Guided Discontinuation Versus Maintenance Treatment in Remitted First-Episode Psychosis: Relapse Rates and Functional Outcome

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Objective: To compare the consequences of a guided discontinuation strategy and maintenance treatment in remitted first-episode psychosis in terms of relapse rates and functional outcome.

Method: The study was conducted in 7 mental health care organizations and the Department of Psychiatry of the University Medical Center Groningen in The Netherlands, covering a catchment area of 3.1 million inhabitants. A sample of 131 remitted first-episode patients, aged 18 to 45 years, with a DSM-IV diagnosis of schizophrenia or related psychotic disorder was included (i.e., all patients with a first psychotic episode from October 2001 through December 2002 who were willing to participate). After 6 months of positive symptom remission, they were randomly and openly assigned to the discontinuation strategy or maintenance treatment. Maintenance treatment was carried out according to American Psychiatric Association guidelines, preferably using lowdose atypical antipsychotics. The discontinuation strategy was carried out by gradual symptomguided tapering of dosage and discontinuation if feasible. Follow-up was 18 months. Main outcome measures were relapse rates and social and vocational functioning.

Results: Twice as many relapses occurred with the discontinuation strategy (43% vs. 21%, p = .011). Of patients who received the strategy, approximately 20% were successfully discontinued. Recurrent symptoms caused another approximately 30% to restart antipsychotic treatment, while in the remaining patients discontinuation was not feasible at all. There were no advantages of the discontinuation strategy regarding functional outcome.

Conclusions: Only a limited number of patients can be successfully discontinued. High relapse rates do not allow a discontinuation strategy to be universal practice. However, if relapse risk can be carefully managed by close monitoring, in some remitted first-episode patients a guided discontinuation strategy may offer a feasible alternative to maintenance treatment. Further research is needed to find predictors of successful discontinuation.

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A lternative strategies to maintenance treatment of schizophrenia are treatment discontinuation and its milder version, guided discontinuation, also called targeted or intermittent treatment. Studies in patients with multiple-episode psychosis showed that guided discontinuation did not redeem its promise of fewer side effects and improved social functioning.¹⁻³ Instead, discontinuation strategies lost favor because of high relapse and hospitalization rates.⁴⁻⁸ In today's guidelines, maintenance treatment is the recommended strategy for both multiple-and first-episode patients.⁹ However, in first-episode patients, no prospective study has yet been carried out comparing relapse rates and functional outcome of guided discontinuation and maintenance treatment.

There are good reasons to compare the consequences of a discontinuation strategy and maintenance treatment in first-episode patients. Though extrapyramidal side effects are less frequent when applying novel antipsy-chotics,^{10,11} these agents confer significant health risks: weight gain,¹² altered glucose and lipid metabolism,^{13,14} and sexual side effects.^{15,16} Given these concerns and the resistance to maintenance antipsychotic treatment frequently expressed by first-episode patients, some authors suggest that some first-episode patients should be considered for discontinuation of antipsychotics.^{5,17} The unknown risks and lack of empirical data place the clinician in a dilemma. There is yet another argument to study guided discontinuation in first-episode patients. Studies on the natural course of schizophrenia suggest that

perhaps up to 20% of first-episode patients do not require antipsychotics after recovery from their psychosis.^{17–20} No validated predictors of outcome in the early course of schizophrenia currently exist. It is impossible to predict which patients can do without antipsychotics.

Gitlin et al.,⁵ who found relapse rates of 96% in volunteer patients with recent-onset schizophrenia within 2 years after discontinuation of antipsychotics, nonetheless recommend a discontinuation trial in patients who are stable with few psychotic symptoms for many months and who agree to participate in ongoing clinical monitoring. Furthermore, some authors noted that the consequences of relapse were limited.^{4,5} Only a minority of relapsed patients were hospitalized. They recommend a discontinuation trial in selected cases, implying gradual tapering of antipsychotic dose and discontinuation if feasible, since abrupt discontinuation increases the risk of relapse.²¹ Patients have to be monitored closely for reemerging prodromal or psychotic symptoms; if such symptoms reemerge, antipsychotics should be restarted immediately. The proposed guided discontinuation strategy is also known as targeted treatment. The only study reporting data on targeted treatment in first-episode patients is a reanalysis of data from a multicenter study.²² In that study, 2-year relapse rates in first-episode patients were found to be similar in targeted (42%) and maintenance treatment (38%).

We are not aware of any study that prospectively compared the outcome of guided discontinuation and maintenance treatment in patients with a remitted first-episode psychosis. We studied patients from an incident cohort showing 6 months' remission within the first year of treatment who were then randomly assigned to guided discontinuation or maintenance treatment. The consequences of both treatment strategies carried out during 18 months in terms of relapse rates and social and vocational functioning are presented.

METHOD

Setting

The study was conducted in 7 district mental health care centers and the Department of Psychiatry of the University Medical Center Groningen (all in The Netherlands), covering a catchment area of 3.1 million inhabitants. Protocols recommending second-generation antipsychotics at low dosages were implemented in all districts.

Subjects

Patients included in the study had first-episode schizophrenia or a related psychotic disorder, were aged 18 to 45 years, lived in the catchment area, received no prior antipsychotic medication for more than 3 months, mastered the Dutch language, and had an estimated IQ score above 70. In addition, patients had to show response of positive symptoms within 6 months of antipsychotic treatment and sustained remission during 6 months.

Study Design

The study was a prospective 2-year randomized controlled trial with 2 treatment conditions; it was approved by the Medical Ethical Committee of the University Medical Center Groningen for all participating institutions. From October 2001 through December 2002, all patients with a first psychotic episode were registered. Patients were asked to participate in the study as soon as they were able to understand the consequences of participation. They were informed about the pros and cons of discontinuation and maintenance strategies and gave written consent. Diagnosis was established using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN).²³ A DSM-IV diagnosis of schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified was required.²⁴ All patients were treated with antipsychotics until remission.

Randomization

Patients were randomly assigned to the discontinuation strategy or maintenance treatment. Randomization was carried out by an independent agent, in separate blocks for the 7 sites to prevent effects of site. Within these blocks a minimization procedure was applied for gender and age (under or over 25 years). Raters were blinded for the allotted strategy throughout.

Interventions

Maintenance treatment was carried out according to American Psychiatric Association guidelines, with preferential prescription of low-dose second-generation antipsychotics. In the discontinuation strategy, the dosage was gradually tapered and discontinued if feasible. Tapering was allowed to be guided by symptom severity levels and patients' preferences. If early warning signs of relapse emerged or positive symptoms recurred, clinicians were to restart or increase the dosage of antipsychotics. The frequency of patient monitoring was at the clinicians' discretion.

The strategies were intention-to-treat. If patients did not comply with the treatment intention, they remained in the trial. The clinician was expected to maintain the assigned treatment strategy.

Assessments

Patients were assessed at first treatment response (T0), 6 months later when remitted and entering the trial (T6), the halfway point of the trial (T15; 15 months after first treatment response), and at the end of trial (T24; 24 months after first treatment response). Psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS)²⁵ at T0, T6, T15 and T24. The PANSS was used to measure observer-rated severity of symptoms during the preceding week. The 3 subscores for positive, negative, and general symptoms have been included in the analysis.

Side effects were assessed at T6, T15, and T24 with the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS),^{26,27} a self-rating scale with 41 items. Side effects are rated on a 5-point scale from 0 (not at all) to 4 (very much) covering the last month. Total scores in the range of 0 to 40 are considered to be low; 41 to 80, medium; 81 to 100, high; and above 101, very high.

Social functioning was assessed at T0, T15, and T24 with the Groningen Social Disabilities Schedule (GSDS),²⁸ a semistructured interview with observer ratings of functioning over the preceding month, in 8 social role domains: vocational functioning, community integration, peer relationships, relationship with family members, parental functioning, partner relationship, house-keeping, and self-care. Disabilities are rated on a 4-point scale from no to serious disability. A total disability score ranging from 0 to 21 is calculated combining 7 domains, excluding parental functioning because of limited applicability.^{28,29} At T0, social functioning during the month preceding referral was assessed.

Quality of life was assessed at T0, T6, T15, and T24 with the brief version of the World Health Organization (WHO) Quality of Life scale (WHOQoL-Bref),³⁰ a 26item self-report questionnaire comprising satisfaction with health, psychological functioning, social relationships, and environmental opportunities as experienced over the last 2 weeks. Each item is scored on a 5-point scale, higher scores indicating better quality of life. We used the total score, ranging from 26 to 130. The fidelity to both treatment strategies was monitored during the experimental phase (T6-T24), recording relapses, dose and type of medication, and the reasons not to discontinue or maintain medication in the corresponding strategy. Hospital admission days were recorded at T6, T15, and T24. Demographic data (age at onset of psychosis, living and working conditions, level of education) were collected at baseline and at T24.

Definition of Response, Remission, and Relapse

Treatment response was defined by clinical improvement to a nonflorid psychotic state of at least 1 week's duration, reported by the clinician and subsequently confirmed by PANSS positive symptom subscale ratings assessed by a research team member. One rating of 4 (moderate) was allowed.²⁵ Remission required sustained improvement of positive symptoms, reflected by symptom severity levels at or below the level of response during at least 6 months. Negative and disorganization symptoms, included in recently proposed remission criteria,³¹ were left aside. During remission, mild exacerbations of positive symptoms of less than 1 week's duration were allowed. Relapse was defined by clinical deterioration during at least 1 week, having consequences (augmentation of antipsychotic dosage, hospital admission, or more frequent consultations), reported by the clinician and subsequently confirmed by PANSS positive subscale item scores assessed by a research team member, of at least one score of 5 (moderately severe).

Conversion of Antipsychotics to Haloperidol Equivalents

In order to compare medication use, prescribed antipsychotics were converted to haloperidol equivalents. Because of different mechanisms of action, there is no generally accepted algorithm to convert the novel or even the first-generation antipsychotics to haloperidol equivalents. We used existing conversion and dose range recommendation tables to convert the applied antipsychotic agents to haloperidol equivalents.⁹

Training and Reliability

Psychiatrists who were trained at the Groningen WHO Training Centre administered the SCAN interview. Training for other scales was provided at investigator meetings. Regular booster meetings were organized to maintain interrater reliability for the PANSS and GSDS. Reliability of the GSDS was established by 12 raters all rating the same 11 subjects. Weighted κ values for each GSDS item were calculated. The square weighted κ scores ranged from 0.55 to 0.88 for each GSDS item, with a mean of 0.67. We used another 12 subjects, all rated by 11 raters, to establish the reliability of the PANSS. The 2-way mixed model intraclass correlation coefficient (ICC) was used to assess the reliability of the PANSS scales. The ICC for the PANSS subscale of positive symptoms was 0.84 and for the subscale of negative symptoms, 0.83.

Statistical Analysis

Analyses were carried out with the statistical package SPSS (version 12.0.2; SPSS Inc., Chicago, III.). Betweengroup baseline characteristics were analyzed using Student t tests for continuous variables and Pearson χ^2 tests for categorical variables. The Cox regression survival analysis was applied to compare time to first relapse. Censored cases were defined as observations without relapse during follow-up. For censored cases, the follow-up time (18 months = 547 days) was used in the analysis.

A linear mixed-model repeated-measures analysis of covariance was used to analyze repeated outcome measures (PANSS positive, negative, and general subscales; LUNSERS; GSDS; WHOQoL). Dependent variables were sum scale scores. Fixed effects were treatment condition (maintenance or discontinuation), time (assessments T0, T6, T15, and T24), and the interaction of treatment condition and time. The general covariance matrix



Figure 1. Flow Diagram: Guided Discontinuation vs. Maintenance Treatment in Patients With First-Episode Psychosis

(unstructured) was specified for the covariance structure of the residuals of the repeated measurements. The subjects (the observational units in the analysis) were included as a random effect. The Type III method to calculate the sums of squares of the fixed effects in the model was applied.

The proportion of time spent in hospital across strategies during trial was analyzed with univariate analysis of variance, with the proportion of time admitted from T6 until T24 as a dependent variable, treatment strategy as a fixed factor, and the proportion of time admitted before trial from T0 until T6 as a covariate. The vocational status of having a paid job for at least 16 hours a week at the end of the study was analyzed with binary logistic regression with the outcome working for 16 hours a week at T24 as a dependent variable and working for 16 hours a week at T0 as a covariate.

RESULTS

Subjects

Of 378 patients who were screened during a period of 15 months, 257 patients met study criteria. Of these patients, 157 (61%) gave informed consent. The 100 non-participants refused to participate or did not engage in treatment. Two nonparticipants committed suicide. Of the 157 included patients, 131 patients entered the trial and

26 did not because of not showing response of positive symptoms within 6 months of antipsychotic treatment (N = 8), not reaching stable remission because of relapse within 6 months after treatment response (N = 9), refusal to participate in the trial (N = 8), and suicide (N = 1). Sixty-eight patients were randomly assigned to the discontinuation strategy and 63, to maintenance treatment. Three patients in the discontinuation strategy group revoked informed consent (Figure 1).

Data were obtained on nonparticipants anonymously. At least 44 nonparticipating patients hardly accepted any contact with mental health services. Nonparticipants also differed significantly from included patients in having a lower level of education, being less often employed, and showing a longer duration of untreated psychosis. Treatment response seemed to occur less frequently in non-participants. There were no significant differences between participants and nonparticipants regarding gender, age at first contact, marital status, living situation, and illicit drug abuse.

Baseline Data

There were no significant differences between patients in the 2 strategy groups (see Table 1). There was no significant difference in the proportion of time spent in hospital before entry into trial (about 20% of the mean observation time of 6.8 months).

Table 1. Baseline Characte	ristics of the Sam	ple by Stud	y Condition ^a
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Characteristic	Discontinuation Strategy $(N = 65)$	Maintenance Treatment $(N - 63)$	Statistia	n Valua
Characteristic	Strategy $(N = 03)$	Treatment $(N = 03)$	Statistic	p value
Male	45 (69.2)	44 (69.8)	Pearson $\chi^2 = 0.006$.94
Acute onset within 4 wk ^b	25 (42.4)	25 (41.7)	Pearson $\chi^2 = 0.006$.94
Living alone	21 (32.3)	25 (39.7)	Pearson $\chi^2 = 0.75$.38
Married or cohabiting	11 (16.9)	9 (14.3)	Pearson $\chi^2 = 0.17$.68
Paid job > 16 h/wk	33 (50.8)	24 (38.1)	Pearson $\chi^2 = 2.08$.15
Low educational level ^c	16 (24.6)	15 (23.8)	Pearson $\chi^2 = 0.17$.92
Middle educational level ^c	35 (53.8)	36 (57.1)		
High educational level ^c	14 (21.5)	12 (19.0)		
Schizophrenia	25 (38.5)	33 (52.4)	Pearson $\chi^2 = 2.501$.11
Other nonaffective psychotic disorders	40 (61.5)	30 (47.6)	,,	
Alcohol dependence/abuse	14 (21.5)	10 (15.9)	Pearson $\chi^2 = 0.67$.41
Cannabis dependence/abuse	15 (23.1)	16 (25.4)	Pearson $\chi^2 = 0.09$.76
Any dependence/abuse	26 (40.0)	19 (30.2)	Pearson $\chi^2 = 1.36$.24
Urban living	7 (10.8)	5 (7.9)	Pearson $\chi^2 = 1.46$.83
Rural living	15 (23.1)	16 (25.4)	,,	
Duration of untreated psychosis, mean (SD) [median], d	250 (581) [31]	278 (476) [61]	t = -0.27, $df = 126$.77
Duration of prodromal symptoms, mean (SD) [median], d	619 (1285) [91]	541 (990) [92]	t = 0.38, $df = 126$.65
Age at onset of psychosis, mean (SD), y	26.0 (6.7)	25.2 (6.6)	t = 0.68, df = 126	.49
Age at start of treatment, mean (SD), y	26.7 (6.4)	26.0 (6.4)	t = 0.65, df = 126	.52
Time to response, mean (SD) [median], d	72.4 (48.5) [61]	78.2 (56.5) [61]	t = -0.62, df = 126	.53

^aUnless otherwise indicated, data are given as N (%) of subjects.

^b9 missing cases: discontinuation strategy, N = 59; maintenance treatment, N = 60.

^cEducational levels: low = primary school, middle = secondary school, high = university level.

Implementation of Treatment Strategies

The mean duration of prescription of the applied antipsychotic agents did not differ between discontinuation and maintenance strategies. The 4 most commonly used antipsychotic agents were all second-generation antipsychotics: risperidone (mean [SD] = 5.6 [7.8] months), olanzapine (5.3 [7.5] months), quetiapine (1.6 [4.8] months), and clozapine (0.8 [3.5] months); these accounted for 86.9% of the total duration of antipsychotic treatment. The mean (SD) duration of discontinuation was 4.6 (6.1) months with the discontinuation strategy (25.5% of the time), and 0.8 (2.9) months with maintenance treatment (4.4% of the time).

Antipsychotics were not discontinued in 30 patients (46.2%) with the discontinuation strategy, versus 58 patients (92.1%) with maintenance treatment.

In the discontinuation strategy group, 14 patients (21.5%) stopped successfully, meaning they did not restart medication and had no relapses, with a mean duration of treatment discontinuation of 13.2 months (95% CI = 10.2 to 16.2, median = 15.0 months), whereas 16 patients (24.6%) restarted because of relapse (mean duration of discontinuation = 5.6 months, 95% CI = 3.4 to 7.7, median = 4.5 months) and 5 patients (7.7%) restarted because of mild recurrent symptoms without relapse (mean duration of discontinuation = 3.2 months, 95% CI = 1.0 to 5.4, median = 3.0 months). Contrary to the allotted strategy, in the maintenance treatment group, 5 patients were discontinued: 3 patients (4.8%) were stopped successfully (mean duration of discontinuation = 12.7 months, 95% CI = 3.3 to 22.1, median = 11.0 months), and 2 patients (3.2%) restarted because of relapse (mean duration of discontinuation = 5.5 months, 95% CI = -0.8 to 11.5 months).

The 5 most applied antipsychotic agents, their prescribed mean daily doses, and the corresponding haloperidol equivalents in both conditions at 3 time points during follow-up are presented in Table 2.

Time to Relapse

In the Cox regression analysis of time to first relapse, the proportion of censored cases (no relapse during follow-up) was 57% with the discontinuation strategy and 79% with maintenance treatment (see Figure 2). Thus, the relapse rate was 21% versus 43% in favor of the maintenance condition. The hazard ratio of relapse was 2.3 (p = .011) for the discontinuation strategy, which implies that the risk of relapse was twice as high with the discontinuation strategy during follow-up. The risk of relapse in both groups proved to be constant over time without leveling off.

Other Outcomes of Psychopathology and Functioning

Outcome measures showed no significant differences between the 2 conditions during follow-up. The actual values of the outcome parameters are presented in Table 3. Side effects scores were very low, around 20, in both strategies and with all assessments.

The analysis of repeated outcome measures using linear mixed models demonstrated no significant effect of treatment strategy, but only a significant time effect for positive symptoms (F = 9.744, p = .000), negative symptoms (F = 3.195, p = .026), and general symptoms

		1 n	no After Start of	Trial (T7)	Т	rial Halfway Po	int (T15)		End of Trial ((T24)
Antipsychotic Agent	Treatment Strategy	Ν	Daily Dose, mean (SD)	Hal Eq, mean (SD)	N	Daily Dose, mean (SD)	Hal Eq, mean (SD)	N	Daily Dose, mean (SD)	Hal Eq, mean (SD)
Discontinued	DS	14	NA	NA	15	NA	NA	14	NA	NA
	MT	1	NA	NA	4	NA	NA	3	NA	NA
Risperidone	DS	20	2.2(0.9)	2.2 (0.9)	17	2.2 (1.2)	2.2 (1.2)	18	2.4 (1.5)	2.4 (1.5)
*	MT	26	2.8 (1.4)	2.8 (1.4)	22	3.0 (1.1)	3.0(1.1)	21	2.9 (1.7)	2.9 (1.7)
Olanzapine	DS	18	10.5 (4.7)	2.1 (0.9)	18	9.7 (5.7)	1.9 (1.1)	16	10.6 (5.2)	2.1 (1.0)
*	MT	19	9.7 (4.8)	1.9 (1.0)	21	11.2 (5.1)	2.2 (1.0)	22	10.2 (5.8)	2.0 (1.2)
Quetiapine	DS	4	395 (164)	3.9 (1.6)	3	345 (250)	3.5 (2.5)	4	650 (412)	6.5 (4.1)
	MT	8	437 (288)	4.4 (2.9)	8	445 (330)	4.5 (3.3)	7	479 (586)	4.8 (5.9)
Clozapine	DS	2	425 (106)	5.7 (1.4)	2	475 (177)	6.3 (2.4)	2	475 (177)	6.3 (2.4)
1	MT	1	300	4.0	3	347 (90)	4.6 (1.2)	5	281 (142)	3.7 (1.9)
Zuclopenthixol	DS	2	7.9 (3.0)	1.6 (0.6)	3	5.9 (4.0)	1.2 (0.8)	3	22.6 (32.4)	4.5 (6.5)
*	MT	4	12.5 (8.2)	2.5 (1.6)	2	6.0 (5.7)	1.2 (0.1)	3	6.6 (4.1)	1.3 (0.8)
Abbreviations: $DS = d$	iscontinuation	strateg	y, Hal Eq = halo	peridol equiva	lents, N	IT = maintenand	ce treatment, N	A = not	applicable.	

Table 2. Mean Daily Doses (mg) and Their Haloperidol Equivalents (mg) of the 5 Most Applied Antipsychotics in the Discontinuation Strategy and Maintenance Treatment at 3 Time Points During Follow-Up

Figure 2. Relapse Rates for the Discontinuation Strategy vs. Maintenance Treatment (survival function)



 ${}^{a}T6 = start of trial (6 months after first treatment response).$

(F = 5.837, p = .001) as well as social functioning (F = 24.574, p = .000) and quality of life (F = 22.038, p = .000). There was also no interaction effect of treatment strategy and time. Regarding side effects, no effect of treatment strategy or time was found.

The proportion of time spent in hospital during followup was 7% in the targeted group and 12% in the maintenance treatment group, a difference that was not statistically significant, adjusted for the proportion of admission time during the 6 months before the trial (F = 0.43; df = 1; p = .514).

Information about vocational functioning, operationally defined as having a paid job for at least 16 hours a week at T24, was available for 116 patients and missing for 8 patients in the discontinuation strategy group and 4 in the maintenance treatment group. Binary logistic regression analysis, adjusted for having a job at baseline, showed a nonsignificant trend toward higher probability of having a job with the discontinuation strategy (35% vs. 17%, odds ratio = 2.4, p = .06).

DISCUSSION

The main result of the study is that only a minority of remitted first-episode patients can be taken off treatment with antipsychotic drugs successfully. Roughly speaking, of all patients assigned to the discontinuation strategy, only 50% were actually taken off treatment with antipsychotic drugs, 30% had to restart antipsychotics because of recurrent symptoms, and only the remaining 20% were able to stay off antipsychotic drugs successfully during the remaining observation period. If the observation period had been longer, the number of successfully withdrawn patients very likely would have been even smaller. However, the mean discontinuation time of successfully withdrawn patients was significantly longer than in patients who had to resume antipsychotic treatment, suggesting the relapse risk in successfully withdrawn patients levels off with survival time.

The selection of the patient sample very likely enhanced the proportion of patients successfully taken off treatment with drugs. In a nonselected patient sample, also including patients not achieving remission within the first year of antipsychotic treatment, the proportion of successfully withdrawn patients would probably be smaller.

In almost half the patients assigned to the discontinuation strategy, the aim of discontinuation apparently was not feasible. This may be due to recurrent and exacerbating symptoms of mild severity during taper of the dosage of antipsychotics that did not allow for a complete or even partial withdrawal of antipsychotics for more than a short interval. A limitation of our study is the open nature of the design, which might have led to a more conservative treatment strategy in patients assigned to the discontinuation condition. Clinicians might have been very keen on the prodromal symptoms in these patients, being aware of the risk of relapse, while tapering the dose or discontinuing antipsychotics.

A further point of interest is the definition of remission. In the present study, this definition was based solely on the

Table 3. Outcor	nes of the D	Discontinuat	ion Strategy	and	Maintenanc	e Treatmen	t at Baselin	ne anc	13 Time Po	ints During	Follow-Up					
	Baseline (re	sponse of posi	tive symptoms	; T0)		Start of Trial	(T6)		Half	way Point of	Trial (T15)			End of Trial	(T24)	
	Score, N	Aean (SD)			Score, M	ean (SD)			Score, M	ean (SD)			Score, Me	can (SD)		
Dutcome Variable	DS	MT	95% CI	d	DS	MT	95% CI	d	DS	MT	95% CI	d	DS	MT	95% CI	d
PANSS P	9.9 (2.8)	10.7 (3.0)	-1.9 to 0.2	.116	8.8 (1.7)	9.6 (2.7)	-1.6 to 0.1	.073	9.7 (3.0)	10.5 (3.7)	-2.0 to 0.4	.213	11.0(4.3)	10.8 (3.8)	-1.2 to 1.8	.688
PANSS N	13.1 (4.6)	14.0 (5.6)	-2.8 to 0.8	.276	12.5 (4.4)	13.3(5.0)	-2.5 to 0.9	.360	11.8(4.0)	13.0(5.9)	-3.0 to 0.5	.170	12.1 (5.2)	13.3 (6.2)	-3.3 to 0.8	.241
PANSS G	25.4 (6.2)	26.4 (6.9)	-3.3 to 1.3	.391	22.8 (5.1)	24.4 (6.8)	-3.7 to 0.5	.139	22.9 (6.2)	24.5 (7.4)	-3.9 to 0.9	.205	24.7 (7.3)	24.9 (6.7)	-3.3 to 0.8	.930
GSDS	8.3 (4.0)	8.6 (4.5)	-1.8 to 1.2	.681	:	:	:	:	5.8 (4.1)	5.7 (4.1)	-1.4 to 1.5	900.	5.8 (4.5)	6.4 (4.2)	-2.2 to 1.0	.449
WHOQoL-Bref	91.0 (11.8)	92.5 (12.8)	-5.8 to 2.8	.491	89.6 (10.7)	90.3(9.9)	-4.3 to 3.0	.720	96.0 (11.8)	95.8 (13.6)	-4.4 to 4.6	.963	96.9 (12.6)	97.8 (13.3)	-5.5 to 3.7	.700
LUNSERS	÷	:	÷	÷	18.7 (15.3)	20.3 (13.8)	-6.8 to 3.7	.557	19.3 (13.4)	19.3 (15.2)	-5.2 to 5.2	<u> 995</u>	24.5 (36.6)	22.2 (19.0)	-8.3 to 13.0	.661
Abbreviations: D: treatment, PAN	S = discontinu SS = Positive	uation strateg and Negative	y, GSDS = Gr Syndrome So	oninge cale, P	en Social Fur ANSS G = P	ANSS genera	Disability Solution S	chedul ubscal	e, LUNSERS e, PANSS N =	= Liverpool	University Si ative symptoi	ide Effe m subs	ects Rating Sc	ale, MT = m P = PANSS p	aintenance ositive sympto	Ę
subscale, WHO	QoL-Bref = b	prief version c	of the WHO Q	uality	of Life scale)	-)	*			•	*	

Guided Discontinuation vs. Maintenance in Psychosis

positive symptoms, because these symptoms are the main target for antipsychotic treatment. The multidimensional remission criteria recently proposed by Andreasen et al.³¹ might represent a more valid concept of remission. In another article,³² we have shown that those criteria have additional value in predicting social functioning and symptom outcome. In future studies, the application of those criteria might be preferable. However, a preliminary analysis of our data in the present study (not presented) did not show a difference in successful discontinuation.

In this first-episode study, we replicated the findings of the early studies on targeted treatment in multiple-episode patients showing that higher relapse rates were a consequence of this strategy.^{1–3,33} However, the results do not confirm the findings by Gaebel et al.²² Those authors did not find significantly higher relapse rates in targeted treatment in first-episode patients. However, their study was a reanalysis of formerly gathered data, which may have biased the results. It seems justified to conclude that guided discontinuation leads to higher relapse rates in first-episode patients, and that antipsychotic maintenance treatment reduces relapse risk in first-episode patients to the same extent as in multiple-episode patients.

The nature of relapse was benign in all cases; the duration was rarely longer than 1 month, and subsequent hospitalization was an exception. This was probably a consequence of frequent monitoring, low-threshold access to services, and patient education about prevention of relapse and recurrent symptoms. Very likely because of these precautions, relapse rates did not have any measurable impact on functional or symptomatic outcome or hospitalization, which were equivalent across the treatment strategies. The nonsignificant trend toward better vocational functioning in the discontinuation strategy is an interesting finding. Though this finding may be spurious, it may indicate that some patients on lower dosages of antipsychotics have an advantage in the domain of executive functioning. Interestingly, the finding that patients in the discontinuation strategy group contributed significantly more to the family income was reported before, as well as the finding that placebo-treated patients had a better vocational outcome.^{2,34} However, this finding was not always replicated.³ Moreover, many patients who might have regained the ability to work will not necessarily apply for a job again. Final conclusions on this issue cannot be drawn from the present results. Concerning side effects, the discontinuation strategy did not show an advantage over maintenance treatment. In both strategies, the mean severity level of side effects was very low, probably a consequence of the applied low-dose regimen in maintenance strategy.

It may be concluded that, in remitted first-episode patients, a discontinuation strategy is not universally applicable as an alternative to maintenance treatment. Given the relatively small number of patients who were successfully discontinued (21.5%), the twice-higher relapse rates with

... = data not available.

Symbol:

the discontinuation strategy, the selected patient sample of stably remitted and cooperative patients included in the trial, and the lack of substantial advantages of the discontinuation strategy over maintenance treatment, the discontinuation strategy does not seem to offer sufficient benefits over maintenance treatment to implement the strategy in regular practice for all remitted first-episode patients. On the other hand, 1 in 5 patients successfully discontinued antipsychotics for a median period of 15 months through application of the strategy. For these patients, the gains cannot be easily overestimated, particularly from a recovery point of view. We conclude that a discontinuation strategy may be considered in firstepisode patients with full remission during at least 6 months who feel inclined to try it, but only if relapse risk can be carefully managed by close monitoring and by resuming treatment if needed. If these conditions are met, negative consequences for functional outcome are absent. The gain is either successful discontinuation or personal empirical evidence on the usefulness of medication. Further research is needed to establish the predictors of successful discontinuation and to distinguish patients who have a reasonable chance to discontinue medication from those who definitively need maintenance treatment.

Drug names: clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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