Generalizability of the Results of Efficacy Trials in First-Episode Schizophrenia:

Comparing Outcome and Study Discontinuation of Groups of Participants in the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) Trial

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ABSTRACT

Objective: In the majority of randomized controlled trials (RCTs) conducted in schizophrenia populations, patients suffering from a substance use disorder (SUD) or suicidality are excluded. Excluding these patients from RCTs might impact the generalizability of results. The aim of this study is to determine whether excluding patients with suicidality and/or SUD impacts RCT results on symptomatic remission, premature study discontinuation, symptom severity, and social functioning.

Methods: Across Europe and Israel, 481 patients with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder, based on *DSM-IV* criteria, were recruited between May 26, 2011, and May 15, 2016, for the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trial. Baseline characteristics and follow-up assessments were compared between patients with versus without baseline SUD and/or suicidality.

Results: A total of 446 patients met eligibility criteria for the OPTiMiSE trial and initiated amisulpride treatment, of whom 404 (91%) had data available on suicidality, SUD, duration of illness, and CDS score. Of the 360 eligible patients with baseline data on suicidality and SUD, 106 patients had comorbid suicidality and/or SUD while 254 patients had neither of these comorbidities. No significant differences in the likelihood to achieve symptomatic remission or to prematurely discontinue the study were found when comparing comorbid versus non-comorbid patients ($P = .27$). There were no significant differences in symptom severity and social functioning between the groups. Comorbid patients had a higher level of depressive symptoms and more impaired social functioning compared to non-comorbid patients.

Discussion: Excluding first-episode schizophrenia patients with comorbidities from clinical trials unlikely affects key outcome measures. It is recommended to include patients with comorbidities in clinical trials while carefully monitoring suicidality and implementing safety plans to gain insight into efficacy and safety of treatment in this substantial patient population.

Trial Registration: ClinicalTrials.gov identifier: NCT01248195

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Randomized controlled trials (RCTs) are required for obtaining marketing authorization for pharmacotherapy. RCTs are described as providing the most reliable scientific evidence in the hierarchy of clinical research methods; due to the randomized controlled nature, causal relationships can be identified while the influence of known and unknown sources of bias is minimized. RCTs commonly apply strict exclusion criteria to recruit samples of patients with symptoms that emanate exclusively from their primary diagnosis in the absence of any potential safety concerns (such as suicidal ideation) that may also affect the primary efficacy measure, therefore optimizing internal validity.[1,2] Even though high internal validity is essential in scientific research, the use of strict exclusion criteria for selecting RCT participants can bias the study sample and substantially diminish the external validity, or generalizability, of an RCT.[3,4]

When focusing on external validity in schizophrenia research, approximately 4 of 5 patients with schizophrenia would be ineligible to be enrolled in an RCT given the commonly applied exclusion criteria.[2,5] Regularly applied exclusion criteria in schizophrenia trials concern the presence of suicidality and substance use disorder (SUD).[3,4,6] Presence of suicidal ideation at study entry is often implemented as an exclusion criterion as a measure to ensure patient safety.[7] In patients with schizophrenia, the lifetime risk to commit suicide is 4% to 13%, with a modal rate of approximately 10%.[8] An even larger proportion of patients (42%) with schizophrenia suffer from SUD,[9] the second commonly applied exclusion criterion, intended to avoid interference of effects of substance use on symptom severity and to reduce the risk of poorer treatment compliance in an RCT.[10] An important

Clinical Points

- About 30% of the first-episode schizophrenia patients with comorbidities (suicidality or substance use disorder) are excluded from randomized controlled trials (RCTs), which might impact the generalizability of the results.
- Potential impacts on key clinical trial outcome measures are found to be unaffected by the exclusion of patients with commonly applied comorbidities.
- Careful review of the current eligibility criteria when designing an RCT and inclusion of patients with comorbidities when possible are recommended.

consequence of excluding patients with comorbidities from RCTs is that the RCT results may not translate well to the overall patient population undergoing pharmacotherapy.[11,12]

Despite the common application of these exclusion criteria in RCTs, the actual effects of these comorbidities on symptom severity measurements seem to be limited. Nordon and colleagues[12] report that schizophrenia patients with or without SUD did not differ in symptom improvement after 3 months of treatment. Furthermore, excluding suicidality and SUD patients in first-episode schizophrenia, schizophreniform disorder, and schizoaffective disorder patients does not severely affect the generalizability of the results, as psychopathology and subject retention were similar when patients with comorbidities were included versus excluded.[6] On the basis of these findings, the authors recommend being cautious with excluding patients with comorbidities from RCTs, as 31% of their patient sample suffered from suicidality and/or SUD and the remaining sample might not be representative of the schizophrenia patient population. Indeed, excluding these patients from RCTs complicates the treatment decision process of clinicians when clinical trial results are taken into account; it is debatable whether physicians consider the discrepancy between their patients in clinical practice and clinical trial participants.[13]

Altogether, the proportion of patients with schizophrenia excluded from RCTs is relatively high and mostly driven by the presence of comorbid SUD and/or suicidality. Therefore, the aim of this study is to investigate whether excluding patients with SUD and/or suicidality impacts key aspects of clinical trial conduct and interpretation of results: symptomatic remission, premature study discontinuation, symptom severity, and social functioning.

METHODS

Study Setting and Population

Data from the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) trial were used for the current analyses. An elaborate description of the study design was published previously.[14,15]

Patients

Patients were recruited between May 26, 2011, and May 15, 2016, from 27 centers in 14 European countries and Israel. Eligible patients were 18–40 years old and diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorder as defined by *DSM-IV* and confirmed by the Mini-International Neuropsychiatric Interview 5.0.0 Plus (M.I.N.I. 5.0.0 Plus).[16] An elaborate description of the eligibility criteria has been published previously All patients provided written informed consent.

Procedures

The trial complied with the Declaration of Helsinki, was approved by competent authorities in all countries and the ethics committees of the participating centers, and was registered at ClinicalTrials.gov (NCT01248195). The study was monitored according to Good Clinical Practice International Conference on Harmonization guidelines and the Clinical Trial Directive.

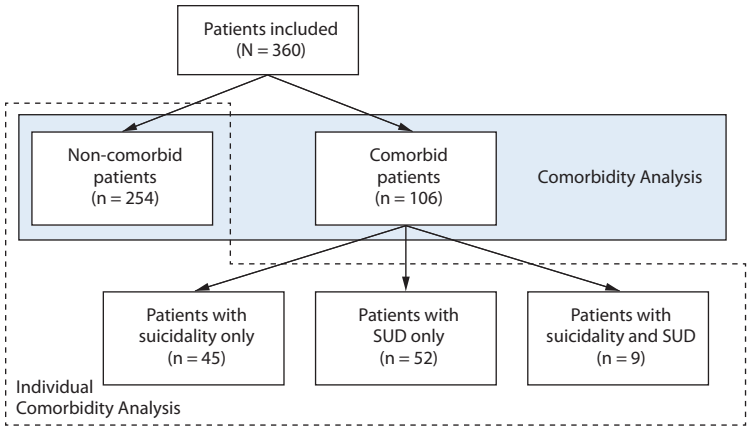
Outcome Measures

The primary endpoint was the number of patients who achieved symptomatic remission after 4 weeks of treatment with amisulpride, comparing non-comorbid patients with comorbid patients. Symptomatic remission was measured through 8 specific Positive and Negative Syndrome Scale (PANSS)[17] items (P1, P2, P3, N1, N4, N6, G5, and G9), rated not higher than "mild severity" (maximum item score of 3) as defined by Andreasen and colleagues.[18] Furthermore, premature study discontinuation, symptom severity (PANSS total score), depressive symptoms (Calgary Depression Scale [CDS][19]), severity of illness (Clinical Global Impressions scale, both Severity of Illness and Improvement[20]), and social functioning (Personal and Social Performance scale [PSP][21]) were compared between non-comorbid patients versus comorbid patients over the 4-week amisulpride treatment period as secondary outcomes. Additionally, analyses were performed on the differences in symptomatic remission, premature study discontinuation and symptom severity (PANSS total score), depressive symptoms (CDS score), severity of illness (CGI score, both Severity of Illness and Improvement), and social functioning (PSP score) between non-comorbid patients compared to (1) patients with suicidality only, (2) patients with SUD only, and (3) patients with both suicidality and SUD.

Statistics

Baseline demographics and clinical characteristics were expressed in descriptive statistics per defined comorbidity group and tested with a 2-sample independent t test for continuous variables and a χ^2 test or a Fisher exact test for categorical data. Logistic regression analysis was used to compare symptomatic remission (primary outcome) and premature study discontinuation (secondary outcome) between comorbidity groups. The assumption of linearity of continuous variables was assessed with restrictive cubic splines.[22] In case the assumption of linearity of continuous variables was violated, splines were added to improve the fitting of the model. Mixed-model analyses were used to analyze PANSS total, CGI, and PSP scores at follow-up

Figure 1. Distribution of Patients Included in the Current Study Across Comorbidity Groups



Abbreviation: SUD = substance use disorder.

visits. The mixed model included an unstructured residual (ie, generalized estimating equation [GEE]–type) covariance matrix to correct for multiple measurements in the same patients over time. CDS scores were analyzed with general linear models (GLMs), as this outcome was measured only at end of treatment. All models included PANSS total and CDS baseline scores in addition to age, gender, and duration of illness (number of months) as confounders. CDS baseline scores were adjusted by excluding the suicidality score (item 8) to minimize bias in the analyses. Patients who met symptomatic remission criteria at baseline were excluded from the analyses. Patients who discontinued the study before completing the 4-week amisulpride treatment and achieved symptomatic remission at their last study visit were categorized as remitters in the current analyses. All analyses were primarily performed comparing comorbid patients versus non-comorbid patients (ie, comorbidity analyses) and repeated in the individual comorbid groups, with the non-comorbid group as comparator group (ie, individual comorbidity analyses). The threshold for significance of the primary and secondary outcomes was defined based on the Bonferroni correction for multiple testing (comorbidity analyses: 7 tests; P value < .007 and individual comorbidity analyses: 14 tests; P value < .004). A sensitivity analysis was performed for the premature study discontinuation outcome in which the patients who met symptomatic remission at baseline were included, as a remission status at baseline is not expected to have a differential effect on premature study discontinuation across the comorbidity groups. The sensitivity analyses results are presented in Supplementary Appendix 1. Data were analyzed with IBM SPSS statistics version 25.0[23] and SAS v9.4.[24]

RESULTS

A total of 481 patients were recruited and 446 met eligibility criteria for the OPTiMiZE trial and initiated amisulpride treatment, of whom 404 (91%) had data available on suicidality, SUD, duration of illness, and CDS score. Forty-four patients met symptomatic remission criteria at baseline and were therefore removed from our analyses. Of the remaining 360 patients, 254 (71%) were neither suicidal nor using substances. The comorbid patients group (n = 106, 29%) was divided in 3 individual comorbidity groups: 45 patients (42%) with suicidality only, 52 patients (49%) with SUD only, and 9 patients (8%) with both suicidality and SUD. Given the small size of the latter group, it was excluded from both the baseline and outcome analyses. An overview of the patient groups is presented in Figure 1.

Baseline Comparisons

Demographic and clinical baseline characteristics of the non-comorbid and the comorbid group are presented in Table 1. In the comorbidity analyses, significant differences were found for comorbid patients when compared to non-comorbid patients: comorbid patients were younger (mean = 25.0 vs 26.4 years; P = .043), were more likely to be male (83% versus 66%; P = .001), had fewer years of education (mean = 11.7 versus 12.5; P = .011), were less often antipsychotic naive (34% versus 46%; P = .046), had more severe depressive symptoms (mean CDS score of 6.0 versus 4.1; P = .001), and had more impaired social functioning (mean PSP score of 45.2 versus 49.1; P = .024). Results of the baseline comparisons in the individual comorbidity analyses are presented in Supplementary Appendix 2.

Symptomatic Remission

Of the 360 patients included in the analyses, 200 patients (56%) achieved symptomatic remission: 139 non-comorbid patients (55%) and 61 comorbid patients (58%). Remission rates were high in all individual comorbidity groups: 24 patients (53%) in the suicidality-only group, 33 patients (63%) in the SUD-only group, and 4 patients (44%) in the suicidality and SUD group achieved remission after 4 weeks of treatment with amisulpride. There was no significant difference in the likelihood to achieve symptomatic remission between non-comorbid patients and comorbid patients (P = .27). When comparing non-comorbid patients

Table 1. Baseline Characteristics of Non-Comorbid and Comorbid Patient Groups[a]

Variable	Non-Comorbid (n = 254)	Suicidality and/or SUD (n = 106)	*P* Value	Comorbid Patient Groups Distinguished by Comorbidity: Suicidality Only (n = 45)	*P* Value	Substance Use Only (n = 52)	*P* Value	Suicidality and Substance Use (n = 9)
Age, mean (SD), y	26.4 (6.3)	25.0 (5.7)	**.043**	26.3 (7.0)	.935	24.0 (4.1)	**.001**	24.2 (5.6)
Men	167/254 (66)	88/106 (83)	**.001**	33/45 (73)	.319	47/52 (90)*	**<.001**	8/9 (89)
White	222/254 (87)	86/106 (81)	.139	36/45 (80)	.183	42/52 (81)	.205	8/9 (89)
Married at present	16/254 (6)	6/106 (6)	1	4/45 (9)	.518	2/52 (4)	.748	0/9 (0)
Living alone	47/254 (19)	19/106 (18)	1	10/45 (22)	.558	8/52 (15)	.594	1/9 (11)
Living environment			.498		.168		.974	
City > 500,000	125/254 (49)	49/106 (46)	…	20/45 (44)	…	25/52 (48)	…	4/9 (44)
City 100,000–500,000	60/254 (24)	33/106 (31)	…	17/45 (38)	…	14/52 (27)	…	2/9 (22)
City 10,000–100,000	53/254 (21)	18/106 (17)	…	5/45 (11)	…	10/52 (19)	…	3/9 (33)
Village/rural < 10,000	16/254 (6)	6/106 (6)	…	3/45 (7)	…	3/52 (6)	…	0/9 (0)
Education, mean (SD), y[b]	12.5 (3.2)*	11.7 (2.2)*	**.011**	11.7 (2.5)	.119	11.8 (2.0)*	.077	10.9 (2.1)*
Employed or student	102/254 (40)	36/106 (34)	.287	20/45 (44)	.590	14/52 (27)	.073	2/9 (22)
Diagnosis[c]			.080		.209		**.047**	
Schizophreniform disorder	102/254 (40)	45/106 (43)	…	14/45 (31)	…	26/52 (50)	…	5/9 (56)
Schizoaffective disorder	10/254 (4)	10/106 (9)	…	4/45 (9)	…	5/52 (10)	…	1/9 (11)
Schizophrenia	142/254 (56)	51/106 (48)	…	27/45 (60)	…	21/52 (40)	…	3/9 (33)
Inpatient	149/254 (59)	64/106 (60)	.814	24/45 (53)	.550	35/52 (67)	.246	5/9 (56)
Antipsychotic naive	117/253 (46)	36/105 (34)	**.046**	16/45 (36)	.197	18/51 (35)	.167	2/9 (22)
Duration of untreated psychosis, mean (SD), mo	7.0 (6.7)	6.3 (6.2)	.365	7.7 (6.3)	.543	5.3 (6.2)	.089	5.6 (5.3)
CGI score, mean (SD)[d]	5.6 (0.9)	5.6 (0.8)	.654	5.7 (0.7)	.204	5.4 (0.8)	.298	6.1 (0.8)
CDS score, mean (SD)[e]	4.1 (4.2)	6.0 (5.2)	**.001**	8.7 (5.7)*	**<.001**	3.3 (2.9)	.093	8.1 (5.4)
PANSS score, mean (SD)[f]								
Total	79.2 (17.4)	80.2 (16.6)	.643	86.9 (17.1)	**.007**	74.7 (14.9)	.082	77.9 (10.9)
Positive subscale	20.4 (5.4)	21.2 (4.4)	.141	22.2 (4.5)	**.035**	20.3 (4.4)	.977	21.0 (3.3)
Negative subscale	20.0 (7.2)	18.9 (6.5)	.170	20.8 (6.0)	.481	17.9 (6.7)	.044	15.6 (5.2)
General subscale	38.9 (9.1)	40.1 (9.5)	.252	43.9 (9.9)	**.001**	36.6 (8.2)	.094	41.3 (7.5)
PSP score, mean (SD)[g]	49.1 (14.6)*	45.2 (15.6)*	**.024**	45.2 (15.9)*	.110	46.4 (16.1)*	.241	37.7 (9.0)

[a]Data are shown as n/total n (%) unless otherwise noted. Percentages may not sum up to 100 due to rounding. Boldface indicates statistical significance.
[b]Years in school from 6 years of age onward.
[c]Diagnosis determined with the M.I.N.I. 5.0.0 Plus.
[d]Score ranges from 1 to 7; a higher score indicates greater illness severity.
[e]Score ranges from 0 to 27; a higher score indicates more severe depressive symptoms.
[f]Total score ranges from 30 to 210; positive score ranges from 7 to 49, negative score ranges from 7 to 49, general score ranges from 16 to 112; the higher the score, the greater the severity of the symptoms.
[g]Score ranges from 1 to 100; a higher score indicates better social functioning.
*Variable contains incomplete data; an overview of the missing continuous data is presented in Supplementary Appendix 3.
Abbreviations: CDS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions scale, M.I.N.I. 5.0.0 Plus = Mini-International Neuropsychiatric Interview 5.0.0 Plus, PANSS = Positive and Negative Syndrome Scale, PSP = Personal and Social Performance scale, SUD = substance use disorder.

Table 2. Odds Ratios of Comorbidity Associations With Remission and Premature Study Discontinuation

Comparison	Remission OR	Remission 95% CI	Remission *P* Value	Premature Study Discontinuation OR	Premature Study Discontinuation 95% CI	Premature Study Discontinuation *P* Value
Comorbid vs non-comorbid patients*	1.321	0.802 to 2.174	.27	1.051	0.549 to 2.013	.88
Suicidality vs non-comorbid patients†	1.128	0.557 to 2.284	.74	0.515	0.166 to 1.600	.25
SUD vs non-comorbid patients†	1.673	0.862 to 3.247	.13	1.189	0.520 to 2.720	.68

*Bonferroni-corrected threshold for significance ($P < .007$).
†Bonferroni-corrected threshold for significance ($P < .004$).
Abbreviations: OR = odds ratio, SUD = substance use disorder.

with the two individual comorbidity groups, no significant differences in the likelihood to achieve symptomatic remission were found. Results from the logistic regression analyses are presented in Table 2. The assumption of linearity was violated for duration of illness; we therefore included splines with 3 knots in the analyses.

Premature Study Discontinuation

In total, 60 patients (17%) of the 360 did not complete the 4-week amisulpride treatment period, including 42 of 254 non-comorbid patients (17%) and 18 of 106 comorbid patients (17%); the comorbid patients included 4 of 45 patients (9%) in the suicidality-only group, 10 of 52 patients (19%) in the SUD-only group, and 4 of 9 patients (44%) in the suicidality and SUD group. There was no significant difference in the risk to prematurely discontinue the study between non-comorbid and comorbid patients. When comparing the individual comorbidity groups with the non-comorbid group, no significant differences in the risk to discontinue the study prematurely were found. Results from

Table 3. Regression Results for the Symptom Severity and Social Functioning Outcomes[a]

Comparison	PANSS Total		CDS		CGI-Improvement		CGI–Severity of Illness		PSP	
	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Comorbid vs non-comorbid patients*	−1.21 (−4.16 to 1.75)	.42	−0.17 (−0.99 to 0.65)	.68	−0.08 (−0.29 to 0.70)	.46	−0.13 (−0.31 to 0.04)	.13	0.95 (−2.41 to 4.31)	.58
Suicidality vs non-comorbid patients†	0.94 (−3.43 to 5.31)	.67	−0.17 (−1.33 to 0.97)	.76	0.03 (−0.29 to 0.35)	.85	−0.13 (−0.39 to 0.12)	.32	1.29 (−3.88 to 6.46)	.62
SUD vs non-comorbid patients†	−3.11 (−6.78 to 0.55)	.10	−0.10 (−1.17 to 0.96)	.85	−0.13 (−0.38 to 0.13)	.32	−0.16 (−0.38 to 0.04)	.16	0.65 (−3.40 to 4.70)	.75

[a]An overview of the number of patients included in the symptom severity and social functioning analyses is presented in Supplementary Appendix 3.
*Bonferroni-corrected threshold for significance ($P < .007$).
†Bonferroni-corrected threshold for significance ($P < .004$).
Abbreviations: CDS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions scale, OR = odds ratio, PANSS = Positive and Negative Syndrome Scale, PSP = Personal and Social Performance scale, SUD = substance use disorder.

the logistic regression analysis are presented in Table 2. The assumption of linearity was violated for duration of illness; we therefore included splines with 3 knots in the analyses.

Symptom Severity and Social Functioning

The results from the regression analyses are presented in Table 3. An overview of the number of patients included in the symptom severity and social functioning analyses is presented in Supplementary Appendix 3. When comparing non-comorbid versus comorbid patients, no significant differences in PANSS total score were found at end of treatment. Additionally, no differences between non-comorbid patients and comorbid patients were found in CDS, CGI (Severity of Illness and Improvement), and PSP scores at end of treatment. When comparing the individual comorbidity groups to the non-comorbid group, no significant differences in PANSS total, CDS, CGI (Severity of Illness and Improvement), and PSP scores were found at end of treatment.

DISCUSSION

The present study investigated whether commonly applied clinical trial exclusion criteria (suicidality and SUD) impact key aspects of clinical trial results, namely symptomatic remission, premature study discontinuation, symptom severity, and social functioning, in a large sample of first-episode schizophrenia, schizophreniform disorder, and schizoaffective disorder patients. Our results show a consistent picture across outcomes: no significant difference was found in the likelihood to achieve symptomatic remission or to prematurely discontinue the study, nor were any significant differences found in symptom severity (PANSS total, CDS, CGI–Severity of Illness, and CGI-Improvement scores) or social functioning (PSP scores) between non-comorbid patients versus comorbid patients after 4 weeks treatment with amisulpride. Similarly, in the individual comorbidity analyses (suicidality only, SUD only, and suicidality and SUD), no significant differences were found in the likelihood to achieve symptomatic remission or the likelihood to prematurely discontinue the study, nor were any significant differences found in symptom severity and social functioning between the individual comorbidity groups and the non-comorbid patients. When comparing patient demographics and clinical characteristics of comorbid patients with those of non-comorbid patients at baseline, we found that comorbid patients were younger, more likely to be male, had fewer years of education, were less likely to be antipsychotic naive, and have a higher level of depressive symptoms and more impaired social functioning.

These results corroborate previous findings.[6,12,25] Nordon and colleagues[12] compared symptom improvement over a period of 3 months between patients with schizophrenia with or without SUD, reporting an absence of a difference in symptom improvement. Lambert and colleagues[25] studied whether baseline SUD was related to the likelihood of achieving remission after 18 months of treatment and did not find a significant association, which is in line with our findings. Boter and colleagues[6] investigated a patient population similar to the study sample from the current study with similar sized comorbidity groups, comparing symptom severity (PANSS total, Global Assessment of Functioning, and CDS scores) and premature study discontinuation over a 12-month treatment period between non-comorbid patients and comorbid (suicidality and/or SUD) patients. Similar to our findings, those of Boter and colleagues did not demonstrate differences in PANSS total scores or premature study discontinuation. At baseline in the present study, the severity of depressive symptoms was significantly higher and social functioning was more impaired in the comorbid patients when compared to the non-comorbid patients. However, despite this difference at treatment initiation, no significant differences in depressive symptoms or social functioning were found between non-comorbid and comorbid patients at end of treatment. Additionally, no difference in treatment effectiveness was found regarding symptomatic remission, premature study discontinuation, and symptom severity when comparing non-comorbid patients with comorbid patients, which implies that differences in depressive symptoms and social functioning at baseline do not affect key clinical trial outcome measures. In contrast to our findings, higher levels of depression were found at end of treatment in the comorbid group in the study by Boter and colleagues[6]; small

sample sizes prevented the authors from determining which comorbid group caused this difference.

Subjects with suicidal ideation or past attempts are commonly excluded from RCT participation, which is mainly driven by safety concerns. However, given the high prevalence of suicidal ideation (up to 51%) reported in populations of first-episode psychosis patients[26] and the lifetime risk to commit suicide of 4%–13% in schizophrenia patients,[8] suicidality is likely to be encountered during trials despite the commonly applied selection at the gate. Indeed, in the current study, 4 patients who were not suicidal at baseline developed severe suicidality during the study, including 1 patient committing suicide, while none of the patients who were diagnosed with suicidality at baseline were hospitalized due to suicidal ideations during the study. These findings indicate that patients suffering from suicidality cannot be avoided in RCTs, and measures to ensure patient safety are required to be implemented anyway. Regulatory authorities (eg, the US Food and Drug Administration [FDA] and European Medical Agency [EMA]) provide extensive guidance on how to monitor patients who present with suicidal ideation throughout RCTs while indicating that suicidal ideation may not be a valid reason for exclusion from RCTs. With frequent assessments using the Columbia Suicide Severity Rating Scale (C-SSRS),[27] continuous safety monitoring, and a referral guideline in place, inclusion of patients with suicidal ideation in RCTs can be safely done.[28] An overview of the serious adverse events is presented in Supplementary Appendix 4.

The results of this study need to be interpreted in the light of several limitations. First, data from 86 patients (19%) were excluded from the analyses: 45 patients who met symptomatic remission criteria at baseline and 41 patients due to missing data at baseline (M.I.N.I. 5.0.0 Plus SUD/suicidal ideation sections, CDS, and duration of illness). Additionally, the analyses described in this study are post hoc group analyses, comparing outcomes of smaller groups instead of a large study population for whom this sample was initially intended. This study may therefore be underpowered, which reduced the chance to find a true effect. Second, the sample used in the current study may not be fully representative of patients with first-episode schizophrenia; specifically, the proportion of patients with suicidality and/or SUD may be underreported in the current study. In our sample, 15% of the patients suffered from suicidality, which is considerably lower when compared to 40% reported at baseline in a longitudinal study in first-episode schizophrenia patients by Pelizza and colleagues.[29] Similarly, a lower proportion of SUD patients (17%) was found in our sample when compared to 63% presented in an epidemiologic study in first-episode psychosis patients.[30] However, the proportions of suicidality and SUD patients found in the current study are similar to the proportions reported by Boter and colleagues[6] in their first-episode psychosis sample: 12% of the patients suffered from suicidality, and 23% of the patients suffered from SUD.[6] A potential cause of these lower proportions might be that patients who are suicidal or using substances are less willing to participate in an RCT and/or physicians may be more reluctant to enroll patients with these comorbidities in RCTs. Another explanation for the lower proportions might be that the studies which described higher percentages focused on suicidality and/or SUD in first-episode schizophrenia patients as a primary objective.

The current study demonstrates a lack of substantiation for the main drivers to apply the exclusion of patients with suicidality and/or SUD as comorbidity; potential impacts on key clinical trial outcome measures are found to be unaffected by the exclusion of patients with specific comorbidities. However, when testing new interventions, one should carefully consider a potential interaction between these comorbidities and the new intervention before including these groups of patients. Excluding first-episode schizophrenia, schizoaffective disorder, and schizophreniform disorder patients with suicidality and/or SUD as comorbidity from RCTs or non-pharmacologic trials (eg, those for cognitive-behavioral therapy) leads to the exclusion of a substantial proportion of patients. Clinicians currently do not have an extensive scientific basis for treatment decisions in first-episode schizophrenia patients suffering from suicidality or SUD. Collecting efficacy and safety data in patients with suicidality and/or SUD is essential for decision making in daily clinical practice. Moreover, when excluding these patients systematically from RCTs, we miss the opportunity to gain insight into potential positive effects of antipsychotic treatment on suicidality and SUD. Finally, by including patients with comorbidities, an important opportunity is created in that including these subgroups of patients can substantially facilitate recruitment. The exclusion of 30% of the target population due to comorbidities wastes research resources and endangers trials due to underenrollment. Therefore, it is important to reduce exclusion criteria to a minimum, when possible, as including patients with comorbidities is an opportunity to enrich RCT study samples.

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Supplementary Material

Article Title: Generalizability of the Results of Efficacy Trials in First-Episode Schizophrenia: Comparing Outcome and Study Discontinuation of Groups of Participants in the Optimization of Treatment and Management of Schizophrenia in Europe (OPTiMiSE) Trial

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List of Supplementary Material for the article

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Supplementary Appendix 1: Sensitivity analyses premature study discontinuation

A sensitivity analyses was conducted on the premature study discontinuation outcome in the study sample including patients who met remission criteria at baseline. The sample contained 404 patients; 288 non-comorbid patients and 116 comorbid patients; the latter group was further divided in the following three individual comorbidity groups; 47 patients with suicidality only, 59 patients with SUD only and 10 patients with suicidality and SUD. In total, 66 patients (17%) did not complete the four week amisulpride treatment period; 46 of the non-comorbid patients (16%) and 20 comorbid patients (17%); 5 patients (11%) with suicidality only, 11 patients with SUD only (17%) and 4 patients (40%) with suicidality and SUD. No significant differences in the likelihood to discontinue the study prematurely were found when comparing comorbid patients versus non-comorbid patients at end of treatment (OR 1.157, 95% CI 0.626 – 2.137, p=0.64). When comparing the individual comorbidity groups with the non-comorbid group at end of treatment, no significant differences in the likelihood to discontinue the study prematurely were found for patients with suicidality only (OR 0.647, 95% CI 0.230 – 1.815, p=0.41) nor for patients with SUD only (OR 1.277, 95% CI 0.585 – 2.789, p=0.54), nor for patients with suicidality and SUD (OR 4.639, 95% CI 1.149 – 18.725, p=0.03, significant effect is lost after Bonferroni correction for multiple testing (3 tests; p<0.017)) when compared to non-comorbid patients.

Supplementary Appendix 2: Baseline comparisons of individual comorbidity groups

In the individual comorbidity analyses, when comparing suicidality only patients with non-comorbid patients, suicidality only patients had significantly more severe depressive symptoms (8.7 versus 4.1; p<0.001), more severe psychosis symptoms (as measured with PANSS total)(86.9 versus 79.2; p=0.007), more severe PANSS positive symptoms (22.2 versus 20.4; p=0.035), more severe PANSS general symptoms (43.9 versus 38.9; p=0.001). Significant differences were found when comparing SUD only patients with non-comorbid patients; SUD patients were younger (24.0 versus 26.4; p=0.001) and were more likely to be male (90 versus 66%; p<0.001). When comparing the suicidality and SUD patients with non-comorbid patients significant differences were found as well; suicidality and SUD patients had more severe depressive symptoms (8.1 versus 4.1; p=0.006) and more impaired social functioning (37.7 versus 49.1; p=0.02).

Supplementary Appendix 3 – Overview of missing data of baseline characteristics and symptom severity

Missing data of continuous variables in Table 1: Comparisons of baseline characteristics between comorbid and non-comorbid patient groups

		Comorbid patients			
			Subgroups distinguished by comorbidity		
Variable	Non-comorbid	Suicidality and/or SUD	Suicidality only	Substance use only	Suicidality and substance use
Education	247/254	104/106	45/45	51/52	8/9
PSP	249/254	104/106	43/45	52/52	10/9

outcomes

Missing outcome data Table 3: Symptom severity outcomes at end of treatment

		Comorbid patients			
			Subgroups distinguished by comorbidity		
Variable	Non-comorbid (n = 212)	Suicidality and/or SUD (n = 88)	Suicidality only (n = 41)	Substance use only (n = 42)	Suicidality and substance use (n = 5)
PANSS	212/212	88/88	41/41	42/42	5/5
CDS	205/212	85/88	38/41	42/42	5/5
PSP	205/212	82/88	36/41	41/42	5/5
CGI severity and improvement	209/212	86/88	40/41	41/42	5/5

Supplementary Appendix 4: Serious adverse events (SAEs)

In total, for 26 patients (7%) adverse events meeting one of the SAE criteria were reported during the four week amisulpride treatment period. The majority of the SAEs occurred in the non-comorbid group (n=22; 8%); 14 patients were hospitalized due to psychotic exacerbation, two patients were hospitalized due to suicidal ideations, one patient committed suicide, one patient was hospitalized for social reasons, one patient was hospitalized due to side-effects, one patient was hospitalized due to acute dystonia, one patient attempted suicide and one patient was diagnosed with cerebellar glioma. The remaining SAEs (n=4; 4%) occurred in the comorbidity groups; one hospitalization in the suicidality only group was due to psychotic exacerbation, two hospitalizations in the SUD only group were due to psychotic exacerbation and one severe epileptic seizure occurred in the suicidality and SUD group.