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The role of depression in the prediction of a "late" remission in first-episode psychosis: An analysis of the OPTiMiSE study

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ABSTRACT

Objective: The identification of predictors of psychosis remission could guide early clinical decision-making for treatment of first-episode schizophrenia (FES).
Methods: We analyzed two non-independent subsamples of patients with FES ages 18–40 years from the OPTiMiSE study dataset to investigate the demographic and clinical factors that might help to differentiate "late" remitters (i.e., not in remission at week 2 or 4, but achieving remission within a 10-week follow-up period) from non-remitters within the same period.
Results: Subsample 1 included 216 individuals (55 females, mean age 25.9 years) treated with amisulpride in an open-label design who were not in remission at week 2. Early symptomatic response between baseline and week 2 (odds ratio (OR) = 4.186, 95% confidence interval (CI) = 2.082–8.416, $p < 0.001$) and older age (OR = 1.081, 95% CI = 1.026–1.138, $p = 0.003$) were the only variables significantly associated with a higher probability of psychosis remission at week 4. Subsample 2 was composed of the 72 participants (19 females, mean age 25.1 years) who were not in remission at week 4 and completed a 6-week double-blind randomized trial comparing continuation of amisulpride with switch to olanzapine. Depression at baseline (as measured with the Calgary Depression Scale for Schizophrenia) was significantly associated with a nearly 3-fold lower likelihood of psychosis remission during the 10-week follow-up (hazard ratio = 2.865, 95% CI = 1.187–6.916, $p = 0.019$).
Conclusion: Our results reinforce the importance of assessing depressive symptoms in people with FES and support the relevance of an early response (as early as 2 weeks) as a predictor of clinical outcome in this population.
Clinical trials registration: ClinicalTrials.gov identifier: NCT01248195, https://clinicaltrials.gov/ct2/show/NCT01248195.

1. Introduction

Predictors of treatment response and resistance during the early phases of schizophrenia constitute major indicators of long-term outcomes and are the focus of extensive recent research (Bozzatello et al., 2019; Robinson et al., 1999). Most known predictors of response to antipsychotics in first-episode schizophrenia (FES) are non-specific and fixed, such as age at onset, sex, or type of onset (i.e., gradual or acute) (Carbon and Correll, 2014). Some clinical predictors that are potentially treatable or modifiable include substance use or non-adherence to treatment (Bozzatello et al., 2019), but much less is known about the effect of comorbidities –including the presence of comorbid affective symptoms– or concomitant treatments on treatment outcome. For instance, depressive symptomatology is present in 20–50% of people with schizophrenia (Gregory et al., 2017; Upthegrove et al., 2010; Upthegrove et al., 2017) and has been previously associated with poorer

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clinical and functional long-term outcomes (Conley et al., 2007; Gardsjord et al., 2016; Gregory et al., 2017). However, its association with treatment response in the first episode has so far been relatively understudied, with previous studies yielding inconsistent results (Geddes et al., 1994; Lieberman et al., 1992).

An early response to antipsychotics – conventionally defined as a reduction of more than 20% in the Positive and Negative Syndrome Scale (PANSS) total score (Samara et al., 2015) – is a replicated predictor of achieving and maintaining clinical response and psychosis remission in the longer term (Bozzatello et al., 2019). However, not all studies conducted in FES have found such an association, and a PANSS reduction of 20% may not reflect a meaningful improvement in a clinical setting (Gallego et al., 2011). Instead, standardized definitions of clinical remission might be preferable (Leucht, 2014). The decision of about how long to wait before switching antipsychotic treatments in cases of insufficient clinical response or non-remission has decisive clinical consequences. Even though patients with minimal improvement in positive symptoms during the first two weeks of treatment are unlikely to respond to a longer trial (e.g., a 4- or 6-week trial) with the same antipsychotic compound (Correll et al., 2003; Leucht and Zhao, 2014; Samara et al., 2015; Stentebjerg-Olesen et al., 2015), relevant clinical guidelines recommend that each antipsychotic treatment trial should last at least 4–6 weeks before considering an antipsychotic switch (Howes et al., 2017). The Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) study also showed that around 45% of patients who did not achieve remission after the first 4 weeks of amisulpride treatment were in remission at 10 weeks, irrespective of having been randomized to staying on amisulpride or switching to olanzapine (Kahn et al., 2018), thus suggesting that there is a subgroup of patients in whom a later remission may be expected, for whom it might be indicated to wait before considering a change in treatment strategy.

Clinical decision-making in this context could be significantly aided by an early differentiation of this subgroup of patients with FES who do not achieve an early remission (i.e., during the first 2 or 4 weeks of treatment) but are likely to show a "late" remission from those unlikely to achieve remission during longer follow-ups –who may warrant more intensive interventions at earlier stages, including clozapine treatment, as suggested by the OPTiMiSE trial (Kahn et al., 2018)–. To this end, we used two subsamples from the OPTiMiSE study to investigate the demographic and clinical factors including illness severity, severity of positive and negative symptoms and presence of depression at baseline that might help to differentiate "late" remitters from non-remitters at the start of treatment.

2. Methods

2.1. Study design

We used data from the OPTiMiSE study (identifier: NCT01248195) (Kahn et al., 2018; Leucht et al., 2015), which was a three-phase clinical trial conducted in 27 clinical centers in 14 European countries and Israel. We included patient aged 18–40 years with FES (including DSM-IV diagnoses of schizophrenia, schizophreniform disorder and schizoaffective disorder confirmed with the Mini-International Neuropsychiatric Interview plus (Sheehan et al., 1998)), and a time interval between the onset of psychosis and study entry not longer than two years. All patients were treated during 4 weeks with amisulpride in an open-label design (OPTiMiSE Phase 1). Patients who did not meet clinical remission criteria at 4 weeks were randomly assigned to continue on amisulpride or to switch to olanzapine during a 6-week double-blind trial (OPTiMiSE Phase 2). Randomization was stratified by site and sex, and applied the minimization method for randomization (Kahn et al., 2018; Leucht et al., 2015). Patients who did not meet remission criteria at 10 weeks were prescribed clozapine for an additional 12-week open-label trial (OPTiMiSE Phase 3). Concomitant medications (except for antipsychotic agents) were allowed during the follow-up. The complete methodology of OPTiMiSE study is described in detail elsewhere (Kahn et al., 2018; Leucht et al., 2015). The study was approved by the local ethics committees. All participants provided written informed consent.

2.2. Participants

For the purposes of the present study, we selected two non-independent subsamples from the whole OPTiMiSE dataset for two different analyses. These subsamples comprised participants who had not achieved an early remission at either the 2-week (Subsample 1) or 4-week (Subsample 2) follow-up. Thus, Subsample 1 included a total of 216 participants who were not in remission at week 2. Subsample 2 was composed of the 72 participants who were not in remission at week 4 and had completed OPTiMiSE Phase 2. Fig. 1 shows the participant flowchart.

2.3. Remission criteria

Clinical remission of psychosis was defined as per Andreasen's remission criteria (i.e., a maximum rating of 3 on all the following PANSS (Kay et al., 1987) items: P1, P2, P3, N1, N4, N6, G5 and G9) without applying the 6-month minimum duration of symptom severity criterion (Andreasen et al., 2005).

2.4. Other measures

Symptomatic response was defined as a reduction of the PANSS total score equal or greater than 20% between baseline and follow-up.

Depressive symptoms were assessed with the Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990). The CDSS comprises nine items, providing scores ranging from zero to 27. The CDSS is widely used to evaluate depression in patients with schizophrenia as distinct from negative symptoms, subjective reports of hopelessness, guilt, or suicidal ideation (Addington et al., 1996), and its scores have been shown to be reliable across different illness stages (Grover et al., 2017). Depression was defined as a CDSS total score of 5 or more (Sarro et al., 2004). Previous research found this cut-off valid for both stabilized and acute patients with schizophrenia in a European population (with 94.7% sensitivity, 86.5% specificity, and 70% and 98% positive and negative predictive values, respectively)(Sarro et al., 2004). We also calculated the PANSS Depression Factor (PANSS-D). PANSS-D is the combined score of items G1 (somatic concerns), G2 (anxiety), G3 (guilt feelings), and G6 (depression) from the general psychopathology PANSS subscale (El Yazaji et al., 2002).

Insight was assessed using the PANSS item G12, which is a global clinical assessment of lack of judgment and insight.

Illness severity was assessed using the Clinical Global Impression (CGI) scale (Guy, 1976).

Cumulative dose of antipsychotics at baseline (between four weeks before baseline and baseline assessment) and over follow-up was computed for each patient and transformed into chlorpromazine equivalents (Gardner et al., 2010).

2.5. Statistical analysis

For each subsample, demographic and clinical variables were compared between participants who remitted and those who did not using ANOVA analyses and chi-square tests, after checking normality and homoscedasticity, as appropriate.

For Subsample 1 (i.e., patients not in remission at week 2), we created a predictive model of "remission at week 4", using a stepwise logistic

regression model. The model investigated the association between patient status (remitter vs. non-remitter at week 4) and putative predictive variables (sex; age at first episode; diagnosis of schizophrenia at baseline (as a dichotomous variable yes/no versus schizophreniform disorder or schizoaffective disorder); employment status at baseline (as a dichotomous variable: employed/student yes/no); duration of the psychotic episode at baseline; days on antipsychotic treatment before baseline; antipsychotic cumulative dose at week 2; CGI at baseline; depression at baseline (CDSS total score ≥5; as a dichotomous variable yes/no); and symptomatic response between baseline and week 2 (as a dichotomous variable yes/no)).

For Subsample 2 (i.e., patients in non-remission in week 4), we used Cox-proportional hazard curves to illustrate survival over time (probability of remission vs. non-remission up to week 10). After checking the proportional hazards assumptions, we used a Cox regression to model the association between remission status from week 4 to week 10 and putative predictive variables (antipsychotic used in OPTiMiSE Phase 2 (amisulpride or olanzapine); sex; age at onset; diagnosis of schizophrenia at baseline; employment status; duration of the psychotic episode until baseline; days on antipsychotics before baseline; antipsychotic cumulative dose at week 4; CGI at baseline; depression at baseline; symptomatic response (between baseline and week 4 as a dichotomous variable yes/no); and concomitant treatment with antidepressants or mood stabilizers during at least 2 weeks between baseline and week 4 (as a dichotomous variable yes/no)).

Effect sizes are provided as odds ratios (OR) for logistic regression and hazard ratios (HR) for Cox regressions. Both estimates can be interpreted as the strength of the association between a particular predictor and the outcome. OR and HR values >1 indicate that the predictor increases the likelihood of the occurrence of the outcome, while values <1 indicate that it decreases the likelihood of the occurrence of the outcome (Roberts et al., 2019).

For all analyses, alpha was set at $p < 0.05$. Analyses were performed using IBM SPSS Statistics 25.

3. Results

3.1. Clinical and demographic characteristics

Table 1 summarizes the clinical and demographic characteristics of participants. Subsample 1 was composed of 216 participants. Mean (SD) age was 25.9 (6.3) years, 55 (25.5%) were female. Of them, 127 (58.8%) had a diagnosis of schizophrenia, 12 (5.6%) of schizoaffective disorder and 77 (35.6%) of schizophreniform disorder. Per study protocol, all patients in Subsample 1 received treatment with amisulpride (up to 800 mg/day; mean dose 502.8 mg/d).

Subsample 2 included 72 participants. Mean age was 25.1 (5.7) years, 19 (26.4%) of the participants were female, 39 received treatment with olanzapine and 33 received treatment with amisulpride between the 4- and 10-week visits. Of the 72 subjects, 48 (66.7%) had a diagnosis of schizophrenia, 1 (1.4%) of schizoaffective disorder and 23 (31.9%) of schizophreniform disorder.

3.2. Predictors of clinical remission at week 4 (Subsample 1)

Out of the 216 participants, 103 (47.7%) met clinical remission criteria at week 4. Table 1 shows the comparisons in demographic and clinical variables between the 4-week remitter and non-remitter groups.

Logistic regression analysis showed that the only variables significantly associated with a higher probability of remission at week 4 were an early symptomatic response (between baseline and week 2) ($B = 1.432$, odds ratio (OR) = 4.186, 95% confidence interval (CI) = 2.082–8.416, $p < 0.001$) and an older age at first episode ($B = 0.077$, OR = 1.081, 95% CI = 1.026–1.138, $p = 0.003$).

A receiver operating characteristic (ROC) analysis showed that symptomatic response (between baseline and week 2) predicted remission at week 4 with a sensitivity of 0.447, a specificity of 0.823, a positive predictive value (PPV) of 0.697, and a negative predictive value (NPV) of 0.620 (area under curve (AUC) = 0.635, 95% CI = 0.560–0.710, $p = 0.001$).

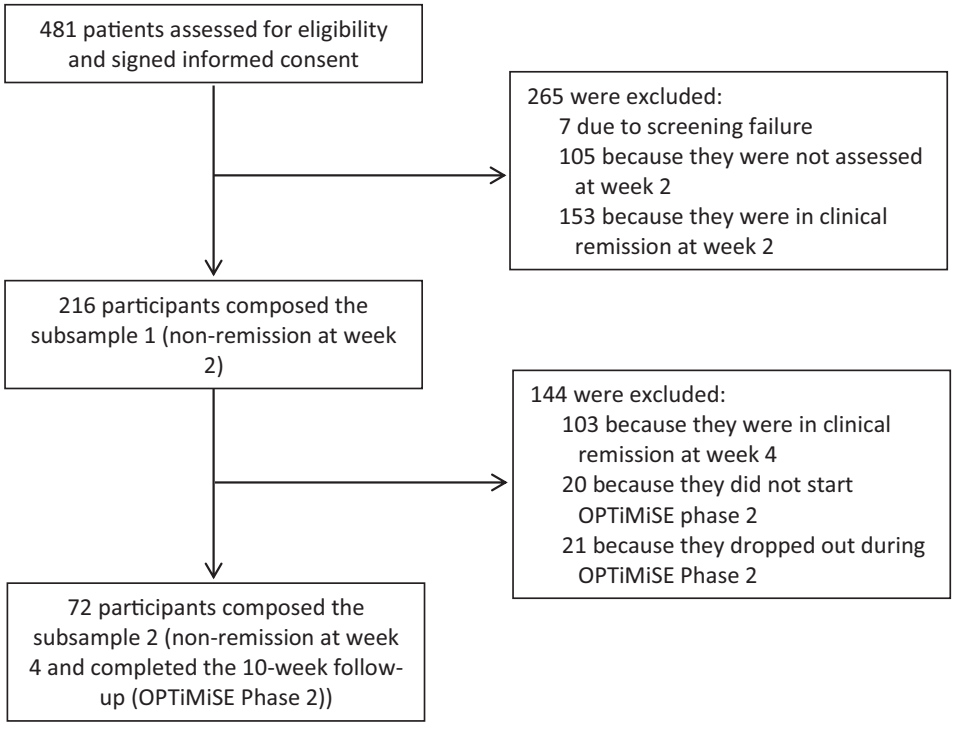

Fig. 1. Participant flowchart.

3.3. Predictors of clinical remission at week 10 (Subsample 2)

Out of the 72 participants, 32 (44.4%) met remission criteria over follow-up: 11 (34.4% of those who remitted) at week 6, 9 (28.1% of those who remitted) at week 8, and 12 (37.5% of those who remitted) at week 10. Table 1 shows the comparisons in demographic and clinical variables between participants who achieved clinical remission and those who did not between the 4- and the 10-week follow-ups.

A Cox proportional-hazards model showed that depression at baseline was significantly associated with a nearly 3-fold lower likelihood of

Table 1
Characteristics of the sample.

	Subsample 1[a]				Subsample 2[b]			
	All subsample 1	Remission[c] at week 4	Non-remission[c] at week 4	Statistics btw remission and non-remission (Subsample 1)	All subsample 2	Remission[c] at week 10	Non-remission[c] at week 10	Statistics btw remission and non-remission (Subsample 2)
N	216	103 (47.7% of the subsample1)	113 (52.3% of the subsample1)	NA	72	32 (44.4% of the subsample2)	40 (55.6% of the subsample2)	NA
Study drug				NA				$Chi^2 = 0.025$
Amisulpride	216 (100%)	103 (100%)	113 (100%)		33 (45.8%)	15 (46.9%)	18 (45.0%)	$p = 0.874$
Olanzapine	0 (0%)	0 (0%)	0 (0%)		39 (54.2%)	17 (53.1%)	22 (55.0%)	
Antipsychotic mean daily dose up to week 4, CPZ equivalents	377.12 (166.12)	366.85 (166.40)	385.93 (166.17)	$F = 0.638$ $p = 0.425$	406.37 (179.35)	435.19 (201.63)	385.89 (161.35)	$F = 1.197$ $p = 0.278$
Age, years	25.95 (6.33)	27.23 (7.01)	24.77 (5.42)	$F = 8.399$ $p = 0.004$	25.06 (5.67)	23.68 (3.87)	26.16 (6.62)	$F = 3.516$ $p = 0.065$
Sex				$Chi^2 = 2.228$				$Chi^2 = 1.891$
Women	55 (25.5%)	31 (30.1%)	24 (21.2%)	$p = 0.136$	19 (26.4%)	11 (34.4%)	8 (20.0%)	$p = 0.169$
Men	161 (74.5%)	72 (69.9%)	89 (78.8%)		53 (73.6%)	21 (65.6%)	32 (80.0%)	
Race				$Chi^2 = 1.227$				$Chi^2 = 0.053$
White	192 (88.9%)	89 (86.4%)	103 (91.2%)	$p = 0.268$	68 (94.4%)	30 (93.8%)	38 (95.0%)	$p = 1.000$
Other	24 (11.1%)	14 (13.6%)	10 (8.8%)		4 (5.6%)	2 (6.3%)	2 (5.0%)	
Education, years[d]	12.17 (2.91)	12.33 (3.11)	12.03 (2.72)	$F = 0.587$ $p = 0.445$	11.87 (2.49)	12.50 (12.51)	11.34 (2.35)	$F = 3.954$ $p = 0.051$
Employment status, employed or student	74 (36.6%)	31 (30.1%)	43 (38.1%)	$Chi^2 = 0.470$ $p = 0.493$	23 (31.9%)	10 (31.3%)	13 (32.5%)	$Chi^2 = 0.013$ $p = 0.910$
Diagnosis, schizophrenia	127 (58.8%)	53 (51.5%)	74 (65.5%)	$Chi^2 = 4.378$ $p = 0.036$	48 (66.7%)	17 (53.1%)	31 (77.5%)	$Chi^2 = 4.753$ $p = 0.029$
Duration of current psychotic episode, months	7.83 (6.73)	7.90 (6.48)	7.77 (6.98)	$F = 0.018$ $p = 0.894$	7.77 (6.91)	6.06 (6.29)	9.18 (7.15)	$F = 3.720$ $p = 0.058$
Clinical setting at baseline, inpatient	112 (51.9%)	52 (50.5%)	60 (53.1%)	$Chi^2 = 0.147$ $p = 0.701$	40 (55.6%)	18 (56.3%)	22 (55.0%)	$Chi^2 = 0.011$ $p = 0.916$
Clinical scores at baseline								
PANSS total score	82.91 (17.69)	81.53 (18.83)	84.16 (16.57)	$F = 1.188$ $p = 0.277$	86.19 (16.83)	84.63 (16.86)	87.45 (16.91)	$F = 0.497$ $p = 0.483$
PANSS positive subscale score	21.25 (5.43)	20.92 (5.79)	21.54 (5.08)	$F = 0.697$ $p = 0.405$	22.11 (5.12)	21.78 (5.65)	22.38 (4.72)	$F = 0.236$ $p = 0.628$
vPANSS negative subscale score	20.92 (7.49)	19.96 (7.50)	21.80 (7.42)	$F = 3.268$ $p = 0.072$	22.53 (7.01)	22.63 (6.95)	22.45 (7.15)	$F = 0.011$ $p = 0.917$
PANSS general subscale score	40.74 (9.28)	40.65 (9.70)	40.82 (8.93)	$F = 0.019$ $p = 0.892$	41.56 (9.11)	40.22 (9.25)	42.63 (8,96)	$F = 1.246$ $p = 0.683$
PANSS depression factor[e] score	10.41 (3.84)	10.83 (3.63)	10.03 (4.01)	$F = 2.343$ $p = 0.498$	10.43 (3.76)	10.09 (3.61)	10.70 (3.90)	$F = 0.459$ $p = 0.797$
PANSS insight item (G12)	3.88 (1.33)	3.81 (1.40)	3.95 (1.27)	$F = 0.601$ $p = 0.861$	3.94 (1.34)	3.84 (1.32)	4.03 (1.37)	$F = 0.321$ $p = 0.859$
CGI severity	5.79 (0.78)	5.93 (0.72)	5.67 (0.81)	$F = 5.947$ $p = 0.016$	5.36 (0.92)	5.54 (1.00)	5.69 (0.86)	$F = 0.470$ $p = 0.495$
CDSS total score	5.19 (4.80)	5.44 (4.90)	4.96 (4.71)	$F = 0.508$ $p = 0.477$	4.74 (4.54)	3.47 (4.57)	5.70 (4.33)	$F = 4.346$ $p = 0.041$
Depression[f]	102 (47.2%)	50 (49.5%)	52 (47.3%)	$Chi^2 = 0.105$ $p = 0.746$	34 (48.6%)	9 (30.0%)	25 (62.5%)	$Chi^2 = 7.249$ $p = 0.007$
Symptomatic response[g]	63 (29.2%) btw baseline and week 2	44 (42.7%)	19 (16.8%)	$Chi^2 = 22.732$ $P < 0.001$	21 (29.2%) btw baseline and week 4	12 (37.5%)	9 (22.5%)	$Chi^2 = 1.936$ $p = 0.164$
BMI at baseline	23.44 (4.13)	23.42 (4.00)	23.45 (4.27)	$F = 0.003$ $p = 0.953$	23.17 (4.51)	23.52 (5.24)	22.88 (3.86)	$F = 0.352$ $p = 0.555$
Overweight (BMI ≥25) at baseline	64 (29.6%)	27 (26.2%)	37 (32.7%)	$Chi^2 = 1.502$ $p = 0.220$	19 (26.4%)	8 (25.0%)	11 (27.5%)	$Chi^2 = 0.092$ $p = 0.761$
Waist circumference, cm at baseline	84.24 (12.24)	83.80 (12.82)	84.62 (11.76)	$F = 0.215$ $p = 0.643$	83.74 (11.53)	83.84 (11.01)	83.66 (12.08)	$F = 0.004$ $p = 0.949$
Days on antipsychotic treatment before baseline	6.55 (7.62)	7.08 (8.53)	6.13 (6.78)	$F = 0.779$ $p = 0.379$	5.97 (6.54)	6.13 (6.87)	5.85 (6.36)	$F = 0.031$ $p = 0.861$
Cumulative antipsychotic dose[h]	14,669.84 (7915.90)	14,552.52 (8160.17)	14,770.40 (7738.30)	$F = 0.037$ $p = 0.849$	15,810.42 (8727.42)	17,250.15 (9661.74)	14,787.45 (7972.89)	$F = 1.262$ $p = 0.266$
Treatment with antidepressants or mood stabilizers[i]	22 (10.2%)	11 (10.7%)	11 (9.7%)	$Chi^2 = 0.218$ $p = 0.641$	8 (11.1%)	6 (18.8%)	2 (5.0%)	Chi^2 (Fisher test) $= 3.408$ $p = 0.125$

Data are shown as mean (statistical deviation, SD), or n (%).
Abbreviations: BMI, body mass index; btw, between; CDSS, Calgary Depression Scale for Schizophrenia; CGI, clinical global impression; CPZ, chlorpromazine; NA, not applicable; PANSS, Positive and Negative Syndrome Scale.
[a] Subsample 1 was composed of subjects who were non-remitters at week 2.
[b] Subsample 2 was composed of participants who were non-remitters at 4 week and who completed the 10-week follow-up.
[c] As per Andreasen's remission criteria without applying the 6-month minimum duration of symptom severity criterion.
[d] Years in school from age 6 years onwards.
[e] PANSS depression subscale is the combined score of items G1, G2, G3, and G6 of the general psychopathology part of the PANSS.
[f] Depression at baseline was defined as a CDSS total score of 5 or more.
[g] Reduction in PANSS total score equal or greater than 20% between baseline and follow-up assessment (week 2 for subsample 1, and week 4 for subsample 2).
[h] Cumulative dose of antipsychotic treatment between the month prior to baseline and week 4, in chlorpromazine equivalents.
[i] Concomitant treatment with antidepressants or mood stabilizers during at least 2 weeks between baseline and week 4.

remission during the 10-week follow-up (B = 1.053, HR = 2.865 (95% CI = 1.187–6.916), p = 0.019). Fig. 2 shows the Cox proportional-hazard curve.

A ROC analysis showed that depression at baseline predicted not achieving remission from week 4 to week 10 with a sensitivity of 0.625, a specificity of 0.700, a PPV of 0.735, and a NPV of 0.583 (AUC = 0.663, 95% CI = 0.533–0.792, p = 0.021).

A supplementary Cox proportional-hazards model showed that depression at week 4 (as a single putative predictive variable) was not significantly associated with remission at week 10 (B = 0.163, HR = 1.178 (95% CI = 0.572–2.425), p = 0.658).

3.4. Predictors of clinical remission at week 4 (Subsample 1) and 10 (Subsample 2) among those patients with depression at baseline

Considering the significant effect of depression at baseline, we conducted additional post-hoc exploratory analyses in the subsamples of patients with depression at baseline. Out of the 216 patients of Subsample 1, 102 (47.2%) had depression at baseline. Logistic regression analysis within these 102 subjects showed that the only variable significantly associated with a higher probability of remission at week 4 was an early symptomatic response (between baseline and week 2) (B = 1.245, OR = 3.474, 95% CI = 1.305–9.248, p = 0.013).

Out of the 72 patients in Subsample 2, 34 (48.6%) had depression at baseline. A stepwise Cox proportional-hazards model in these 34 subjects with depression at baseline showed that the only variable significantly associated with a higher probability of remission at week 10 was receiving concomitant treatment with antidepressants or mood stabilizers for at least 2 weeks between baseline and week 4, which was associated with a 10-fold higher likelihood of remission (B = 2.344, HR = 10.417, 95% CI = 2.309–47.619, p = 0.002). We found no significant predictors of antidepressant prescription between baseline and week 4 in patients with depression at baseline within Subsample 2. In this subsample, depression at week 4 and change in CDSS total score between baseline and week 4 were not significantly associated with remission of psychotic symptoms at week 10.

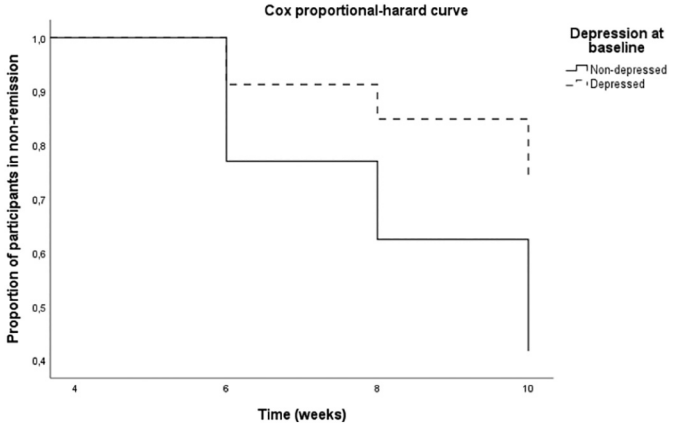

Fig. 2. Cox proportional-hazard curve. X-axis represents time (weeks). Y-axis represents proportion of participants among Subsample 2 in non-remission of psychosis. The dashed line represesents the participants in Subsample 2 with depression at baseline (i.e. Calgary Depression Scale for Schizophrenia (CDSS) total score equal or higher than 5). The continuous line represents participants in Subsample 2 without depression at baseline (i.e. CDSS total score at baseline lower than 5).

4. Discussion

This study showed that nearly half of all patients with a first episode of a schizophrenia-spectrum disorder who did not meet remission criteria after a 2-week trial with an antipsychotic did meet remission criteria if they spent two more weeks on the same drug. Furthermore, among patients in non-remission at week 2, the history of a symptomatic response between baseline and week 2 (i.e., a reduction of at least 20% in the PANSS total score) was associated with a 4-fold greater probability of remission at week 4. These results are in agreement with previous data showing that an early symptomatic response to an antipsychotic is a reliable clinical marker of subsequent clinical outcome (Kinon et al., 2010), and they support the hypothesis that although non-remission at week 2 does not seem to be a predictor to guide early clinical decision-making on its own, its combination with a lack of symptomatic response between baseline and week 2 may warrant consideration of an early revision of the therapeutic strategy (Loebel et al., 2015).

This study also showed that among patients with FES who did not meet remission criteria after a 4-week trial with an antipsychotic (amisulpride), nearly 45% may still achieve clinical remission in the following 6 weeks. However, those with depressed mood at baseline showed a nearly 3-fold greater probability of not achieving remission of psychosis within this period. In particular, the presence of depression at baseline predicted non-remission at week 10 with a specificity of 0.700 and a PPV of 0.735, regardless of the severity of psychotic symptoms at baseline. Our findings also suggest that the effect of depression at baseline on the likelihood of non-remission at week 10 may be independent of the patient continuing on the same antipsychotic (amisulpride) or switching to another antipsychotic with a different mechanism of action (olanzapine).

Our results show that depressive mood at the first episode may be a relevant prognostic marker of symptomatic remission among those patients with FES who do not achieve clinical remission at week 4 (Subsample 2). However, in our study, depressive mood was not a significant predictor of remission at week 4 in the sample of participants who were not in remission at week 2 (Subsample 1). This suggests that the combination of depressive mood at baseline with insufficient clinical response after a few weeks of treatment could help to identify a subgroup of patients less likely to respond to conventional antipsychotic therapy. Depressive mood may be especially relevant in the first few weeks of treatment, as depression at week 4 (and change in CDSS total score between baseline and week 4) was not associated with remission of psychotic symptoms during the following 6 weeks of follow-up.

As a whole, the OPTiMiSE trial indicated that nearly half of the patients who did not achieve clinical remission after 4 weeks of antipsychotic treatment did achieve remission in the following 6 weeks, with similar results for an antipsychotic switch versus maintaining the

same treatment (Kahn et al., 2018). The OPTiMiSE trial also supported the potential utility of an earlier initiation of clozapine in FES (Kahn et al., 2018). Our study adds to the previous general clinical recommendations of the OPTiMiSE trial by guiding the identification of potential subgroups less likely to benefit from the OPTiMiSE standard treatment algorithm – including patients who did not achieve symptomatic response at week 2 or those with depression at baseline and in non-remission at week 4 – who may require more intensive monitoring or interventions at earlier stages, potentially including clozapine initiation. Further studies should test specific treatment options for these subgroups in clinical trials.

The association between depression and schizophrenia has been a longstanding subject of debate (Kraepelin, 1990; Upthegrove et al., 2017). Affective symptoms, especially depressive mood, often appear during the prodromal phases of schizophrenia. Recent data suggest that the true prevalence of depression in schizophrenia may be underestimated, and suggests that at least in the early phase, mood symptoms may be more than "comorbid" experiences (Upthegrove et al., 2017), especially in women (Dai et al., 2018; Hafner, 2019; Wang et al., 2019). Depression and schizophrenia might show some overlapping genetic underpinnings (Cross-Disorder-Group of the Psychiatric Genomics Consortium, 2013; Postolache et al., 2019), as well as neuroimaging (Lee et al., 2016) and phenomenological (Upthegrove et al., 2010) features. However, even though depression in schizophrenia is increasingly recognized, it remains inadequately treated (Lako et al., 2012; Upthegrove et al., 2017).

Although we did not find a significant association of concomitant prescription of antidepressants or mood stabilizers during the first 4 weeks and clinical remission at week 10 in the whole Subsample 2 ($n = 72$), among the subgroup of participants with depression at baseline within this subsample ($n = 34$) those who received concomitant treatment for depression during the first 4 weeks did have a 10-fold greater probability of achieving remission in the following 6 weeks. These findings suggest that clinicians should address depressive symptoms in people with FES and consider introducing appropriate concomitant interventions. Although it cannot be assumed that conventional pharmacological interventions or cognitive behavioral therapy for depression will always be effective in schizophrenia (Upthegrove et al., 2017), antidepressants have proven effective for treating depression in people with schizophrenia (Gregory et al., 2017) and could constitute an adequate strategy for a subgroup of patients. The fact that we did not find a significant association between baseline severity of depressive symptoms (according to CDSS total score) and prescription of antidepressants or mood stabilizers in Subsample 2 seems to reflect that depressive symptoms remain inadequately treated in this population (Lako et al., 2012; Upthegrove et al., 2017).

Except for a weak effect of age at onset on remission at week 4 in Subsample 1, we did not find any significant effect on remission of other variables previously associated with clinical outcomes in first-episode psychosis, such as sex or duration of untreated psychosis (Drake et al., 2020; Leighton et al., 2019) in either Subsample 1 or 2. This may be the result of differences in study design (since we did not assess prognostic markers in the global FES sample, as most of the previous studies have done, but in subsamples selected for not showing a favorable early clinical outcome, in which prognostic variables could differ) or the relative homogeneity of the OPTiMiSE sample with regards to diagnoses, duration of untreated psychosis, previous exposure to antipsychotics and treatments received (Kahn et al., 2018).

Several limitations to this study should be considered when interpreting the results. First, due to the exploratory nature of the study we did not conduct any formal corrections for multiple comparisons, which carries a risk of false positive discoveries. Results therefore need to be replicated in future studies. Second, despite a large dataset, high remission and dropout rates left relatively small sample sizes to assess our main outcome measures, especially in Subsample 2. Nevertheless, this was a very homogenous sample that allows testing of this clinically relevant question without the potentially confounding effect of differing antipsychotic treatments, which might also be the consequence of an indication bias. Third, the study assessed only patients treated with amisulpride or amisulpride and olanzapine, which might limit the generalizability of our results. Fourth, some patients dropped out of the study due to poor outcomes in both phases of the OPTiMiSE trial, which may limit the representativeness of the samples finally assessed. Fifth, the inclusion of additional biological or cognitive variables could have enabled a deeper characterization of the subgroup of patients with baseline depression who did not reach clinical remission. It is unclear whether the subgroup with depressed mood at baseline that did not reach remission at week 4 might constitute a distinct subgroup within FES. Future studies should try to characterize it further and identify premorbid, clinical, and biological variables associated with this clinical presentation. Sixth, we used 2-week PANSS scores to assess an early symptomatic response and remission. As the PANSS takes into account symptoms during the week prior to the assessment (Kay et al., 1987), these scores reflect very early symptomatic changes. However, we included this time point based on the study protocol and definitions of early symptomatic response in previous studies (Kinon et al., 2010; Loebel et al., 2015). Seventh, we focused on the identification of clinical predictors of symptomatic remission in FES. However, remission and recovery are multidimensional constructs that also encompass functional outcomes (AlAqeel and Margolese, 2012; Andreasen et al., 2005). Future studies should expand our findings by specifically assessing the association of baseline depressive mood with functional outcomes, including disability. Eighth, although previous research found a CDSS cut-off of 5 to be valid in schizophrenia samples similar to ours (Sarro et al., 2004), the choice of this cut-off may have affected our results. We decided a lower cut-off than previous studies (e.g. Addington et al., 2014; Rajkumar, 2015; Rekhi et al., 2018) was worth that risk in order to increase the sensitivity to detect subgroups of patients with depressive symptoms and minimize the risk of false negatives.

5. Conclusions

This study includes a large and homogeneous sample with minimal prior exposure to antipsychotics, which was carefully assessed using a randomized clinical trial design with comprehensive clinical assessments at multiple time points. Our results support the relevance of an early response (as early as 2 weeks) as a predictor of early clinical outcome and reinforce the importance of assessing depressive symptoms in patients with schizophrenia. In particular, we found that the CDSS may hold potential for clinical decision-making in FES. The CDSS is an easy-to-administer tool, which is currently available in 44 language versions and can be used in routine clinical practice in a time-efficient manner with no need for specific permission (https://www.ucalgary.ca/cdss/). Assessment of depressive symptoms might thus help to optimise treatment algorithms for people with FES and improve the clinical care of this population.

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CRediT authorship contribution statement

Inge Winter van Rossum, Iris E. Sommer, Stefan Leucht and René S. Kahn designed the OPTiMiSE study; Covadonga M. Díaz-Caneja, Laura Pina-Camacho, Inge Winter van Rossum, Lone Baandrup, Iris E. Sommer, Birte Glenthøj, René S. Kahn, Stefan Leucht and Celso Arango participated in the collection of data for the OPTiMiSE study; David Fraguas, Covadonga M. Díaz-Caneja, Laura Pina-Camacho and Celso Arango designed the current paper; David Fraguas carried out data analysis; David Fraguas and Covadonga M. Díaz-Caneja interpreted the data and drafted the manuscript; all other authors contributed to the critical revision of the manuscript and have approved the final version to be published.

Declaration of competing interest

Dr. Fraguas has been a consultant and/or has received fees from Angelini, Eisai, IE4Lab, Janssen, Lundbeck, and Otsuka. He has also received grant support from Instituto de Salud Carlos III (Spanish Ministry of Science, Innovation and Universities) and from Fundación Alicia Koplowitz.

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