenance (N=22)		Discontinuation (N=46)			
Clinical characteristics at 3 years	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**U**	**p**
SAPS total score	0.2	1.0	0.0	0.2	0.3	1.2	483.5	0.515
SANS total score	0.9	3.0	0.8	3.4	1.0	2.8	475.5	0.497
BPRS total score	25.9	3.9	25.9	4.7	25.9	3.6	493.0	0.837
CGI score	1.5	1.1	1.3	1.1	1.5	1.1	442.5	0.210
Positive dimension	0.2	0.9	0.0	0.2	0.3	1.0	483.5	0.515
Negative dimension	0.8	2.7	0.7	3.0	0.9	2.7	475.0	0.490
Disorganized dimension	0.0	0.2	0.0	0.0	0.0	0.3	495.0	0.489
Functional characteristics at 3 years	**N**	**%**	**N**	**%**	**N**	**%**	**χ^2 (df=1)**	**p**
DAS global score =0	59	86.8	20	90.9	39	84.8	0.486	0.486

Abbreviations: BPRS: Brief Psychiatric rating Scale; CGI: Clinical Global Impression; SANS: Scale Assessment of Negative Symptoms. SAPS: Scale Assessment of Positive Symptoms. DAS: Disability Assessment Schedule

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Supplementary Table 3. Comparison of clinical characteristic at 3 years between relapsed (N = 38) and non-relapsed (N = 30) patients.

	Not relapse (N=30)		Relapse (N=38)			
Clinical characteristics at 3 years	**Mean**	**SD**	**Mean**	**SD**		**p**
SAPS total score	0.2	0.9	0.3	1.0	U=530.0	0.275
SANS total score	0.0	0.0	1.6	3.9	U=435.0	0.005
BPRS total score	24.8	1.9	26.8	4.9	U=455.5	0.089
CGI score	1.1	0.4	1.7	1.4	U=451.0	0.027
Positive dimension	0.1	0.5	0.3	1.0	U=530.0	0.275
Negative dimension	0.0	0.0	1.5	3.6	U=435.0	0.005
Disorganized dimension	0.1	0.4	0.0	0.0	U=551.0	0.260
Functional characteristics at 3 years	**N**	**%**	**N**	**%**	**χ^2 (df=1)**	**p**
DAS global score =0	29	96.7	30	78.9	4.584	0.032

Abbreviations: BPRS: Brief Psychiatric rating Scale; CGI: Clinical Global Impression; SANS: Scale Assessment of Negative Symptoms. SAPS: Scale Assessment of Positive Symptoms. DAS: Disability Assessment Schedule

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Supplementary table 4. Comparison of sociodemographic, premorbid and clinical characteristic at PAFIP entry between non-relapsed (N = 15) and relapsed (N = 31) patients in the discontinuation group.

	Not Relapse (N=15)		Relapse (N=31)			
Characteristics	**Mean**	**SD**	**Mean**	**SD**		**p**
Age at admission, y	30.5	9.2	30.5	7.8	F=0.000	0.988
Age at psychosis onset, y	29.6	8.9	29.9	7.6	F=0.011	0.916
Duration of illness, mo	16.8	26.4	18.3	16.8	F=0.056	0.813
Duration of psychosis, mo	10.5	24.3	6.8	9.0	U=156.0	0.071
Duration of Treatment until discontinuation, d	881.7	256.3	967.6	212.3	F=1.443	0.236
Initial SAPS total score	12.3	4.1	14.1	3.9	F=2.141	0.150
Initial SANS total score	5.7	6.0	6.0	5.1	F=0.031	0.860
Initial BPRS total score	57.9	12.5	61.2	12.0	F=0.725	0.399
Initial CGI score	6.0	0.7	6.1	0.7	U=214.5	0.633
Initial positive dimension	6.3	1.8	7.4	2.3	U=161.5	0.075
Initial negative dimension	4.1	6.0	4.0	4.8	U=212.5	0.624
Initial disorganized dimension	6.0	3.1	6.7	3.8	F=0.365	0.549
	N	**%**	**N**	**%**	**χ^2 (df=1)**	**p**
Diagnosis						
Schizophrenia	4	26.7	12	38.7	0.646	0.421
Other diagnoses	11	73.3	19	61.3		
Brief psychotic disorder	4	26.7	1	3.2		
Unspecified psychotic disorder	2	13.3	2	6.5		
Schizophreniform psychosis	5	33.3	15	48.4		
Schizoafective	0	0.0	1	3.2		
Sex(male)	6	40.0	17	54.8	0.890	0.345
Race(caucasian)	15	100.0	31	100.0		
Education level (elementary)	5	33.3	11	35.5	0.021	0.886
Socioeconomic status of parents (Not/Low qualified worker)	9	60.0	16	51.6	0.287	0.592
Living in urban area (yes)	6	40.0	10	32.3	0.267	0.605
Living with family (yes)	14	93.3	22	71.0	2.972	0.085
Student (yes)	3	20.0	8	25.8	0.187	0.665
Single (yes)	9	60.0	23	74.2	0.962	0.327
Unemployed (yes)	5	33.3	12	38.7	0.125	0.723
Family history of psychosis (yes)	5	33.3	4	12.9	2.681	0.102
Hospital at intake (yes)	7	46.7	21	67.7	1.885	0.170
Tobacco (yes)	10	66.7	18	58.1	0.314	0.575
Cannabis (yes)	6	40.0	12	38.7	0.007	0.933
Alcohol (yes)	7	50.0	19	61.3	0.504	0.478
Other drugs (yes)	1	6.7	7	22.6	1.782	0.182

Abbreviations: BPRS: Brief Psychiatric rating Scale; CGI: Clinical Global Impression; SANS: Scale Assessment of Negative Symptoms. SAPS: Scale Assessment of Positive Symptoms.

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