Original Investigation

Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy

Long-term Follow-up of a 2-Year Randomized Clinical Trial

Lex Wunderink, MD, PhD; Roeline M. Nieboer, MA; Durk Wiersma, PhD; Sjoerd Sytema, PhD; Fokko J. Nienhuis, MA

Editorial page 898

IMPORTANCE Short-term outcome studies of antipsychotic dose-reduction/discontinuation strategies in patients with remitted first-episode psychosis (FEP) showed higher relapse rates but no other disadvantages compared with maintenance treatment; however, long-term effects on recovery have not been studied before.

OBJECTIVE To compare rates of recovery in patients with remitted FEP after 7 years of follow-up of a dose reduction/discontinuation (DR) vs maintenance treatment (MT) trial.

DESIGN Seven-year follow-up of a 2-year open randomized clinical trial comparing MT and DR.

SETTING One hundred twenty-eight patients participating in the original trial were recruited from 257 patients with FEP referred from October 2001 to December 2002 to 7 mental health care services in a 3.2 million–population catchment area. Of these, 111 patients refused to participate and 18 patients did not experience remission.

PARTICIPANTS After 7 years, 103 patients (80.5%) of 128 patients who were included in the original trial were located and consented to follow-up assessment.

INTERVENTION After 6 months of remission, patients were randomly assigned to DR strategy or MT for 18 months. After the trial, treatment was at the discretion of the clinician.

MAIN OUTCOMES AND MEASURES Primary outcome was rate of recovery, defined as meeting the criteria of symptomatic and functional remission. Determinants of recovery were examined using logistic regression analysis; the treatment strategy (MT or DR) was controlled for baseline parameters.

RESULTS The DR patients experienced twice the recovery rate of the MT patients (40.4% vs 17.6%). Logistic regression showed an odds ratio of 3.49 (P = .01). Better DR recovery rates were related to higher functional remission rates in the DR group but were not related to symptomatic remission rates.

CONCLUSIONS AND RELEVANCE Dose reduction/discontinuation of antipsychotics during the early stages of remitted FEP shows superior long-term recovery rates compared with the rates achieved with MT. To our knowledge, this is the first study showing long-term gains of an early-course DR strategy in patients with remitted FEP. Additional studies are necessary before these results are incorporated into general practice.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN16228411.

JAMA Psychiatry. 2013;70(9):913-920. doi:10.1001/jamapsychiatry.2013.19
Published online July 3, 2013.

Author Affiliations: Department of Research and Education, Friesland Mental Health Services, Leeuwarden, the Netherlands (Wunderink, Nieboer); Department of Psychiatry, Rob Giel Research Center, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands (Wunderink, Wiersma, Sytema, Nienhuis).

Corresponding Author: Lex Wunderink, MD, PhD, Department of Research and Education, Friesland Mental Health Services, Sixmastraat 2, PO Box 8932 PS, Leeuwarden, the Netherlands (lex.wunderink@ggzfriesland.nl).

In naturalistic conditions, a substantial number of patients with first-episode psychosis (FEP) will stop taking antipsychotic drugs, resulting in increased relapse risk and lower rates of recovery.[1] Robinson et al[2] studied self-elected discontinuation in patients with FEP and found a 5-fold increase in relapse rates compared with patients who continued to take antipsychotics. In patients with multiple episodes who were receiving intermittent treatment, higher relapse rates were demonstrated compared with the rates in patients receiving maintenance treatment (MT).[3] The first randomized clinical trial in patients with remission of FEP comparing MT with dose reduction/discontinuation (DR) also showed higher relapse rates and no advantages of DR.[4] More recent studies confirmed these results.[5-7] This further supported the guidelines stating that MT with antipsychotics is recommended for at least 1 year when a first episode has remitted.[8,9] However, all studies on treatment strategies have a short-term follow-up of 2 years or less.[4,10] The long-term effects of treatment strategies are therefore unknown. Moreover, treatment recommendations and guidelines are undifferentiated regarding stability and remission of the illness.[11,12] The present guidelines are directed mainly toward the prevention of relapse. However, awareness is growing that, in addition to relapse, functional status should be included in outcome evaluation. Therefore, recovery, including both symptomatic and functional remission, would be a more adequate concept for outcome evaluation.[13]

The aim of the present study was to evaluate the long-term outcome of an early-course DR strategy on recovery compared with MT. Therefore, a 7-year follow-up assessment was conducted in a cohort of patients with FEP who originally participated in an early-course DR trial.[4]

Methods

Participants

Patients seen for the first time in mental health care services with a first episode of psychosis from October 1, 2001, until December 1, 2002 (N = 257), in a 3.2 million-population catchment area were asked to participate in the original 2-year trial comparing DR with MT.[4] Of these, 111 patients refused to participate or were lost to follow-up, and 18 patients did not show response of symptoms within 6 months of antipsychotic treatment or sustained symptom remission during 6 months. One hundred twenty-eight patients were included in the original trial and completed it. At the end of this trial, all patients consented to follow-up. Research assistants who recruited the patients in the original study contacted them 5 years later, requesting their participation in a one-time interview regarding the course and outcome of psychosis during the follow-up period.

Assessments

Baseline data were sampled as part of the original trial. These included sex; duration of untreated psychosis (DUP); age at onset of psychosis; educational level; having a regular job for at least 16 hours a week; living alone vs with others; diagnosis of alcohol and cannabis use, and dependence or abuse of any substance; diagnostic category of nonaffective psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, or psychotic disorder not otherwise specified); symptom severity; social functioning; quality of life; and time from start of antipsychotic treatment to first remission. A detailed description of the instruments and measurement methods was reported by Wunderink et al.[14]

In the present study, the patients were followed up after 7 years, which was calculated from the start of the original trial (the start date of the first remission). The follow-up assessment included symptom severity and level of social functioning during the past 6 months, relapses during the whole follow-up period, and the type and dose of antipsychotics used during the past 2 years. Dosage data registered in patient records were verified during the assessment interviews.

Symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS).[15] The PANSS was used to measure observer-rated severity of symptoms during the preceding week, as well as during the past 6 months.

Social functioning was assessed with the Groningen Social Disability Schedule (GSDS), a semistructured investigator-based interview measuring disabilities in social functioning in 8 domains (7 of which were included in this study) over the past 4 weeks, as well as during the past 6 months.[16] The 7 domains are self-care, housekeeping, family relationships, partner relationships, relationships with peers, community integration, and vocational functioning. The parenthood domain was omitted because of limited applicability. A disability is rated by the investigator on a 4-point scale: none (0), minimal (1), obvious (2), and serious (3).

Training for administration of PANSS and GSDS was provided for all research assistants before the study. Training included ratings of videotaped and real-life interviews, followed by discussions and review of ratings.

At baseline, predictors of recovery (symptomatic and functional remission) were recorded as part of the original trial: demographic variables, DUP, psychopathologic characteristics (PANSS), cannabis and any other substance abuse, social functioning (GSDS), quality of life (World Health Organization Quality of Life [WHOQoL]), living situation, and vocational situation. Details on the measurement of DUP and other baseline variables have been described elsewhere.[14]

Definitions of Recovery, Symptomatic Remission, Relapse, and Functional Remission

Criteria for recovery were met when patients had symptomatic and functional remission for at least 6 months at the 7-year follow-up. Criteria for symptomatic remission were adopted from Andreasen et al.[17] All relevant PANSS item scores have to be 3 (mild) or less on a scale ranging from 1 (not present) to 7 (severe) during an observational period of 6 months. Patients were assessed retrospectively for any symptomatic relapse occurring during this period. A symptomatic relapse was defined as an exacerbation of symptoms during at least 1 week with at least 1 relevant PANSS item score above 3 (mild). Any relapse in symptoms during the 6 months preceding the as-

sessment prevented the individual from being categorized as recovered at the time of the assessment.

According to generally accepted views, functional remission implies proper social functioning in the main domains of everyday life. The 7 domains of the GSDS included in the present study adequately represent these domains. A patient with functional remission should function adequately in all 7 domains with none or only a minimal disability in any of them (not allowing a score of 2 or 3 on any GSDS domain).[13] Patients were considered to have functional remission if, during an observational period of 6 months before assessment, all functional domain scores remained at 1 or lower.

Conversion of Antipsychotics to Haloperidol Equivalents

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 dose range recommendation tables to convert the applied antipsychotic agents to haloperidol equivalents.[9,18]

Calculation of Mean Daily Dose of Antipsychotics and Timeline of Dosing

The calculation of the mean daily doses of antipsychotics during the last 2 years of follow-up was based on registration of dosage data in patient records verified during assessment interviews. Prescription data are accurately registered in electronic patient files in all participating services in this study. First, the mean daily dose for each month was calculated, including days of zero intake, to get an impression of the timeline of dosing. The mean daily dose during the 2-year period was then calculated by adding the means for each month and dividing by 24. To obtain a more accurate impression of prescribed dosages, we also calculated the mean daily dose during the last 2 years of the 7-year follow-up, excluding days of zero intake. To get an impression of the timeline of dose reduction and discontinuation, we calculated the mean number of months per patient and the mean number of patients per month with zero intake, as well as with doses below 1 mg of haloperidol equivalents during the last 2 years of the 7-year follow-up.

Statistical Analysis

Analyses were carried out using commercial software (SPSS, version 18.0; SPSS Inc). Baseline characteristics of participants and nonparticipants and of DR and MT groups were evaluated with Pearson χ^2 tests for categorical variables and unpaired 2-tailed *t* tests for continuous variables. Selection of variables to be included in the regression models was based on bivariate analyses, Pearson χ^2 tests for categorical variables, and *t* tests for continuous variables of baseline variables and recovery, as well as symptomatic and functional remission at follow-up. The DUP was log transformed in these analyses for its skewed distribution. *z* Scores for skewness of the distribution were 13.95 for non–log-transformed DUP days vs −0.75 for log-transformed DUP days. However, the same conclusions were obtained by including DUP days in the analyses instead of the log-transformed DUP days.

Potential explanatory variables included demographic measures, baseline symptoms (positive, negative, and general), baseline social functioning, substance abuse, and DUP. Logistic regression analyses were used to study the contributions of relevant predictors to recovery and its constituents (symptomatic and functional remission) as dependent variables. Relevant variables were entered in the regression model if bivariate analysis showed a significant association ($P < .05$) with recovery, symptomatic remission, or functional remission at the 7-year follow-up. Time to first relapse during follow-up from random assignment to DR or MT groups was analyzed with a Kaplan-Meier survival analysis. The mean number of relapses with DR and MT was compared using an unpaired 2-tailed *t* test, and the cross tabulation of number of relapses and treatment arm was analyzed with a Pearson χ^2 test. The difference of the mean daily dose of antipsychotic medication during the last 2 years of follow-up between DR and MT, calculated by determining the mean daily dosage including periods with zero intake of antipsychotics, was analyzed with an unpaired 2-tailed *t* test. The same analysis was done comparing the mean daily doses excluding periods with zero intake, the mean number of months with zero intake and with daily doses below 1 mg of haloperidol equivalents per patient, and the mean number of patients per month with zero intake and with doses below 1 mg of haloperidol equivalents. Finally, we performed an as-treated post hoc analysis to compare the outcome of patients who successfully discontinued or achieved substantial dose reduction (mean daily dose <1 mg of haloperidol equivalents) determined with Pearson χ^2. To find predictors of successful dose reduction/discontinuation of antipsychotic medication during the last 2 years of follow-up, we performed another logistic regression analysis. Relevant predictors of dose reduction/discontinuation were selected by bivariate analyses (showing a significant association with dose reduction/discontinuation) and entered into a stepwise logistic regression analysis with discontinuation or dose reduction to a mean daily dose of less than 1 mg of equivalents of haloperidol during the last 2 years of follow-up as a dependent variable.

Results

Of the 128 patients who participated in the original study, 103 patients (80.5%) were located and consented to participate in the 7-year follow-up. Of the 25 nonparticipants, 1 patient had committed suicide, 18 patients refused further participation, and 6 individuals were lost to follow-up. There were no significant differences in baseline characteristics and functional data between participants and nonparticipants in the 7-year follow-up study and also none between the 2 treatment strategy groups (**Table 1**).

The variable DUP has been log transformed in Table 1 because of its skewed distribution. The actual values of DUP in the follow-up sample (n = 103) were mean (SD), 266.6 (529.9) days; median, 31.0 days; 25th percentile, 0 days; 50th percentile, 31 days; 75th percentile, 184 days; and maximum, 3560 days (interquartile range, 0-184 days).

Table 1. Baseline Characteristics of Participants and Nonparticipants and of DR and MT Participants

Characteristic	No. (%)		Statistic	P Value	Strategy, No. (%)		Statistic	P Value
	Participants (n = 103)	Nonparticipants (n = 25)			DR (n = 52)	MT (n = 51)		
DUP, mean (SD) [median], d[a]	1.51 (1.10) [1.49]	1.39 (1.17) [1.49]	$t_{126} = -0.48$	.63	1.45 (1.13) [1.49]	1.56 (1.08) [1.78]	$t_{101} = -0.50$	.62
Age at onset of psychosis, mean (SD), y	25.83 (6.87)	24.93 (5.84)	$t_{126} = -0.60$	.55	26.26 (6.79)	25.39 (6.99)	$t_{101} = 0.64$	.52
Regular job for ≥16 h/wk[b]	45 (45)	12 (48)	Pearson $\chi^2 = 0.07$	.79	27 (54.0)	18 (36.0)	Pearson $\chi^2 = 3.27$	.07
Living alone	37 (35.9)	9 (36)	Pearson $\chi^2 = 0.00$	.99	19 (36.5)	18 (35.3)	Pearson $\chi^2 = 0.02$	.89
Dependence or abuse								
Alcohol	22 (21.4)	2 (8.0)	Pearson $\chi^2 = 2.36$	.12	13 (25.0)	9 (17.6)	Pearson $\chi^2 = 0.83$	.36
Cannabis	26 (25.2)	5 (20)	Pearson $\chi^2 = 0.30$	.58	14 (26.9)	12 (23.5)	Pearson $\chi^2 = 0.16$	.69
Any	37 (35.9)	8 (32.0)	Pearson $\chi^2 = 0.14$	.71	22 (42.3)	15 (29.4)	Pearson $\chi^2 = 1.86$	.17
Schizophrenia	45 (43.7)	13 (52.0)	Pearson $\chi^2 = 3.80$	.58	19 (36.5)	26 (51.0)	Pearson $\chi^2 = 7.05$	.22
Schizophreniform disorder	26 (25.2)	3 (12.0)			14 (26.9)	12 (23.5)		
Schizoaffective disorder	6 (5.8)	1 (4.0)			4 (7.7)	2 (3.9)		
Delusional disorder	12 (11.7)	5 (20.0)			8 (15.4)	4 (7.8)		
Brief psychotic disorder	3 (2.9)	0			0	3 (5.9)		
Psychotic disorder, NOS	11 (10.7)	3 (12.0)			7 (13.5)	4 (7.8)		
PANSS subscale, mean (SD)								
Positive	10.28 (3.08)	10.44 (2.43)	$t_{126} = 0.24$	.81	9.79 (2.96)	10.78 (3.15)	$t_{101} = -1.66$	.10
Negative	13.50 (5.14)	14.12 (4.89)	$t_{126} = 0.62$	.53	12.87 (4,80)	13.96 (5.51)	$t_{101} = -1.08$	.28
General	25.85 (6.53)	26.24 (6.78)	$t_{126} = 0.29$	.77	25.27 (6.44)	26.45 (6.62)	$t_{101} = -0.92$	.36
Total score, mean (SD)								
GSDS	8.46 (4.19)	8.56 (4.64)	$t_{126} = 0.11$	.91	8.48 (4.10)	8.43 (4.33)	$t_{101} = 0.06$	.95
WHOQoL	91.48 (11.50)	93.08 (15.18)	$t_{125} = 0.58$	.56	90.42 (11.21)	92.55 (11.79)	$t_{101} = -0.94$	.35

Abbreviations: DR, dose reduction strategy; DUP, duration of untreated psychosis; GSDS, Groningen Social Disability Schedule; MT, maintenance treatment; NOS, not otherwise specified; PANSS, Positive and Negative Syndrome Scale; WHOQoL, World Health Organization Quality of Life scale.

[a] DUP days were log transformed because of the skewed distribution.

[b] Three cases missing in follow-up sample: 2 in the DR group and 1 in MT group.

Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Characteristic	No. (%)		
	DR (n = 52)	MT (n = 51)	Total Sample (n = 103)
Recovery	21 (40.4)	9 (17.6)	30 (29.1)
Remission			
Symptomatic	36 (69.2)	34 (66.7)	70 (68.0)
Functional	24 (46.2)	10 (19.6)	34 (33.0)

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.

Recovery, Symptomatic Remission, and Functional Remission

Recovery rates were significantly higher in patients who received DR than in those who received MT (Pearson $\chi^2_1 = 8.2$; $P = .004$). Symptom remission after 7 years did not differ significantly across the original treatment strategies of DR and MT (Pearson $\chi^2_1 = 0.08$; $P = .78$), but functional remission differed significantly in favor of DR (Pearson $\chi^2_1 = 6.45$; $P = .01$) (**Table 2**).

Symptomatic remission without functional remission was achieved by 38.8% of all patients (DR, 28.8%; MT, 49.0%). Functional remission without symptomatic remission was reached by 3.9% of all patients (DR, 5.8%; MT, 2.0%). In addition, 28.2% of all patients (DR, 25.0%; MT, 31.4%) achieved neither symptomatic remission nor functional remission.

Predictors of Recovery, Symptomatic Remission, and Functional Remission

Table 3 reports the results of the bivariate analyses of associations of conceivable predictors at baseline and recovery, symptomatic remission, and functional remission at the 7-year follow-up. Recovery was bivariately significantly associated with PANSS positive symptoms, negative symptoms, general symptoms (less severe), living with others vs living alone, social functioning (better), and trial arm (DR). When entered stepwise in

Table 3. Bivariate Analyses of Conceivable Baseline Predictors of Recovery, Symptomatic Remission, and Functional Remission at 7-Year Follow-up

	Recovery		Remission			
			Symptomatic		Functional	
Baseline Variable	Statistic	*P* Value	Statistic	*P* Value	Statistic	*P* Value
Sex	Pearson χ^2 = 1.58	.21	2.20	.14	1.22	.27
Educational level	Pearson χ^2 = 0.78	.68	1.38	.50	0.59	.74
Living alone	Pearson χ^2 = 6.82	.009	0.89	.34	7.36	.007
Holding a regular job for ≥16 h/wk	Pearson χ^2 = 3.06	.08	1.07	.30	3.15	.08
DUP (log transformed)	t_{101} = 1.62	.11	2.41	.02	1.46	.15
Age at onset of psychosis	t_{101} = −0.05	.96	0.82	.42	−0.40	.69
Total score						
GSDS	t_{101} = 2.99	.004	1.99	.049	3.62	<.001
WHOQoL	t_{101} = −1.34	.18	−0.64	.53	−1.75	.08
Diagnosis	Pearson χ^2 = 4.61	.46	8.14	.15	3.07	.69
PANSS subscale						
Positive	t_{101} = 2.41	.02	1.57	.12	2.63	.01
Negative	t_{101} = 3.16	.002	2.19	.03	3.89	<.001
General	t_{101} = 2.65	.009	1.23	.22	3.22	.002
Dependence or abuse						
Alcohol	Pearson χ^2 = 1.88	.17	1.11	.29	0.79	.37
Cannabis	Pearson χ^2 = 0.04	.83	0.42	.52	0.08	.78
Time to remission, d	t_{101} = −0.32	.75	−0.17	.87	−0.25	.80
Arm (DR vs MT)	Pearson χ^2 = 6.45	.01	0.08	.78	8.20	.004

Abbreviations: DR, dose reduction/discontinuation; DUP, duration of untreated psychosis; GSDS, Groningen Social Disability Schedule; MT, maintenance treatment; PANSS, Positive and Negative Syndrome Scale; WHOQoL, World Health Organization Quality of Life scale.

a logistic regression analysis, less severe negative symptoms (odds ratio [OR_1], 0.84; P = .007), living together (OR_1, 4.44; P = .01), and trial arm (DR) (OR_1, 3.49; P = .01) remained as variables significantly related to recovery at the 7-year follow-up.

Three baseline variables were significantly associated with symptom remission in the bivariate analyses: DUP (shorter), social functioning (better), and PANSS negative symptoms (less severe). Entered stepwise in a logistic regression analysis, only DUP (shorter) was significantly related to symptom remission at follow-up (OR_1, 0.62; P = .02).

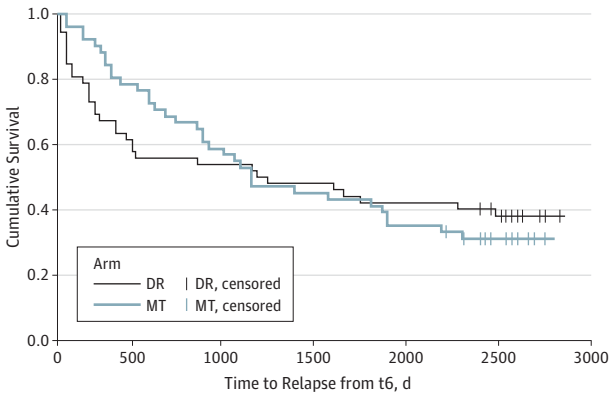
Functional remission was bivariately associated with the same variables as recovery. Stepwise logistic regression analysis showed that less severe negative symptoms (OR_1, 0.85; P = .02), living together (OR_1, 4.68; P = .01), better social functioning (OR_1, 0.86; P = .04), and treatment arm (DR) (OR_1, 4.62; P = .004) were significantly related to functional remission.

Relapse Rates During 7 Years of Follow-up

The mean (SD) number of relapses in the sample was 1.24 (1.37). Categorized by group, the mean numbers were DR, 1.13 (1.22) and MT, 1.35 (1.51); this difference was nonsignificant (t_{101} = -0.81, P = .42).

Time to first relapse from entry into the experimental phase of the trial (which was at 6 months of stable remission from baseline) was entered in a Kaplan-Meier survival analysis, comparing the survival curves of the patients who were in the DR and MT strategies (**Figure 1**). The initial relapse rates appeared to be about twice as high in the DR group, but the curves then approached each other and came on par at approximately 3 years of follow-up. From then on, the findings were not significantly different (log-rank [Mantel-Cox] χ^2_1 = 0.003; P = .96).

Figure 1. Kaplan-Meier Survival Analysis



Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18 months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT).

Overall, 67 of the participants (65.0%) had at least 1 relapse during the 7 years of follow-up. Categorized by group, 32 relapses occurred in the DR group (61.5% of all DR patients) and 35 in the MT group (68.6% of all MT patients).

No relapse occurred in 36 patients (34.9%), 20 of whom were in the DR group (38.5% of all DR patients) and 16 in the MT group (31.4% of all MT patients). The number of patients with a certain

Figure 2. Mean Daily Dose in Dose Reduction/Discontinuation (DR) and Maintenance Treatment (MT) During the Last 2 Years of 7-Year Follow-up

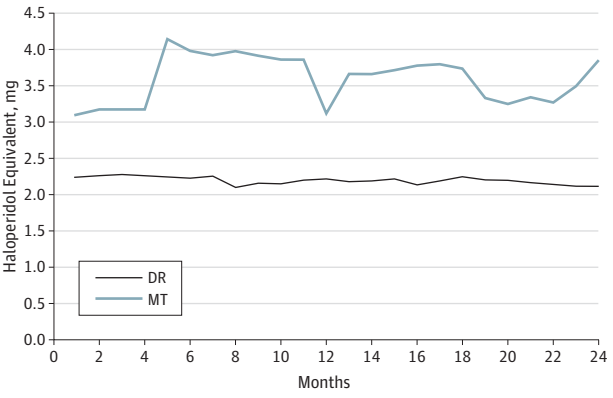
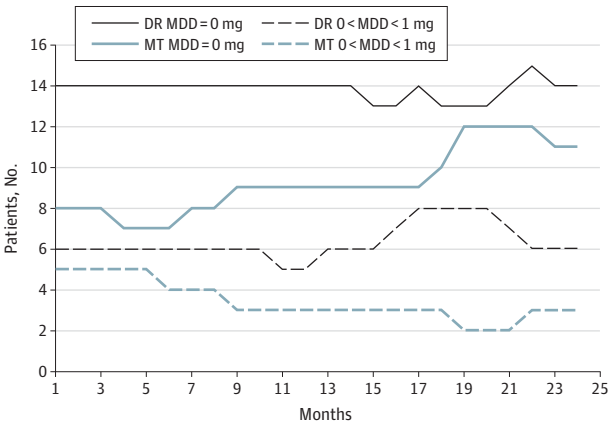


Figure 3. Dose Reduction/Discontinuation in DR and MT During the Last 2 Years of 7-Year Follow-up



DR indicates dose reduction strategy; MDD, mean daily dose (haloperidol equivalent milligrams); and MT, maintenance treatment strategy.

number of relapses in the DR (range, 0-5) and MT (range, 0-8) groups did not differ significantly (Pearson $\chi^2_6 = 4.96$; $P = .55$).

Antipsychotic Dose During the Last 2 Years of Follow-up

The mean antipsychotic dose (daily dose in haloperidol-equivalent milligrams) in patients originally receiving DR (2.20 [2.27] mg) remained significantly lower during the last 2 years of follow-up compared with the dose in patients who were receiving MT (mean, 3.60 [4.01] mg; $t_{101} = -2.18$; $P = .03$). The time course of mean daily doses during the last 2 years of follow-up in the DR and MT groups is graphically represented in **Figure 2**.

When the patients who discontinued antipsychotics during the last 2 years of follow-up (DR, 11; MT, 6) were left out of the analysis, the difference of mean haloperidol equivalent daily dose still bordered on significance: 2.79 (2.21) mg in the DR group vs 4.08 (4.03) mg in the MT group ($t_{84} = -1.81$; $P = .07$). The mean daily dose in DR vs MT patients, excluding days of zero intake to give an impression of prescribed dosages, bordered on significance: 2.89 (2.19) mg in the DR group vs 4.29 (4.01) mg in the MT group ($t_{84} = -1.98$; $P = .05$).

Discontinuation and Dose Reduction of Antipsychotics Over Time

Of the 17 patients who successfully discontinued antipsychotic treatment in the original trial, 13 were located and included in the present follow-up; 10 of these patients were in the DR group and 3 were in the MT group. Two patients (both DR) restarted antipsychotic therapy; thus, 11 (8 DR and 3 MT) patients still were not using antipsychotic agents during the last 2 years of the 7-year follow-up.

At the 7-year follow-up, an additional 3 DR and 3 MT patients had stopped taking antipsychotics during the last 2 years, amounting to a total of 17 patients who had stopped antipsychotic therapy at follow-up: 11 patients (21.1%) of the DR group and 6 patients (11.8%) of the MT group. In addition, an equal number of patients used a mean haloperidol-equivalent daily dose of less than 1 mg during the last 2 years of follow-up: 11 in the DR group and 6 in the MT group. These patients may be considered to have achieved a major dose reduction of antipsychotics. This would amount to 34 patients (33.0%) without substantial antipsychotic medication: 22 patients (42.3%) in the DR group and 12 patients (23.5%) in the MT group (Pearson $\chi^2_1 = 4.11$; $P = .04$).

The mean number of months per patient with zero intake in the DR (6.38 [10.28]) and MT (4.35 [8.49]) groups during the last 2 years of follow-up did not differ significantly, nor did the mean number of months per patient with a mean daily dose of less than 1 mg (DR, 2.92; MT, 1.61). The mean number of patients per month who had zero intake was 13.8 (26.5%) in the DR group and 9.3 (18.2%) in the MT group, a significant difference ($t_{23} = 12.70$; $P < .001$). The mean number of patients per month who had low doses below 1 mg also differed significantly: 6.3 patients (12.1%) in the DR group and 3.4 patients (6.7%) in the MT group ($t_{23} = 9.17$; $P < .001$). The time course of dose reduction/discontinuation is graphically represented in **Figure 3**.

To explore whether discontinuation was associated with good or bad general outcome, we performed an as-treated post hoc comparison, comparing patients who successfully discontinued antipsychotics or achieved a substantial dose reduction (n = 34) with those who did not (n = 69), regardless of the original treatment strategy.

In the successfully discontinued/dose reduction patients compared with the not discontinued/tapered patients, symptomatic remission was achieved by 29 of 34 patients (85.3%) vs 41 of 69 patients (59.4%) ($\chi^2_1 = 7.00$; $P = .008$), functional remission by 19 of 34 patients (55.9%) vs 15 of 69 patients (21.7%) ($\chi^2_1 = 12.00$; $P = .001$), and recovery by 18 of 34 patients (52.9%) vs 12 of 69 patients (17.4%) ($\chi^2_1 = 13.94$; $P < .001$). The mean number of relapses in the discontinued/tapered patients during the 7-year follow-up was 0.71 (0.94) vs 1.51 (1.47) in the not discontinued/tapered group, a significant difference ($t_{101} = 2.90$; $P = .005$).

Bivariate analysis of predictors of successful discontinuation or dose reduction to a mean daily dose of less than 1 mg of haloperidol equivalents during the last 2 years of follow-up indicated no relapse occurring during follow-up (Pearson $\chi^2_1 = 7.22$; $P = .007$), treatment arm (DR or MT) (Pearson $\chi^2_1 = 4.11$; $P = .04$),

successful discontinuation of antipsychotics during the original trial (Pearson $\chi^2_1 = 23.66$; $P < .001$), short DUP ($t_{101} = 2.67$; $P = .009$), better social functioning ($t_{101} = 2.09$; $P = .04$), and less severe PANSS general symptoms ($t_{101} = 2.23$; $P = .03$). When these variables were entered in a stepwise logistic regression analysis, only successful discontinuation of antipsychotics during the original trial significantly and independently predicted successful discontinuation/dose reduction to a mean daily dose of less than 1 mg of haloperidol equivalents during the last 2 years of the 7-year follow-up (OR_1, 0.03; $P = .001$).

Discussion

To our knowledge, this study is the first to identify major advantages of a DR strategy over MT in patients with remission of FEP. In patients originally assigned to a DR strategy sustained for 18 months, after a long-term follow-up of 7 years, recovery and functional remission rates were more than twice those of patients who were assigned to MT (40.4% vs 17.6% and 46.2% vs 19.6%, respectively). There was no significant difference in symptom remission rate (69.2% vs 66.7%) between the groups.

One of the first things to consider is the selection of the sample included in the original trial. As noted, approximately half the eligible patients with FEP were not willing to participate. Compared with participants, these nonparticipants differed in showing a lower level of functioning, being less adherent to therapy, and being more difficult to engage. In the present study, one could say "the best half" of the FEP patients presenting in clinical practice was evaluated.

The major issue is, of course, whether these striking results may be attributed to the treatment strategies in the original trial. There were no significant differences in any of the conceivable confounding variables between the 2 groups. Therefore, it seems likely that the original treatment strategy, be it DR or MT, has a profound effect on long-term outcome. The difference after 7 years does not appear in the domains of symptom remission or relapse rates but in the domains of functional remission and recovery. Even though the short-term relapse rates showed a significant disadvantage of DR strategy,[4] the long-term relapse rates did not show any significant difference, from approximately 3 years of follow-up onward. On the other hand, short-term outcome did not show any advantages of DR in the domains of recovery or functional remission, but striking differences were seen at longer-term follow-up.

A possible weakness of the present study could be the absence of rater blindness. We cannot rule out the possibility that this may have influenced the results in favor of the DR strategy, although it is not very likely to account for the magnitude of the identified differences.

Another consideration is the mechanism in the DR arm that could be responsible for the gains in functional capacity compared with MT. It was shown that even 5 years after the completion of the original trial the treatment strategies used in that study still had an influence on the dosage of antipsychotics. Successful discontinuation in the early course of FEP was sustained for many years in almost all patients and, on average, patients in the DR strategy used a lower dose of antipsychotic drugs than did their counterparts in the MT strategy. This was mainly a consequence of a higher discontinuation rate in the DR group, but in addition, the patients in the DR group who did not discontinue their antipsychotic medication showed a trend to use of a lower daily dosage. This is in keeping with the findings of a German group.[11]

It might well be the effect of less antipsychotic load that results in better functional capacity in the long term. Antipsychotic postsynaptic blockade of the dopamine signaling system, particularly of the mesocortical and mesolimbic tracts, not only might prevent and redress psychotic derangements but also might compromise important mental functions, such as alertness, curiosity, drive, and activity levels, and aspects of executive functional capacity to some extent.[19,20] On the other hand, the dopamine system might play a more peripheral role in psychosis than previously thought, while hypothesized primary derangements, such as *N*-methyl-D-aspartate receptor and/or interneuron dysfunction, remain untouched by dopamine blockade.[21-23] Thus, dose reduction and, where possible, discontinuation might relieve redundant dopamine blockade, that is, not necessary to redress psychosis, and thereby improve functional capacity in the long term.

However, the psychological impact of having been in a DR strategy might have been effective. We were not able to evaluate this latter factor because we did not measure it. In the original trial we did not observe any differences between the DR and MT groups in the intensity of outpatient or community care, as well as visits to psychiatrists, community psychiatric nurses, or crisis intervention contacts.[24] In clinical practice, we did experience the DR strategy fitting in with the current concept of the physician-patient relationship, positioning the patient as the key player in his or her own treatment, taking the perspectives seriously, and assisting the patient in well-founded decision making on antipsychotic treatment.

Another striking finding is the flattening of the relapse rates in the DR arm after approximately 3 years of follow-up. Although relapse rates in the MT arm did not seem to level off as much, the relapse rates in the DR arm seem to have been running ahead of those in the MT group, but only for the duration of the original trial and about 1 year afterward. Maybe the MT strategy postpones the relapses compared with the DR strategy but does not prevent them. At the 7-year end point, relapse rates were not significantly different.

The results of this study lead to the following conclusions: schizophrenia treatment strategy trials should include recovery or functional remission rates as their primary outcome and should also include long-term follow-up for more than 2 years, even up to 7 years or longer. In the present study, short-term drawbacks, such as higher relapse rates, were leveled out in the long term, and benefits that were not evident in short-term evaluation, such as functional gains, only appeared during long-term monitoring. As a matter of fact, social functioning is mostly measured in a global way, for example, by means of Global Assessment of Functioning or Social Functioning Assessment Scale scores, instead of using an instrument dedicated to measuring the key domains of functional capacity. These key domains are daily living and self-care, working and studying, and relationships with others.

While in the present study we used the GSDS, a dedicated instrument for the evaluation of social functioning in patients with schizophrenia, this instrument has the disadvantage of taking about 1 hour to complete. There is a need to develop an international consensus about the criteria of functional remission and appropriate instruments to measure them. This would also result in an international understanding about the criteria for recovery in a clinical sense.[13]

The present study poses some serious considerations about the long-term benefits of antipsychotic MT following remitted FEP and stresses the need for studying alternative treatment strategies. Apart from a guided DR strategy examined in the present study, the extended-dosing plan (administering antipsychotics with a 1-, 2-, or even 3-day interval), proposed by Remington and colleagues,[25] might offer a useful perspective.

Of course, only one study indicating advantages of a DR strategy in patients with remitted FEP is not enough evidence in such an important matter. However, these results merit replication by other research groups.

ARTICLE INFORMATION

Submitted for Publication: July 11, 2012; final revision received December 21, 2012; accepted December 25, 2012.

Published Online: July 3, 2013. doi:10.1001/jamapsychiatry.2013.19.

Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wunderink, Wiersma, Sytema, Nienhuis.
Acquisition of data: Nieboer, Nienhuis.
Analysis and interpretation of data: Wunderink, Nieboer, Sytema.
Drafting of the manuscript: Wunderink, Sytema.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Wunderink, Sytema.
Obtained funding: Wunderink, Wiersma, Nienhuis.
Administrative, technical, and material support: Nieboer.
Study supervision: Wiersma.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by unconditional grants from Janssen-Cilag Netherlands and Friesland Mental Health Services, Leeuwarden, the Netherlands.

Role of the Sponsors: The sponsors had no further role in any part of the study or preparation of the manuscript.

Additional Contributions: The following mental health care services within the Netherlands participated in data acquisition: Dimence (Deventer), GGNet (Warnsveld), GGZ Drenthe (Assen), GGZ Friesland (Leeuwarden), Lentis (Groningen), Mediant (Enschede), University Psychiatric Center/University Medical Center Groningen (Groningen), and Yulius (Dordrecht).

REFERENCES

1. Perkins DO, Gu H, Weiden PJ, McEvoy JP, Hamer RM, Lieberman JA; Comparison of Atypicals in First Episode study group. Predictors of treatment discontinuation and medication nonadherence in patients recovering from a first episode of schizophrenia, schizophreniform disorder, or schizoaffective disorder: a randomized, double-blind, flexible-dose, multicenter study. *J Clin Psychiatry*. 2008;69(1):106-113.

2. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241-247.

3. Kane JM. Schizophrenia. *N Engl J Med*. 1996;334(1):34-41.

4. Wunderink L, Nienhuis FJ, Sytema S, Slooff CJ, Knegtering R, Wiersma D. Guided discontinuation versus maintenance treatment in remitted first-episode psychosis: relapse rates and functional outcome. *J Clin Psychiatry*. 2007;68(5):654-661.

5. Chen EYH, Hui CLM, Lam MML, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ*. 2010;341:c4024. doi:10.1136/bmj.c4024.

6. Vazquez-Barquero J, Perez-Iglesias R, Crespo-Facorro B, Mata I, van Don J. How long should early intervention last in the first episode psychosis? insights from the discontinuation protocol of the Cantabria's first episode clinical program (PAFIP). *Schizophr Res*. 2010;117(2-3):116. doi:10.1016/j.schres.2010.02.044.

7. Emsley R, Oosthuizen PP, Koen L, Niehaus DJH, Martinez G. Symptom recurrence following intermittent treatment in first-episode schizophrenia successfully treated for 2 years: a 3-year open-label clinical study. *J Clin Psychiatry*. 2012;73(4):e541-e547. doi:10.4088/JCP.11m07138.

8. National Collaborating Centre for Mental Health (UK). *Schizophrenia: Core Interventions in the Treatment and Management of Schizophrenia in Adults in Primary and Secondary Care (Update)*. London, England: National Institute for Health and Clinical Excellence; 2009.

9. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Schizophrenia.* Vol 2. Washington, DC: American Psychiatric Association; 2004.

10. Gilbert PL, Harris MJ, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenic patients: a review of the literature. *Arch Gen Psychiatry*. 1995;52(3):173-188.

11. Gaebel W, Riesbeck M, Wölwer W, et al; German Study Group on First-Episode Schizophrenia. Relapse prevention in first-episode schizophrenia—maintenance vs intermittent drug treatment with prodrome-based early intervention: results of a randomized controlled trial within the German Research Network on Schizophrenia. *J Clin Psychiatry*. 2011;72(2):205-218.

12. Remington G. Antipsychotic dosing: still a work in progress. *Am J Psychiatry*. 2010;167(6):623-625.

13. Wunderink L, Sytema S, Nienhuis FJ, Wiersma D. Clinical recovery in first-episode psychosis. *Schizophr Bull*. 2009;35(2):362-369.

14. Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. *Acta Psychiatr Scand*. 2006;113(4):332-339.

15. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276.

16. Wiersma D, DeJong A, Ormel J. The Groningen Social Disabilities Schedule: development, relationship with I.C.I.D.H., and psychometric properties. *Int J Rehabil Res*. 1988;11(3):213-224.

17. Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162(3):441-449.

18. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry*. 2003;64(6):663-667.

19. Artaloytia JF, Arango C, Lahti A, et al. Negative signs and symptoms secondary to antipsychotics: a double-blind, randomized trial of a single dose of placebo, haloperidol, and risperidone in healthy volunteers. *Am J Psychiatry*. 2006;163(3):488-493.

20. Kim JH, Son YD, Kim HK, et al. Antipsychotic-associated mental side effects and their relationship to dopamine D_2 receptor occupancy in striatal subdivisions: a high-resolution PET study with [^{11}C]raclopride. *J Clin Psychopharmacol*. 2011;31(4):507-511.

21. Grace AA. Dopamine system dysregulation by the hippocampus: implications for the pathophysiology and treatment of schizophrenia. *Neuropharmacology*. 2012;62(3):1342-1348.

22. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci*. 2012;35(1):57-67.

23. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull*. 2009;35(3):549-562.

24. Stant AD, TenVergert EM, Wunderink L, Nienhuis FJ, Wiersma D. Economic consequences of alternative medication strategies in first episode non-affective psychosis. *Eur Psychiatry*. 2007;22(6):347-353.

25. Remington G, Seeman P, Feingold A, Mann S, Shammi C, Kapur S. "Extended" antipsychotic dosing in the maintenance treatment of schizophrenia: a double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2011;72(8):1042-1048.