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Reprint of: Negative symptoms predict high relapse rates and both predict less favorable functional outcome in first episode psychosis, independent of treatment strategy☆,☆☆

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ABSTRACT

Background: In first episode psychosis (FEP) baseline negative symptoms (BNS) and relapse both predict less favorable functional outcome. Relapse-prevention is one of the most important goals of treatment. Apart from discontinuation of antipsychotics, natural causes of relapse are unexplained. We hypothesized that BNS, apart from predicting worse functional outcome, might also increase relapse risk.
Methods: We performed a post-hoc analysis of 7-year follow-up data of a FEP cohort (n = 103) involved in a dose-reduction/discontinuation (DR) vs. maintenance treatment (MT) trial. We examined: 1) what predicted relapse, 2) what predicted functional outcome, and 3) if BNS predicted relapse, whether MT reduced relapse rates compared to DR. After remission patients were randomly assigned to DR or MT for 18 months. Thereafter, treatment was uncontrolled.
Outcomes: BNS and duration of untreated psychosis (DUP) predicted relapse. Number of relapses, BNS, and treatment strategy predicted functional outcome. BNS was the strongest predictor of relapse, while number of relapses was the strongest predictor of functional outcome above BNS and treatment strategy. Overall and within MT, but not within DR, more severe BNS predicted significantly higher relapse rates. Treatment strategies did not make a difference in relapse rates, regardless of BNS severity.
Interpretation: BNS not only predicted worse functional outcome, but also relapses during follow-up. Since current low dose maintenance treatment strategies did not prevent relapse proneness in patients with more severe BNS, resources should be deployed to find optimal treatment strategies for this particular group of patients.

1. Introduction

The study by our group on antipsychotic dose-reduction/discontinuation (DR) vs. maintenance treatment (MT) strategies in remitted first episode psychosis (FEP), showing better long-term functional outcome in DR, fueled the debate on the pros and cons of antipsychotic MT (Wunderink et al., 2013). An unresolved issue to date is the mechanism by which relapse impacts on functional outcome. Because relapse is robustly associated with poor outcome (Wiersma et al., 1998; Emsley et al., 2013; Mayoral-van Son et al., 2016), this relationship is generally assumed to be causal. Since in our trial the initially higher relapse rates in DR strategy came on par with relapse rates in MT from about three years till the end of the 7-year follow-up, no conclusions on this issue were drawn, apart from the initially higher relapse rates having no paramount impact on long-term functional outcome. We found a strong association between relapse-numbers and poor outcome, too, but the causal nature of this relationship remains uncertain. We also found, like many other studies, negative symptoms to predict poor outcome (Austin et al., 2015; Díaz-Caneja et al., 2015; McGorry et al., 2014; Wunderink et al., 2013). In order to determine the predictors of relapse following discontinuation of

☆ Post hoc analysis of 7-years follow-up data of a randomized controlled dose-reduction versus maintenance treatment trial.
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antipsychotics after remission of FEP, we relied on the recent systematic review by Bowtell et al. (2018). This paper thoroughly analyzed the predictors of relapse in 10 studies that were carefully selected, and concluded that no predictors were found in more than one study. Only Chen et al. (2010) and Hui et al. (2013) found negative symptoms to be related to relapse risk. This would concur with Hughlings Jacksons hypothesis already formulated in the 19th century, proposing that negative symptoms could elicit active psychosis (Berrios, 1985). It could be that negative symptoms might be considered a proxy of a functional brain derangement, both related to relapse proneness and functional deficits (Wunderink, 2019). Thus, we questioned whether baseline negative symptoms (BNS) could be related to relapse proneness, and whether the relation between relapse and worse functional outcome might be partially explained by BNS. To test this hypothesis, we examined: 1) which factors predicted relapse, 2) which factors predicted functional outcome, and 3) if BNS predicted relapse, whether MT strategy would make a difference reducing relapse rates in patients with more severe BNS.

2. Methods

The details of the original and 7-year follow-up study have been described previously (Wunderink et al., 2007, 2013). For convenience we summarize the headlines of the original study and its 7-year follow-up below. We used baseline and follow-up data to answer the new research questions.

2.1. The original dose-reduction trial and its 7-year follow-up; sample characteristics

This open randomized controlled trial consisted of a 2-years experimental phase starting in 2002, and a 7-year follow-up assessment 5 years after the original trial ended. The original trial examined whether MT according to the guidelines was the best option in remitted first episode patients, compared with an intention-to-treat DR strategy. We hypothesized that the DR condition would lead to better functional capacity, probably at the cost of higher relapse rates.

The patient flow-chart is depicted in Fig. 1.

Of N = 378 patients who were initially screened, 257 met the eligibility criteria of a non-affective first episode psychosis described previously (Wunderink et al., 2007). Patients referred to mental health care services with a FEP from October 2001 until December 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. Note that all FEP patients who had first contact with mental health care services were immediately registered anonymously to guard against selection bias. Only after patients responded sufficiently to antipsychotic medication they were asked for participation. Of 257 eligible FEP patients, 111 refused to participate or were lost to follow-up, and 18 did not show the required symptomatic response. A sustained positive symptom remission of minimal 6 months duration within 1 year after starting antipsychotic treatment was required. This implied relevant positive symptom scores on the Positive And Negative Syndrome Scale, (PANSS, (Kay et al., 1987)) to be continuously below the severity level of "moderate" (score = 4). N = 128 patients were included in the original trial and completed it. The nonincluded patients (n = 129) generally had a worse clinical and social profile and many of these patients prematurely lost contact with mental health services, often soon after first contact. Included patients had never been treated with antipsychotics before, and the duration of untreated psychosis (DUP) ranged from many years to some days, with a relatively short median of 1 month. The most relevant characteristics of the sample (n = 103 patients also included in the 7-year follow-up) are shown in Table 1.

The 44% diagnosed with schizophrenia at entry were an underestimation because in many cases the duration of symptoms at the time of diagnostic assessment was <6 months. After 6 months of positive symptom remission the patients were assigned to either DR or MT strategy, both intention-to-treat. The applied strategy was such that the assigned treatment condition was discussed with patients and family members, including information about the risks and need for monitoring and, in case of DR, implemented in a personalized timeframe that could take weeks or even months. A substantial number of patients were never completely discontinued, because they had recurrent symptoms before complete discontinuation was achieved, or medication was restarted because symptoms recurred after initial discontinuation. Any type of antipsychotic drug was allowed.

During the first 18 months, about 20% of patients in the DR strategy were successfully discontinued without relapse. At 18 months follow up, the 2-year end point of the study was reached. The results did not show what we hoped for. Though we expected relapse rates in the DR strategy to be higher than in the MT strategy, they turned out to be twice as high: 43% against 21%. Relapses were mild and did not lead to more inpatient days in the DR condition. There were no functional gains in DR, apart from better vocational functioning bordering on significance. After the trial ended, patients were left to the discretion of their attending clinicians. Five years later, we followed the patients up again. A total of 103 patients were willing to participate (characteristics shown in Table 1).

Main outcome of this 7-year follow-up was functional recovery during the last 6 months of follow-up; we also looked at symptom remission during the same period, relapse rates throughout the whole 7-year follow-up period and antipsychotic dose during the most recent 2 years. In view of the negative results after 2 years, and the absence of any experimental intervention thereafter, we expected the tracks of the original trial conditions to be covered up after the 5-year interval. However, the results after 7 years turned out to be strikingly different. Patients who originally were in the DR strategy significantly more often recovered functionally than patients who originally received MT: 46.2% against 19.6%. We were not able to find confounders that might have influenced these results. Symptomatic remission was the same in both conditions, 69.2% versus 66.7%. Predictors of functional recovery were less-severe baseline negative symptoms, living together, better baseline social functioning and DR strategy. The only predictor of symptomatic remission was DUP. Another striking finding was that relapse rates in the DR group came on par with the MT group from about 3 years of follow-up. The mean antipsychotic dose during the last 2 years of follow-up still differed significantly: 2.1 mg daily haloperidol equivalents in former DR patients against 3.6 mg in former MT patients.

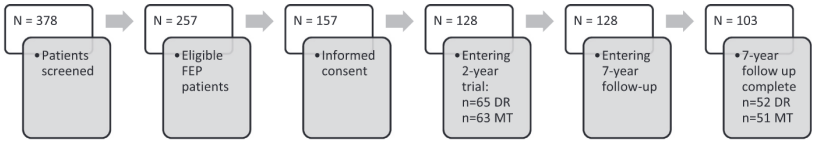

Fig. 1. Patient flowchart original 2-year trial and 7-year follow-up.

Table 1
Characteristics of the 7-year follow-up sample (N = 103).

Characteristic	DR strategy N = 52	MT strategy N = 51	Statistic	*P*-value	Sample overall N = 103
Baseline, n (%)					
Male sex	37 (71.2)	34 (66.7)	Fisher's exact	.674	71 (68.9)
logDUP, mean (SD), days[a]	1.45 (1.13)	1.56 (1.08)	t = −0.495	.622	1.51 (1.10)
Regular job ≥16 h/wk.	27 (54.0)	18 (36.0)	Fisher's exact	.107	45 (43.7)
Living alone	19 (36.5)	18 (35.3)	Fisher's exact	1.000	37 (35.9)
Dependency or abuse, n (%)					
Cannabis	14 (26.9)	12 (23.5)	Fisher's exact	.821	26 (25.2)
Any	22 (42.3)	15 (29.4)	Fisher's exact	.219	37 (35.9)
Diagnostic category, n (%)					
Schizophrenia	19 (36.5)	26 (51.0)	Pearson Chi-Square	.217	45 (43.7)
Schizophreniform disorder	14 (26.9)	12 (23.5)			26 (25.2)
Schizoaffective disorder	4 (7.7)	2 (3.9)			6 (5.8)
Delusional disorder	8 (15.4)	4 (7.8)			12 (11.7)
Brief psychotic disorder	0 (0.0)	3 (5.9)			3 (2.9)
Psychotic disorder NOS	7 (13.5)	4 (7.5)			11 (10.7)
PANSS subscale, mean (SD)					
Positive	9.79 (2.96)	10.78 (3.14)	t = −1.655	.101	10.28 (3.08)
Negative	12.87 (4.80)	14.16 (5.43)	t = −1.279	.204	13.50 (5.14)
General	25.27 (6.44)	26.45 (6.62)	t = −0.918	.361	25.85 (6.53)
Total score, mean (SD)					
GSDS	8.48 (4.10)	8.41 (4.34)	t = 0.083	.934	8.45 (4.20)
WHOQoL	90.41 (11.32)	92.36 (12.20)	t = −0.832	.407	91.38 (11.74)
Last two years of 7-years follow-up					
Haloperidol equivalents mg/d, mean (SD)	2.13 (2.29)	3.57 (4.03)	t = −2.201	.030	2.86 (3.35)
7-years follow-up, n (%)					
Number of relapses, mean (SD)	1.13 (1.22)	1.35 (1.51)	t = −0.808	.421	1.24 (1.37)
Mean time to first relapse, days	1348 (1136)	1374 (940)	t = −0.129	.897	1361 (1038)
No relapse during follow-up	20 (38.5)	16 (31.4)	Fisher's exact	.537	36 (35.0)
Symptom remission	36 (69.2)	34 (66.7)	Fisher's exact	.835	70 (68.0)
Functional recovery	24 (46.2)	10 (19.6)	Fisher's exact	.006	34 (33.0)

Abbreviations: logDUP = log transformed duration of untreated psychosis, PANSS = Positive And Negative Syndrome Scale, GSDS = Groningen Social Disability Scale (higher score = worse), WHOQoL = World Health Organization Quality of Life scale.
[a] DUP days were log transformed because of the skewed distribution.

2.2. Assessments and definitions

Baseline data were sampled as part of the original trial (Wunderink et al., 2007). For this study, the following variables are relevant: sex, age, symptom severity (PANSS), social functioning, and DUP (interval between first positive symptom experience and start of antipsychotic treatment). Due to its skewed distribution, we used log-transformed DUP (logDUP) in the analyses.

Follow-up data included symptom severity using PANSS, level of social functioning during the last six months of follow-up assessed by the Groningen Social Disability Schedule (GSDS, (Wiersma et al., 1988)), number of relapses through the entire follow-up, time to first relapse, and type and dose of antipsychotics during the last two years of follow-up.

The following definitions were used:

Relapse: Operationalized by a two-step criterion set: 1) clinician needs to increase dosage or take any other measures (e.g. additional visits), and 2) any PANSS positive symptom item score exceeding 3 for at least one week. Relapses were assessed concurrently during the first two years, and retrospectively during the last 5 follow-up years by interviewing staff and consulting patient-records.

Symptomatic remission: (a) Criterion to enter trial (defined 3 years before Andreasen's criteria were published): all PANSS positive symptom scores had to be continuously below the severity level of moderate (score = 4) during six consecutive months in the first year of treatment. (b) To evaluate the 7-year follow-up: Andreasen's criteria were used (selected PANSS-item scores had to be below moderate (4), sustained for six consecutive months minimally) (Andreasen et al., 2005).

Functional recovery: Adequate functioning in core domains of everyday life for at least six months. Adequate functioning was operationalized as only having ratings of either 'no' (0) or 'doubtful or some' (1) disability on six out of seven domains of the GSDS. Due to limited applicability, the parenthood domain was excluded. The GSDS item scores range from 'no disability' (0) to 'severe disability' (3).

Recovery: Meeting criteria of both symptomatic remission and functional recovery.

2.3. Statistical analyses

We used IBM-SPSS-24 to run most analyses, including the plots (Figs. 2 and 3) that display the survival functions for relapse. The pseudo-partial correlations were computed in R (version 3.6, R Core Team, 2019), using the functions 'glm' (binominal distribution with logit as link function) and 'pcor' (type 'n').

To determine which factors predicted relapse and functional outcome, we applied forward stepwise logistic regression analyses. Possible predictors were selected based on findings reported in literature and the hypotheses to be tested. For predicting relapse, treatment strategy (Robinson et al., 1999; Uçok et al., 2006; Hui et al., 2013; Pelayo-Terán et al., 2017; Bowtell et al., 2018), log-DUP (Altamura et al., 2001; ten Velden-Hegelstad et al., 2012), and BNS (Dyck et al., 2000; Chen et al., 2010; Hui et al., 2013; Alvarez-Jimenez et al., 2016; Mayoral-van Son et al., 2016) were candidates. The dependent variable 'relapse' was dichotomized into no relapse or any relapse, the variable 'BNS' was continuous (PANSS-negative subscale scores). We left out baseline positive symptoms because in our own study less severe positive symptoms were not predictive of relapse in multivariate analysis (Wunderink et al., 2013). According to Bowtell et al. (2018) only 1 in 7 studies found an association of baseline positive symptoms and relapse: a study by Gaebel et al. (2016). In this study

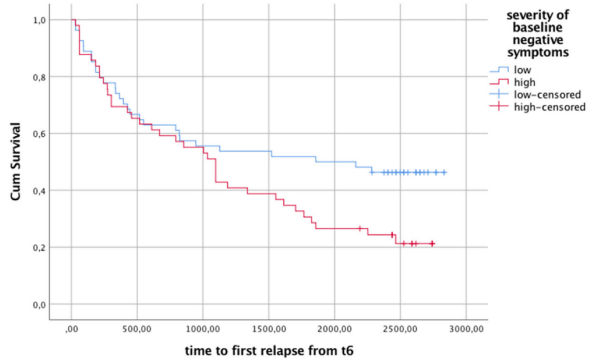

Fig. 2. Relapse survival functions pooled over treatment strategies in patients with high and low severity baseline negative symptoms; numbers of surviving patients indicated below the graph.

however, less severe, and not more severe, positive symptoms counterintuitively predicted relapse after acute treatment and after 1 year of maintenance treatment. For predicting functional outcome candidates were: treatment strategy (Wunderink et al., 2013), number of relapses (Wiersma et al., 1998; Emsley et al., 2013), and BNS (Wunderink et al., 2013; Austin et al., 2015; Díaz-Caneja et al., 2015; Mayoral-van Son et al., 2016). The variable 'BNS' was continuous (PANSS-negative subscale scores). For both logistic regressions, we computed pseudo-partial correlations in order to assess the unique contributions of predictors in the final models.

In order to investigate whether BNS or medication strategies would be the key variable for predicting relapses, we split the sample based on patients' BNS severity (median-split): a low severity BNS group ($PANSS_{neg} < 13$, n = 54) and a high severity BNS group ($PANSS_{neg} \geq 13$, n = 49). We compared relapse survival rates pooled over and within treatment strategies (MT/DR) across low and high negative symptom levels, and relapse survival rates within BNS categories (low/high) across treatment strategies.

3. Results

3.1. Descriptive characteristics of study participants

The characteristics of the 7-year follow-up sample (N = 103) have been presented in Section 2.1, Table 1. Mean age at the end of the follow-up period was 26 years and 4 months (SD 6 years, 7 months). The median DUP in this sample was 1 month, mean 267 days, SD 530 days, which expresses the variability of the interval from the first positive symptom experience until the start of antipsychotic treatment.

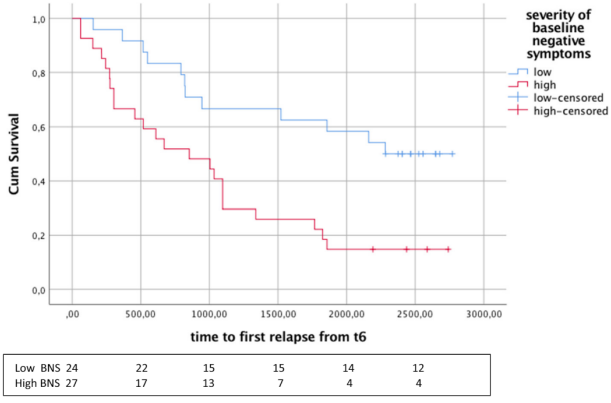

Fig. 3. Relapse survival functions in maintenance treatment in patients with high and low severity baseline negative symptoms; numbers of surviving patients indicated below the graph.

3.2. Number of relapses and functional outcome

At the end of the follow-up period, the majority (68%) of patients were symptomatically remitted, while only a minority (33%) were functionally recovered. Only 29% met both criteria and were considered recovered. In terms of odds ratios, we found an inverse relationship between number of relapses and recovery: no relapse yielded an odds-ratio of one in two, one relapse an odds-ratio of 1 in 4, 2 relapses an odds-ratio of 1 in 5, and 3 or more relapses resulted in no recovery at all.

3.3. Predicting relapse

For the occurrence of relapse (no vs. at least one relapse) as the dependent variable (Table 2), the logistic regression model with log-DUP and BNS as independent variables was significant ($\chi^2(2) = 13.34$, $P < .001$, and Nagelkerke's pseudo $R^2 = 0.167$). Longer DUP and more severe BNS increased the probability of a relapse. The effect of treatment strategy ($\chi^2(1) = 0.10$, df = 1, $P = .754$) on relapse was not significant when controlling for log-DUP and BNS. In order to evaluate the unique contribution of each predictor, we computed pseudo-partial correlations between each predictor and the occurrence of relapse during follow-up (Hosmer et al., 2013). The variance that is accounted for by other predictor(s) is removed from both variables before computing the correlation. In addition, pseudo-partial correlations take the categorical nature of variables into account. The pseudo-partial correlations (r_{pp}) equaled $r_{pp} = 0.33$ for BNS and $r_{pp} = 0.23$ for log-DUP. Thus, the unique contribution of BNS when taking log-DUP into account was larger than vice versa.

3.4. Predicting functional outcome

In Table 3, the results of the logistic regression analysis for the dependent variable functional outcome are displayed. Functional outcome was dichotomized into meeting the criteria for functional recovery during the last 6 months of follow-up or not. The model including treatment strategy, number of relapses and BNS as predictors was significant ($\chi^2(3) = 33.43$, $P < .001$, and Nagelkerke's pseudo $R^2 = 0.386$). More relapses, more BNS and MT were predictive of worse functional outcome. The pseudo-partial correlations between each predictor and the criterion, controlling for the other two predictors in the model, equaled $r_{pp} = 0.44$ for total number of relapses, $r_{pp} = 0.36$ for BNS, and $r_{pp} = 0.29$ for treatment strategy. Thus, the unique contribution of number of relapses was greater than the contributions of either BNS or treatment strategy.

In both regression models, all Variance Inflation Factors (VIFs) were close to one, indicating absence of multicollinearity between predictors.

3.5. Characteristics of low and high severity BNS groups by median split of the sample

For the survival analyses the sample was dichotomized based on patients' BNS severity (median-split): yielding a low severity BNS group ($PANSS_{neg} < 13$, n = 54) and a high severity BNS group ($PANSS_{neg} \geq 13$, n = 49). The characteristics of both groups are presented in Table 4.

Table 2
Logistic regression results for predicting relapse based on patients' characteristics.

Variables	*B*	*SE(B)*	*Wald* χ^2	*df*	*P*	e^B	*95% CI* e^B
BNS	0.13	0.05	7.03	1	.008	1.14	1.04, 1.26
Log-DUP	0.40	0.20	3.80	1	.051	1.49	1.00, 2.22
Model χ^2	13.34			2	<.01		
n	103						

BNS: Baseline Negative Symptoms; Log-DUP: log-transformed Duration of Untreated Psychosis.

Table 3
Logistic regression results for predicting functional outcome based on patients' characteristics and treatment strategy.

Variables	*B*	*SE(B)*	*Wald* χ^2	*df*	*P*	e^B	*95% CI* e^B
Treatment strategy[a]	1.34	0.52	6.73	1	.009	3.81	1.39, 10.47
BNS	−0.22	0.07	10.45	1	.001	0.81	0.71, 0.92
Number of relapses	−0.66	0.24	7.45	1	.006	0.52	0.32, 0.83
Model χ^2	33.43			3	<.001		
n	103						

[a] Maintenance treatment (0) & Dose-reduction (1); BNS: Baseline Negative Symptoms.

The high severity BNS group had significantly more males (79.6% vs. 59.3%), more severe baseline PANSS positive and general symptom subscale scores, and less favorable baseline social functioning, apart from the obvious more severe baseline negative symptom scores.

3.6. Survival functions for high and low severity levels of BNS

In Fig. 2, the survival functions representing relapse likelihood pooled over treatment strategies for patients with high levels of BNS versus low levels of BNS are displayed.

Table 4
Characteristics of low and high severity baseline negative symptoms groups by median split of the sample ($PANSS_{neg} < 13$ and $PANSS_{neg} \geq 13$).

Characteristic	Low BNS group (n = 54)	High BNS group (n = 49)	Statistic	*P*-value
Baseline, n (%)				
Male sex	32 (59.3)	39 (79.6)	Fisher's exact	.033
logDUP, mean (SD), days[a]	1.36 (1.04)	1.67 (1.15)	t = −1.429	.156
Regular job ≥16 h/wk[b]	27 (50.9)	18 (38.3)	Fisher's exact	.231
Living alone	17 (31.5)	20 (40.8)	Fisher's exact	.411
Dependency or abuse, n (%)				
Cannabis	13 (24.1)	13 (26.5)	Fisher's exact	.823
Any	18 (33.3)	19 (38.8)	Fisher's exact	.681
Diagnostic category, n (%)				
Schizophrenia	21 (38.9)	24 (49.0)	Pearson	.931
Schizophreniform disorder	15 (27.8)	11 (22.4)	Chi-Square	
Schizoaffective disorder	3 (5.6)	3 (6.1)		
Delusional disorder	7 (13.0)	5 (10.2)		
Brief psychotic disorder	2 (3.7)	1 (2.0)		
Psychotic disorder NOS	6 (11.1)	5 (10.2)		
PANSS subscale, mean (SD)				
Positive	9.63 (2.91)	11.00 (3.13)	t = −2.303	.023
Negative	9.61 (1.79)	17.80 (4.09)	t = −13.353	.000
General	22.67 (5.13)	29.37 (6.13)	t = −6.038	.000
Total score, mean (SD)				
GSDS	7.33 (1.04)	9.67 (3.75)	t = −2.925	.004
WHOQoL	93.44 (11.94)	89.18 (11.23)	t = 1.843	.068
Treatment strategy during original RCT, n (%)				
Dose reduction strategy	30 (56.6)	22 (44.9)	Fisher's exact	.326
Maintenance treatment	24 (44.4)	27 (55.1)		
Last two years of 7-years follow-up				
Haloperidol equivalents mg/d, mean (SD)	2.88 (4.15)	2.84 (2.18)	t = 0.061	.951
Last 6 months of 7-years follow-up, n (%)				
Symptom remission	41 (75.9)	29 (59.2)	Fisher's exact	.091
Functional recovery	26 (48.1)	8 (16.3)	Fisher's exact	.001

Abbreviations: $PANSS_{neg}$ = PANSS negative symptom subscale score, BNS = baseline negative symptoms, logDUP = log transformed duration of untreated psychosis, PANSS = Positive And Negative Syndrome Scale, GSDS = Groningen Social Disability Scale (higher score = worse), WHOQoL = World Health Organization Quality of Life scale.
[a] DUP days were log transformed because of the skewed distribution.
[b] Three missing cases in follow-up sample.

The effect of BNS pooled over treatment strategies was significant (log rank $\chi^2 = 5.36$, df = 1, $P = .021$), indicating that more severe BNS were associated with higher relapse risk regardless of treatment strategy. When looking into the survival results for each treatment strategy stratum separately, this also holds true for MT strategy (Fig. 3). High levels of BNS were associated with significantly higher relapse risk during follow-up (log rank $\chi^2 = 8.98$, df = 1, $P = .003$). More specifically, in MT, at the end of the follow-up period, the relapse rate for low levels of BNS was 50% (median survival time 2282 days), while the relapse rate for high levels of BNS was 85% (median survival time 854 days).

For the DR strategy, the difference in survival between low and high levels of BNS was not significant, with relapse rates of 57% and 68% respectively (log rank $\chi^2 = 0.06$, df = 1, $P = .804$).

The effect of treatment strategy pooled over strata (low and high levels of BNS) was not significant (log rank $\chi^2 = 0.07$, df = 1, $P = .792$). Neither for low (log rank $\chi^2 = 1.6$, df = 1, $P = .204$) nor for high ($\chi^2 = 2.2$, df = 1, $P = .137$) levels of BNS the difference in survival between treatment strategies was significant.

To test the robustness of our findings, we repeated our survival analyses using slightly different cut-off values for splitting the sample in subgroups with low and high levels of baseline PANSS negative subscale scores. We used BNS < 12 and BNS < 14 for low BNS and BNS ≥ 12 and BNS ≥ 14 for high BNS. The results of the survival analyses with these cut-off values are presented in Table 5.

The significance of the results and thus our conclusions remained the same.

Furthermore, the relationships of BNS with relapse risk and functional outcome were not (partially) influenced by baseline positive symptoms. In the logistic regression analysis with relapse (at least one relapse vs. no relapse) as the dependent variable, controlling for logDUP and BNS (Table 2), baseline PANSS positive subscale scores did not significantly contribute to the model, ($\chi^2 = 0.326$, df = 1, $P = .568$). Neither in the logistic regression analysis with functional recovery as the dependent variable, controlling for treatment strategy, BNS and number of relapses (Table 3), baseline PANSS positive subscale scores contributed to the model ($\chi^2 = 2.42$, df = 1, $P = .126$).

4. Discussion

4.1. Main findings

In the analyses described in this paper, we found that the severity of baseline negative symptoms was a key predictor of (i) relapse during a follow-up period of seven years, and (ii) in predicting levels of social and occupational functioning at the end of this long-term follow-up period. In addition to BNS, DUP was an independent predictor of relapse risk, longer DUP being associated with higher relapse risk. Next to the number of relapses, which was the prime predictor of functional outcome, BNS and treatment strategy were also independent predictors of functional outcome, more severe BNS leading to less favorable functional outcome, and DR strategy having a positive effect on functional outcome compared to MT strategy. Furthermore, after controlling for BNS and DUP, treatment strategies were unrelated to relapse risk.

Table 5
Relapse-survival analyses using different cut-off's for low and high severity BNS groups.

Survival analysis	BNS < 13 and ≥13			BNS < 12 and ≥12			BNS <14 and ≥14		
	χ^2	*df*	*P-value*	χ^2	*df*	*P-value*	χ^2	*df*	*P-value*
BNS groups within MT	8.98	1	.003	7.99	1	.005	4.75	1	.029
BNS groups within DR	0.06	1	.804	0.30	1	.582	1.56	1	.212
Treatment strategies within low BNS	1.62	1	.204	2.65	1	.103	0.20	1	.659
Treatment strategies within high BNS	2.21	1	.137	2.83	1	.093	0.11	1	.735

BNS = baseline negative symptoms, MT = maintenance treatment, DR = dose-reduction strategy.

4.2. Questions and implications for treatment of FEP patients

The results of our study show that although relapses are the key variable predicting functional outcome in patients with FEP (Wiersma et al., 1998; Sheitman and Lieberman, 1998; Penn et al., 2005; Emsley et al., 2013), baseline negative symptoms appear to be a second best independent predictor of worse functional outcome, while at the same time associated with high relapse rates.

Although in our trial we did not find a protective effect of maintenance treatment against higher relapse rates in patients with more severe negative symptoms compared to dose-reduction strategy, these results raise the unanswered question whether maintenance treatment with higher dosages of non-clozapine antipsychotics, or with clozapine, would be beneficial for this particular subgroup of patients who already have more severe negative symptoms at first contact with mental health care.

The fact that treatment strategy did not make a difference regarding relapse rates after controlling for BNS and log-DUP might seem somewhat counterintuitive, because higher dosages of antipsychotics are beneficial in case of relapse as well as to prevent relapse (Tiihonen et al., 2017). A possible explanation might be that the MT strategy in our original trial was also a relatively low dose strategy, which may not be sufficient to prevent relapses in relapse-prone patients. The mean daily dose of haloperidol equivalents during the last 2 years of the 7-years follow-up was 2.2 mg in DR against 3.6 mg in MT.

If baseline negative symptoms are indeed an indication of relapse-proneness, it would be important to build in negative symptoms in profiling of psychosis (Wunderink, 2017, 2018).

4.3. Limitations

The original study had a number of limitations. First, the number of first episode patients willing to participate was much lower than the number of eligible first episode patients. Of 257 eligible first episode patients, only 128 patients consented to participate in the original dose-reduction vs. maintenance treatment RCT (Fig. 1) and completed it. The participating 128 patients had slightly better prognostic characteristics than the non-participants (who had longer DUP, were less frequently employed and lost contact with mental health care services more often). From these 128 patients 103 agreed to participate in the 7-year follow-up. The 25 participants who did not agree to participate in the follow-up did not differ from the participants as regards prognostic characteristics. Second, the blindness of the raters who did the follow-up assessments could not be guaranteed, because the trial was open. Third, the charting of relapse (dating of beginning and end) and severity ratings of symptoms was done retrospectively during the last 5 years of follow-up, using medical records and staff interviews. Another point of discussion may be the threshold of the second relapse criterion (at least one PANSS positive symptom item score ≥ 4 during one week). However, note that this criterion was only applied in case the clinician needed to increase dosage or take any other measures (e.g. additional visits). Therefore, it seems not likely that stricter criteria would have yielded different results.

A further limitation might be the possibility of non-reported treatment non-adherence. At assessments during the trial phase the research assistants asked the patients whether they had been able to take their antipsychotics according to their prescription. The research assistants would not inform the clinician if a patient partially or completely stopped his or her antipsychotics against recommendation. The patients quite often informed the research assistants about non-adherence. We accounted for reported non-adherence calculating the estimated dosage taken. We did no blood level checks to verify the

patients' reports. There might be a possibility that we overestimated the dosage of antipsychotic drugs taken.

Finally, we note that contemporary non-pharmacological treatment options are far more advanced than by the time the original study was conducted. Hence, the positive effect of dose-reduction may be assumed to be larger nowadays.

A limitation of the present study might be that the traditional total score of the PANSS negative symptoms subscale has been criticized (van der Gaag et al., 2006). This generates some questions concerning the validity of negative symptom operationalizations. In future research, it would be worthwhile to examine the negative symptom dimension in greater detail, looking at the effect of subdimensions and individual items on relapse risk and functional outcome.

Another limitation of our post-hoc analysis was that the original study was not powered to detect differences in relapse rates between DR and MT strategies within high and low BNS groups. Our results should be replicated in larger, adequately powered trials.

4.4. Directions for future research

Patients having pronounced primary negative symptoms at their entry in mental health care run a greater risk of relapse and less favorable functional outcome. Since current low dose maintenance treatment strategies did not prevent the relapse proneness in these patients, resources should be deployed to find optimal treatment strategies for this particular group of patients. Maintenance treatment with higher dosages of D2-blocking antipsychotics to prevent relapses might offer better perspectives than the current low-dose strategies, but the potential draw-back of inducing secondary negative symptoms will have to be thoroughly evaluated. The question will be whether the potential gain in relapse prevention compensates for the potential induction of secondary negative symptoms: the primary outcome being functional capacity. The use of clozapine, with a reported beneficial effect on negative symptoms and a less pronounced D2-blocking profile, might offer the best perspectives in FEP patients with more pronounced negative symptoms at baseline, may be even as a first choice treatment.

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Contributors

Lex Wunderink had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Lex Wunderink, Jan van Bebber, Nynke Boonstra and Johanneke Wigman made the first draft of the manuscript.

Lex Wunderink, Jan van Bebber, Sjoerd Sytema and Rob R. Meijer did the analysis and statistics.

All authors contributed to the manuscript.

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Declaration of competing interest

None of the authors has any conflict of interest.

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