Generalizability of the Results of Efficacy Trials in First-Episode Schizophrenia: Comparisons Between Subgroups of Participants of the European First Episode Schizophrenia Trial (EUFEST)

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Objective: Most randomized drug trials in schizophrenia exclude patients with comorbidities such as suicidality or substance use, which may limit the generalizability of the results. We aimed to evaluate the generalizability of the results of these trials in participants of a randomized clinical trial with broad inclusion criteria.

Method: In 50 sites in 14 countries, 498 patients with first-episode psychosis (*DSM-IV* schizophrenia, schizoaffective disorder, or schizophreniform disorder) were recruited between December 2002 and January 2006 in an open, randomized clinical drug trial with 12 months of follow-up. Baseline characteristics and follow-up data were compared between patients with versus patients without baseline suicidality and/or substance use.

Results: Of the 489 participants with data on baseline suicidality and substance use, 153 (31%) patients were suicidal and/or using substances. Groups differed on only a few of the many baseline characteristics tested: comorbid patients were younger (25.1 vs 26.5 years of age; $P < .01$), less often female (25% vs 47%; $P < .001$) or married (4% vs 17%; $P < .001$), had fewer years of education (11.8 vs 12.8; $P < .001$), and experienced lower levels of overall psychosocial functioning (Global Assessment of Functioning; 38.4 vs 40.8; $P \leq .05$) and higher levels of depression (Calgary Depression Scale for Schizophrenia; 6.1 vs 4.6; $P < .001$). At follow-up, comorbid patients showed shorter time to (re)hospitalization and reported higher levels of depression than patients without comorbidity (hazard ratio = 2.02, $P = .004$; $\chi^2_7 = 17.25$, $P = .016$, respectively), without differences on other outcome measures.

Conclusions: Although it appears that the generalizability of antipsychotic treatment trials in first-episode patients is not seriously affected by the exclusion of patients with suicidal symptoms and/or substance use, researchers should be cautious about the exclusion of such patients.

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Most randomized clinical trials studying the efficacy of antipsychotics in schizophrenia exclude patients with certain comorbidities, although, for instance, drug abuse/dependence and suicidality are frequent complicating features of the disorder.[1] However, such decisions may compromise the generalizability of the results of these trials. Indeed, the European First Episode Schizophrenia Trial (EUFEST) included patients with these features in an international, open-treatment, randomized clinical trial with 12 months' follow-up to enhance generalizability of its results. That study compared the effectiveness of a low dose of haloperidol versus standard doses of amisulpride, olanzapine, quetiapine, or ziprasidone in first-episode patients with schizophrenia over a 1-year period.[2,3]

In this article, we report on the influence of comorbid characteristics, specifically suicidality and substance use, of the patients in EUFEST on baseline characteristics and the main outcome measures in that study. We were particularly interested in these 2 comorbidities, since patients with these features are among the most frequently excluded patients.[4,5] Therefore, baseline demographic and clinical characteristics—such as age and psychopathology—of EUFEST patients were compared between subgroups: patients with current suicidality and/or current substance use versus patients with neither current suicidality nor current substance use. Additionally, follow-up data—like treatment discontinuation and study dropout—were compared between these subgroups.

METHOD

Setting and Participants

The design of the study has been published previously[2,3] in more detail but will be described here briefly. A total of 50 sites in 13 European countries and Israel participated. Patients were assessed for eligibility between

December 2002 and January 2006. Eligible patients were 18–40 years of age and met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*)[6] criteria for schizophrenia schizophreniform disorder or schizoaffective disorder confirmed by the Mini International Neuropsychiatric Interview Plus (MINI+).[6] Patients were excluded if (1) more than 2 years had elapsed between onset of positive symptoms and recruitment, (2) any antipsychotic had been used for longer than 2 weeks in the previous year or 6 weeks lifetime, (3) patients had a known intolerance to one of the study drugs, or (4) patients met any of the contraindications for any of the study drugs as mentioned in the (local) package insert texts.

Recruitment and Baseline Assessment

The investigators informed eligible patients orally and in writing about the trial and invited them to participate. Baseline data were obtained between 4 weeks before to 1 week after randomization on demographics; diagnoses (MINI+; including current *suicidality*—ie, medium to high suicide risk in the past month, which includes suicidal thoughts, plans, and attempts—and current *substance use disorder,* ie, substance or alcohol abuse/dependence in the previous year)[7]; current treatment setting, psychopathology with the Positive and Negative Syndrome Scale (PANSS)[8]; severity of illness with the Clinical Global Impressions scale (CGI)[9]; overall psychosocial functioning with the Global Assessment of Functioning scale (GAF)[10]; depression with the Calgary Depression Scale for Schizophrenia (CDSS)[11]; quality of life with the Manchester Short Assessment of Quality of Life Scale (MANSA)[12]; extrapyramidal syndromes with the St Hans Rating Scale (SHRS)[13]; sexual dysfunction with selected items of the Udvalg for Kliniske Undersøgelser (UKU)[14]; clinical and social needs with the Camberwell Assessment of Need (CAN)[15]; and adherence to antipsychotics.[16] All participants or their legal representative provided written informed consent after the procedure, and possible side effects were fully explained. The trial complied with the Declaration of Helsinki and was approved by the ethics committees of the participating centers. The Julius Centre for Health Sciences and Primary Care (Utrecht, The Netherlands) monitored the trial according to Good Clinical Practice and International Conference on Harmonization guidelines.

Outcome Assessment

Follow-up outcomes comprised treatment discontinuation, (re)hospitalization, premature study discontinuation, psychopathology (PANSS), psychosocial functioning (GAF), and depression (CDSS). Data collection was targeted at 1, 2 (with the exception of the PANSS and CDSS), 3, 6, 9 (with the exception of the CDSS), and 12 months.

Data Analysis

Patients' demographic and clinical characteristics were expressed in descriptive statistics for the following (sub) groups: (1) neither suicidality nor substance use (*noncomorbid patients*), (2) suicidality and/or substance use (*comorbid patients*), (3) suicidality only, (4) substance use only, and (5) suicidality and substance use, according to the MINI+[6] (for definitions of suicidality and substance use, see section "Recruitment and Baseline Assessment").

In addition to the primary analyses on comparisons between noncomorbid patients versus comorbid patients, we performed secondary analyses on the differences between noncomorbid patients versus (1) patients with suicidality only and versus (2) patients with substance use only. To compare baseline data between subgroups, we used the χ^2 test for categorical data and the 2-sample *t* test or the Mann-Whitney *U* test, when appropriate. Kaplan-Meier curves were used to estimate the probability of treatment discontinuation, (re)hospitalization, and study dropout within 12 months. Cox proportional hazards regression analysis was used to estimate differences between subgroups of treatment discontinuation, (re)hospitalization, and study dropout probabilities, adjusted for baseline variables that showed statistically significant differences between subgroups. Countries with 15 or fewer patients were clustered to prevent unstable estimates. Differences were expressed in hazard ratios (HRs), with corresponding 95% confidence intervals. Latent growth curve analyses (LCGs)[17] were performed to study the development of psychopathology (PANSS total score), psychosocial functioning (GAF scale), and depression (CDSS) over time. LCG analysis provides a statistical model for the individual growth curves based on 2 latent factors, an initial level and a growth rate. These factors are allowed to vary across subjects. Differences between the noncomorbid and the comorbid subgroups were studied by equating the means and variances of the 2 latent factors, adjusted for baseline variables that showed statistically significant differences between the subgroups. We did not adjust for the GAF baseline score in the statistical analyses of the longitudinal PANSS total scores, since PANSS and GAF scores were substantially correlated. To address whether the results on the comparisons between comorbid and noncomorbid patients depend on the antipsychotic that was prescribed, we performed post hoc subgroup analyses to compare outcomes between patients randomly assigned to a low dose of haloperidol or a standard dose of a second-generation antipsychotic (SGA; amisulpride, olanzapine, quetiapine, or ziprasidone).[2,3] Data obtained after treatment discontinuation were excluded. As this procedure resulted in lower numbers of patients assessed at follow-up visits, we applied a last-observation-carried-forward method, ie, missing observations were substituted with the last observation to compare PANSS, GAF, and CDSS scores assessed at 12 months with analysis of variance.

Mx software (Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia) was used to analyze psychopathology (PANSS), psychosocial functioning (GAF), and depression (CDSS) follow-up data, and

SPSS version 12.0 (SPSS Inc, Chicago, Illinois) was used for analyses of other data. We used a significance level of .05 (2-tailed) for all tests.

Role of Funding Sources

This study was funded by the European Group for Research in Schizophrenia with grants from 3 pharmaceutical companies. The companies had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the article for publication.[2]

RESULTS

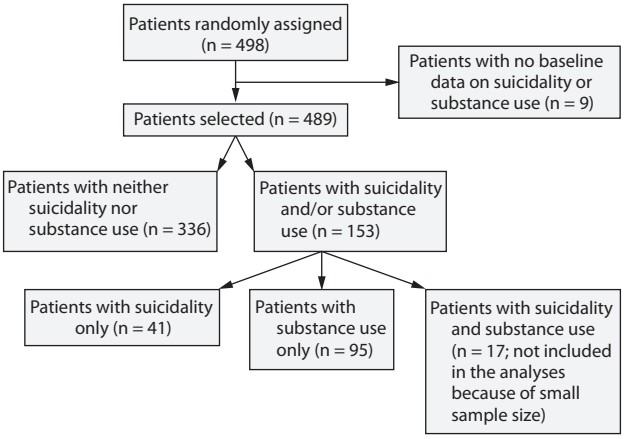
We randomly assigned 498 patients in the main trial, of whom 489 patients (98%) had baseline data on suicidality and substance use (Figure 1). Of the 489 selected participants, 336 patients (69%) were neither suicidal nor using substances. One hundred fifty-three patients (31%) were suicidal and/or using substances, of whom 41 patients (27%) were suicidal only, 95 patients (62%) were using substances only, and 17 patients (11%) were both suicidal and using substances. The last group of 17 patients is very small and was therefore excluded from the baseline and outcome comparisons with the patients who were neither suicidal nor using substances.

Comparisons Between Baseline Demographic Characteristics

Comparisons of demographic characteristics between noncomorbid (neither suicidality nor substance use) versus comorbid subgroups (suicidality and/or substance use) demonstrated that noncomorbid patients were older (26.5 vs 25.1 years of age; $P < .01$; Table 1) and had more years of education (12.8 vs 11.8; $t = 3.44$; $P < .001$). Furthermore, this noncomorbid subgroup comprised higher proportions of patients who were married (17% vs 4%; $\chi^2_1 = 15.93$; $P < .001$) and a lower percentage of men (53% vs 75%; $\chi^2_1 = 21.01$; $P < .001$). Also the proportions of comorbid versus noncomorbid patients differed between countries ($\chi^2_{11} = 72.08$; $P < .001$). Since the differences in age between subgroups might explain the distinctions in years of education and the proportions being married, we studied these associations. The analyses showed that age did not correlate significantly with years of education (Pearson correlation = 0.056; $P = .22$) but that married patients were older (25.3 vs 30.7 years of age; $P < .001$).

In secondary analyses, we compared noncomorbid patients versus (1) patients with suicidality only and versus (2) patients with substance use only. Noncomorbid patients did not differ statistically significantly on baseline characteristics from patients with suicidality only, except that noncomorbid patients were less likely to be employed (49% vs 66%; $\chi^2_1 = 4.25$; $P \leq .05$). However, compared to patients with substance use only, noncomorbid patients were older (26.5 vs 24.6 years of age; $P < .01$), had more years of education (12.8 vs 11.6; $t = 3.35$; $P < .001$), were less likely to be male (53% vs 86%; $\chi^2_1 = 33.85$; $P < .001$), and were more likely to be married (17% vs 1%; $\chi^2_1 = 16.10$; $P < .001$) and employed (49% vs 31%; $\chi^2_1 = 10.01$; $P < .01$). Finally the proportions of patients with substance use only versus noncomorbid patients differed between countries ($\chi^2_{11} = 87.57$; $P < .001$).

Figure 1: Distribution of First-Episode Schizophrenia Patients According to Comorbidity in EUFEST



Abbreviation: EUFEST = European First Episode Schizophrenia Trial.

Comparisons Between Baseline Clinical Characteristics, Needs, and Adherence

Comparisons of patient clinical characteristics, needs, and adherence between noncomorbid versus comorbid patients (Table 2) showed that groups differed on overall psychosocial functioning and depression: ie, noncomorbid patients evidenced higher levels of overall functioning on the GAF (40.8 vs 38.4; $P \leq .05$) and lower levels of depression on the CDSS (4.6 vs 6.1; $P < .001$). The difference on depression can be explained by the lower level of depression found in noncomorbid patients versus patients with suicidality only (4.6 vs 8.4; $P < .001$). Noncomorbid patients did not differ with suicidal patients on the other patient characteristics, except that noncomorbid patients demonstrated lower levels of adherence to antipsychotics (5.5 vs 5.9; $P \leq .05$). Finally, none of the patient characteristics showed statistically significant differences between noncomorbid patients versus patients with substance use only.

Comparisons Between Patient Follow-Up Data

Table 3 shows that all-cause treatment discontinuation and study dropout did not differ between comorbid versus noncomorbid patients. However, compared with noncomorbid patients, time to (re)hospitalization was significantly shorter for comorbid patients (hazard ratio [HR] = 2.01; 95% CI, 1.24–3.26; $P = .004$; Figure 2A) and for patients with suicidality only (HR = 2.99; 95% CI, 1.60–5.59; $P = .001$;

Table 1. Comparisons of Demographic Characteristics Between Comorbid and Noncomorbid Patient Groups in EUFEST[a]

		Comorbid Patients			
			Subgroups Distinguished by Comorbidity		
Variable	Neither Suicidality nor Substance Use (n = 336)	Suicidality and/or Substance Use (n = 153)	Suicidality Only (n = 41)	Substance Use Only (n = 95)	Suicidality and Substance Use (n = 17)[b]
Age, mean (SD), y	26.5 (5.6)	25.1 (5.4)**	25.5 (6.0)	24.6 (5.2)**	27.0 (5.0)
Men, n/n (%)	179/336 (53%)	115/153 (75%)***	20/41 (49)	82/95 (86)***	13/17 (76)
White, n/n (%)	318/336 (95%)	142/153 (93%)	39/41 (95)	86/95 (91)	17/17 (100)
Married at present, n/n (%)	57/336 (17)	6/153 (4%)***	4/41 (10)	1/95 (1)***	1/17 (6)
Living alone, n/n (%)	43/333 (13)	22/153 (14)	3/41 (7)	15/95 (16)	4/17 (24)
Living environment, n/n (%)[c]					
City > 500,000	97/139 (70)	42/139 (30)	11/42 (26)	24/42 (57)	7/42 (17)
City 100,000–500,000	93/131 (71)	38/131 (29)	8/38 (21)	26/38 (68)	4/38 (11)
City 10,000–100,000	75/120 (63)	45/120 (38)	14/45 (31)	27/45 (60)	4/45 (9)
Village/rural < 10,000	69/97 (71)	28/97 (29)	8/28 (29)	18/28 (64)	2/28 (7)
Education, mean (SD), y[d]	12.8 (3.0)	11.8 (2.6)***	12.5 (2.3)	11.6 (2.6)***	11.1 (2)
Employed, homemaker, or student, n/n (%)	164/336 (49)	63/153 (41)	27/41 (66)*	29/95 (31)**	7/17 (41)
Countries, n/n (%)[e]		***		***	
Austria	11/26 (42)	15/26 (58)	1/15 (7)	11/15 (73)	3/15 (20)
Bulgaria	13/17 (76)	4/17 (24)	1/4 (25)	3/4 (75)	0/4 (0)
Czech Republic	23/32 (72)	9/32 (28)	4/9 (44)	5/9 (56)	0/9 (0)
France	9/24 (38)	15/24 (63)	2/15 (13)	12/15 (80)	1/15 (7)
Germany	5/16 (31)	11/16 (69)	0/11 (0)	10/11 (91)	1/11 (9)
Israel	36/61 (59)	25/61 (41)	8/25 (32)	13/25 (52)	4/25 (16)
Italy	29/41 (71)	12/41 (29)	2/12 (17)	9/12 (75)	1/12 (8)
Netherlands	10/23 (43)	13/23 (57)	2/13 (15)	10/13 (77)	1/13 (8)
Poland	72/93 (77)	21/93 (23)	8/21 (38)	9/21 (43)	4/21 (19)
Romania	103/113 (91%)	10/113 (9)	9/10 (90)	1/10 (10)	0/10 (0)
Spain	11/20 (55)	9/20 (45)	2/9 (22)	6/9 (67)	1/9 (11)
Belgium, Sweden, and Switzerland	14/23 (61)	9/23 (39)	2/9 (22)	6/9 (67)	1/9 (11)

[a]Denominators fluctuate due to incomplete data. Because of rounding, proportions may not sum up to 100.
[b]Because of the small sample size this subgroup was not included in analyses on comparisons with patients who were neither suicidal nor using substances.
[c]A χ^2 test of living environment (4 levels) by group was performed.
[d]Years in school from 6 years of age onward.
[e]A χ^2 test of country (12 levels) by group was performed.
*$P < .05$.
**$P < .01$.
***$P < .001$. (P values refer to comparisons with patients who were neither suicidal nor using substances.)
Abbreviation: EUFEST = European First Episode Schizophrenia Trial.

Figure 2B). No differences were found between comorbid versus noncomorbid subgroups on psychopathology (PANSS total; $\chi^2_8 = 12.50$; $P = .130$) and overall psychosocial functioning (GAF; $\chi^2_9 = 9.87$; $P = .361$), although the level of depression was significantly higher in comorbid than in noncomorbid patients (CDSS; $\chi^2_7 = 17.25$; $P = .016$; Figure 3). Due to small sample sizes, we could not compare noncomorbid patients versus patients with suicidality only or substance use only.

Subgroup Analyses

Subgroup analyses by treatment (ie, haloperidol or one of the SGAs) did not show statistically significant differences on (re)hospitalization, psychopathology (PANSS total score), psychosocial functioning (GAF score), and depression (CDSS score). However, a significant interaction between drugs and comorbidity status was found for treatment and study discontinuation. In patients taking an SGA, noncomorbid patients had lower treatment and study discontinuation rates than comorbid patients (HR = 0.51; 95% CI, 0.270.97; $P = .04$) while such a difference was not found in patients taking haloperidol.

DISCUSSION

This study in a large sample of first-episode schizophrenia patients with broad inclusion criteria found that a substantial proportion of patients (31%) were suicidal or using substances during the first stages of their illness. These patients would not have been enrolled in most efficacy trials. Baseline comparisons between noncomorbid versus comorbid patients demonstrated several differences: patients with suicidality and/or substance use were younger, more likely to be male, less likely to be married, had fewer years of education, showed lower overall psychosocial functioning, and experienced higher levels of depression. Secondary analyses showed that most differences found were explained by substance use but not suicidality. During the 12 months' follow-up of the study, comorbid patients had a shorter time to (re)hospitalization and demonstrated higher levels of depression as compared to noncomorbid patients but did not differ statistically significantly on treatment discontinuation, study dropout, psychopathology, or overall psychosocial functioning. Post hoc subgroup

Table 2. Comparisons of Clinical Characteristics, Needs, and Adherence Between Comorbid and Noncomorbid Patient Groups in EUFEST[a]

		Comorbid Patients			
			Subgroups Distinguished by Comorbidity		
Variable	Neither Suicidality nor Substance Use (n = 336)	Suicidality and/or Substance Use (n = 153)	Suicidality Only (n = 41)	Substance Use Only (n = 95)	Suicidality and Substance Use (n = 17)[b]
Diagnosis, n/n (%)					
Schizophreniform disorder	133/196 (68)	63/196 (32)	19/63 (30)	41/63 (65)	3/63 (5)
Schizoaffective disorder	25/34 (74)	9/34 (26)	4/9 (44)	3/9 (33)	2/9 (22)
Schizophrenia	178/259 (69)	81/259 (31)	18/81 (22)	51/81 (63)	12/81 (15)
Inpatient, n/n (%)	294/336 (88)	142/153 (93)	40/41 (98)	86/95 (91)	16/17 (94)
Antipsychotic naive, n/n (%)	108/336 (32)	52/153 (34)	14/41 (34)	33/95 (35)	5/17 (29)
CGI score (severity of illness), mean (SD)[c]	4.8 (0.8)	4.9 (0.8)	5.0 (0.8)	4.9 (0.8)	4.8 (0.8)
GAF score (overall functioning), mean (SD)[d]	40.8 (13.0)	38.4 (14.5)*	37.8 (17.3)	38.2 (13.2)	41.0 (14.2)
PANSS score (psychopathology), mean (SD)[e]					
Total	88.4 (21.0)	89.0 (20.0)	90.1 (20.2)	88.9 (20.2)	87.1 (19.3)
Positive scale	23.1 (6.3)	23.2 (6.0)	22.2 (5.8)	23.7 (6.0)	22.7 (6.9)
Negative scale	21.3 (7.6)	21.0 (7.7)	21.3 (8.0)	20.8 (7.5)	21.0 (8.3)
General psychopathology scale	43.9 (11.0)	44.7 (10.2)	46.5 (9.8)	44.2 (10.4)	43.4 (9.9)
CDSS score (depression), mean (SD)[f]	4.6 (4.8)	6.1 (4.9)***	8.4 (5.0)***	4.8 (4.3)	8.3 (5.2)
MANSA score (quality of life), mean (SD)[g]	4.0 (0.9)	4.1 (0.9)	4.0 (0.9)	4.1 (0.9)	4.1 (0.8)
SHRS category (extrapyramidal syndromes), n/n (%)					
Akathisia	29/335 (9)	20/153 (13)	6/41 (15)	10/95 (11)	4/17 (24)
Dystonia	6/335 (2)	3/153 (2)	1/41 (2)	2/95 (2)	0/17 (0)
Parkinsonism	36/335 (11)	17/153 (11)	5/41 (12)	8/95 (8)	4/17 (24)
Dyskinesia	2/335 (1)	1/153 (1)	1/41 (2)	0/95 (0)	0/17 (0)
UKU scale (sexual dysfunction), n/n (%)[h]					
Male	46/176 (26)	26/115 (23)	4/20 (20)	16/82 (20)	6/13 (46)
Female	34/151 (23)	13/38 (34)	5/21 (24)	4/13 (31)	4/4 (100)
CAN score (number of needs), mean (SD)[i]					
No serious needs	17.1 (3.8)	17.3 (2.9)	17.7 (2.8)	17.3 (2.9)	16.5 (3.1)
Met or partially met needs	2.7 (2.8)	2.3 (1.8)	2.0 (1.8)	2.4 (1.9)	2.4 (1.7)
Serious unmet needs	2.0 (2.1)	2.2 (2.0)	2.1 (2.0)	2.0 (1.9)	2.9 (2.2)
Antipsychotic adherence, mean (SD)[j]	5.5 (1.2)	5.7 (1.2)	5.9 (0.9)*	5.4 (1.3)	6.3 (1.1)

[a]Denominators fluctuate due to incomplete data. Because of rounding, proportions may not sum up to 100.
[b]Because of the small sample size, this subgroup was not included in analyses on comparisons with patients who were neither suicidal nor using substances.
[c]Theoretical scores range from 1 to 7; higher scores indicate greater severity of illness.
[d]Theoretical scores range from 1 to 100; higher scores indicate better functioning.
[e]Theoretical scores of the total scale range from 30–210, positive scale: from 749, negative scale: from 749, and general psychopathology scale: from 16–112; higher scores indicate more severe psychopathology.
[f]Theoretical scores range from 0–27; higher scores indicate more depression.
[g]Theoretical scores range from 1–7; higher scores indicate better quality of life.
[h]Cases scored moderate/severe on at least one of the following outcomes. Males: increased/decreased libido, orgastic dysfunction, gynaecomastia, and erectile/ejaculatory dysfunction (6 items). Females: increased/decreased libido, orgastic dysfunction, menorrhagia, amenorrhea, galactorrhoea, and dry vagina (7 items).
[i]Comprising 22 domains: accommodation, food, looking after the home, self-care, physical health, psychological distress, psychotic symptoms, information about condition and treatment, daytime activities, company, safety to self, safety to others, alcohol, drugs, intimate relationships, sexual expression, basic education, child care, transport, using a telephone, money, and welfare benefits.
[j]Assessed by the investigator at 4 weeks after randomization; theoretical scores range from 1 to 7; higher scores indicate better adherence.
*$P < .05$.
**$P < .01$.
***$P < .001$. (P values refer to comparisons with patients who were neither suicidal nor using substances.)
Abbreviations: CAN = Camberwell Assessment of Need, CDSS = Calgary Depression Scale for Schizophrenia, CGI = Clinical Global Impressions scale, EUFEST = European First Episode Schizophrenia Trial, GAF = Global Assessment of Functioning scale, MANSA = Manchester Short Assessment of Quality of Life scale, PANSS = Positive and Negative Syndrome Scale, SHRS = St Hans Rating Scale, UKU = Udvalg for Kliniske Undersøgelser.

analyses showed that noncomorbid patients taking an SGA had lower treatment discontinuation and study dropout rates as compared to comorbid patients taking an SGA, while the comorbid and noncomorbid groups did not differ in patients taking haloperidol.

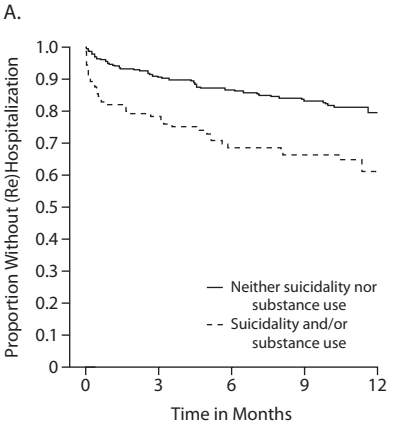
We compared the results of our study with previous studies in first-episode psychosis using comparable criteria for current suicidality and current substance use (*DSM-III* or *DSM-IV* criteria). Twelve percent of the patients in the present study were suicidal with or without substance use, which is a considerably lower proportion as compared to the 26% and 42% of the patients in a previous randomized clinical trial and a cohort study, respectively.[18,19] Our results on comparisons between noncomorbid patients versus patients with suicidality only are consistent with those of the cohort study reporting that suicidality was associated with depressive symptoms but not with age, sex, or positive or negative symptoms.[18] The small number of participants

Table 3. Comparisons of All-Cause Treatment Discontinuation, (Re)Hospitalization, and Lost to Follow-Up Between Patient Subgroups in EUFEST

Variable	Neither Suicidality nor Substance Use	Comorbid Patients		
		Suicidality and/or Substance Use	Subgroups Distinguished by Comorbidity	
			Suicidality Only	Substance Use Only
All-cause treatment discontinuation, d/n, KM estimates	127/336 (44)	80/153 (60)	24/41 (67)	51/95 (60)
Cox model treatment comparisons (HR [95% CI])[a]				
Neither suicidality nor substance use		1.09 (0.79–1.51)	1.41 (0.89–2.24)	1.03 (0.70–1.51)
P value		0.61	0.14	0.90
(Re)hospitalization, d/n, KM estimates	50/322 (21)	44/145 (39)	15/40 (51)	23/89 (33)
Cox model treatment comparisons (HR [95% CI])[a]				
Neither suicidality nor substance use		2.01 (1.24–3.26)	2.99 (1.60–5.59)	1.46 (0.80–2.66)
P value		0.004	0.001	0.22
Lost to follow-up, d/n, KM estimates	95/336 (28)	51/153 (33)	11/41 (28)	35/95 (37)
Cox model treatment comparisons (HR [95% CI])[a]				
Neither suicidality nor substance use		0.82 (0.55–1.22)	1.09 (0.56–2.10)	0.77 (0.49–1.22)
P value		0.33	0.80	0.26

[a]Cox proportional hazards regression models with hazard ratios and corresponding 95% confidence intervals; with adjustments for baseline differences: sex, married at present, country, and standardized scores for age, years of education, GAF, and CDSS.
Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, d = number of events, EUFEST = European First Episode Schizophrenia Trial, GAF = Global Assessment of Functioning scale, HR = hazard ratio, KM = Kaplan-Meier, n = number of patients at risk.

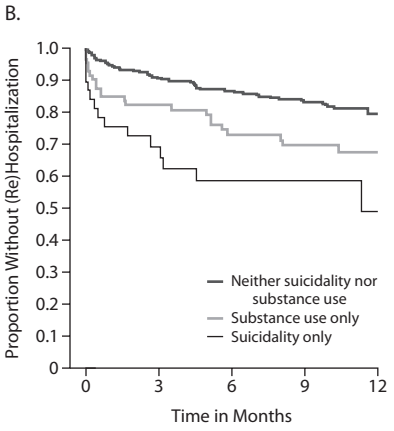
Figure 2A: Time to (Re)Hospitalization for First-Episode Schizophrenia Patients With Neither Suicidality nor Substance Use and Patients With Suicidality and/or Substance Use in EUFEST[a,b]



Patients at risk					
Neither suicidality nor substance use	322	235	210	189	28
Suicidality and/or substance use	145	84	67	56	11

[a]Patients at risk are observed at baseline, 3, 6, 9, and 12 months.
[b]Twenty-two patients had data regarding hospitalization missing and were not included in the analysis.
Abbreviation: EUFEST = European First Episode Schizophrenia Trial.

Figure 2B: Time to (Re)Hospitalization for First-Episode Schizophrenia Patients With Neither Suicidality nor Substance Use, Patients With Suicidality Only, and Patients With Substance Use Only in EUFEST[a,b]



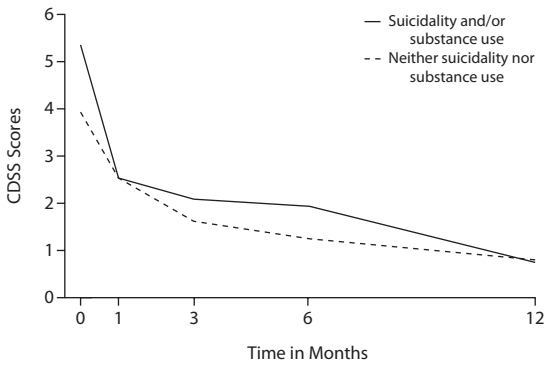
Patients at risk					
Neither suicidality nor substance use	322	235	210	189	28
Substance use only	89	57	46	39	6
Suicidality only	40	20	16	13	3

[a]Patients at risk are observed at baseline, 3, 6, 9, and 12 months.
[b]Twenty-two patients had data regarding hospitalization missing and were not included in the analysis; the group of 17 patients who were using drugs and suicidal was too small to analyze. One patient belonged to both groups.
Abbreviation: EUFEST = European First Episode Schizophrenia Trial.

with suicidality only might explain why no more baseline differences between subgroups were found. We are not aware of any longitudinal studies that compared (1-year) outcome between noncomorbid patients versus patients with suicidality only.

Twenty-three percent of the patients were diagnosed with current substance use disorder, which is within the range of 13%–70% found in early psychosis cohort studies on current substance use.[20–27] Two of these studies compared baseline characteristics between patients with versus patients without substance use and also reported that patients with substance use were younger and more likely to be male.[22,23] Three longitudinal studies compared patient outcomes between patients without versus patients

Figure 3: Depression Scores in First-Episode Schizophrenia Patients With Neither Suicidality nor Substance Use and Patients With Suicidality and/or Substance Use, During 12 Months of Follow Up in EUFEST



Abbreviations: CDSS = Calgary Depression Scale for Schizophrenia, EUFEST = European First Episode Schizophrenia Trial.

with current substance use. Our finding that patients with substance use have a shorter time to (re)hospitalization is consistent with those of 2 studies finding that substance use (cannabis) shortened the time to and increased the risk of psychotic relapse.[22,27] Furthermore, the lack of significant differences in the present study on other follow-up data is in agreement with the results of 2 earlier studies failing to find differences on negative symptoms, affective symptoms, and remission between these subgroups of patients.[21,22]

Several factors may explain why we recruited lower proportions of suicidal or substance-using patients as compared to the above-mentioned studies, which were almost all cohort studies (ie, not randomized clinical trials). Possibly, patients who are suicidal or using substances are less willing to participate in a randomized clinical trial. Furthermore, substance use could have been underreported in our study, since we did not include confirmation by laboratory tests.

A limitation of the current study is that, although we aimed to recruit an unselected sample of first-episode patients, some patients declined to participate because of more severe psychopathology or the randomization procedure, for example.

We conclude that excluding first-episode schizophrenia patients who use substances or show symptoms of suicidality in antipsychotic treatment trials results in the exclusion of substantial proportions of patients. Our results in first-episode schizophrenia suggest that excluding these patients might not severely limit the generalizability of the results of such studies: the patients who would have been excluded in most studies did not differ on many baseline characteristics nor did they vary in their subsequent course of illness or participation in the study. However, the level of depression was higher in comorbid patients; (re)hospitalization rates were higher in patients with suicidality; and post hoc subgroup analyses showed that the effect of comorbidity on study and treatment discontinuation may depend on the drug prescribed. Although it appears that the generalizability of antipsychotic treatment trials in first-episode patients is not seriously affected by the exclusion of patients with suicidal symptoms and/or substance use, researchers should be cautious about the exclusion of such patients.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon).

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Author contributions: **Drs Kahn** and **Fleischhacker** obtained funding and supervised the EUFEST study. **Drs Boter** and **Derks** analyzed the data. **Drs Boter**, **Derks**, and **Kahn** interpreted the data, and **Drs Boter** and **Derks** drafted the manuscript. All authors participated in the critical revision of the manuscript and approved the final report.

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