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Remission in schizophrenia — What are we measuring? Comparing the consensus remission criteria to a CGI-based definition of remission and to remission in major depression

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ABSTRACT

Background: Despite being recommended for use in clinical trials, the consensus remission criteria were found to leave patients with persisting symptoms, relevant areas of functional impairment and a decreased sense of wellbeing. Therefore, to evaluate the appropriateness of the schizophrenia consensus criteria, a definition of remission based on the Clinical Global Impression Scale (CGI) was developed and remitter subgroups were compared.

Methods: 239 patients with a schizophrenia spectrum disorder were evaluated regarding their remission status after inpatient treatment. Remission in schizophrenia was defined according to the symptom-severity component of the consensus criteria by Andreasen et al. and a CGI based definition was calculated using sensitivity and specificity using receiver operating curves (asymptomatic remitter). Both remitter groups (schizophrenia consensus versus asymptomatic remitters) were compared regarding different clinical variables at discharge as well as the likelihood to relapse within a 1-year follow-up period. Both schizophrenia remitter subgroups were compared to remitters in major depression as a reference value.

Results: Following the consensus criteria, 63% of the schizophrenia patients were in remission compared to only 18% following the asymptomatic criterion. The schizophrenia consensus remitters were less likely to be

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concurrent treatment responders ($p < 0.0001$), had a significantly greater illness severity ($p < 0.0001$) and less functioning ($p = 0.0358$) as well as a significantly greater risk to relapse ($p = 0.0174$) compared to the schizophrenia asymptomatic remitters as well as the depressed remitters.
Conclusion: It should be critically re-evaluated if the currently proposed consensus criteria are adequate to measure what is traditionally understood to be remission.

1. Introduction

In schizophrenia research a consensus definition of remission was proposed in 2005 incorporating a symptom-based and a time criterion defining remission in schizophrenia as a level of mild or less illness severity in eight core symptoms held for at least six months (Andreasen et al., 2005). These criteria were found to be valid and are recommended for use in clinical trials (Leucht, 2014; Heering et al., 2015). Besides, Gorwood et al. found the number of manuscripts mentioning remission without documenting specific criteria dropping down by approximately 50% since the implementation of the consensus criteria improving outcome research (Gorwood and Peuskens, 2012). Despite these achievements there have also been critical comments on the consensus criteria still allowing mild symptoms in remitted patients (Schennach-Wolff et al., 2010). Karow et al. reported, for example, that of 131 schizophrenia patients fulfilling the symptom-severity component of the consensus criteria only 39% of these patients judged themselves as remitted, whereas 61% were judged so by the psychiatrist (Karow et al., 2012). Also, when evaluating 112 schizophrenic or schizoaffective outpatients Pinna et al. found that patients in whom clinical remission was confirmed persisting symptoms, relevant areas of functional impairment and a decreased sense of wellbeing could still be observed (Pinna et al., 2013).

Such critical results suggest that schizophrenia consensus remitters might not be "true" remitters questioning the appropriateness to draw any conclusions in terms of the further course of the illness for these patients. In a previous analysis of this patient sample Spellmann et al. examined the validity of remission and recovery criteria in schizophrenia and major depression, yet without challenging the current definition of remission in schizophrenia (Spellmann et al., 2017).

Therefore, aims of this study were (I) to evaluate remission in schizophrenia following the consensus remission criteria and (II) to develop a definition of remission in schizophrenia mirroring "true" remission and (III) to compare the consensus remitters to the "true/asymptomatic" remitters and to patients achieving remission suffering from a different psychiatric disorder as potential reference value.

2. Methods

2.1. Subjects

Data were collected in two multicenter naturalistic follow-up programmes by the German Research Network on Schizophrenia (Wolwer et al., 2003) and the German Research Network on Depression (Seemuller et al., 2010) with the inclusion criteria of an age between 18 and 65 and a signed written informed consent. The study protocols were approved by the local ethics committees (Jager et al., 2007).

Diagnoses were established by clinical researchers following ICD-10 criteria interviewing the patients within the first days of their hospitalization. Patients with the diagnosis of schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder as well as any major depressive episode or for a depressive disorder not otherwise specified were eligible for study inclusion. Exclusion criteria were a head injury, a history of major medical illness and alcohol or drug dependency. Within the follow-up programmes, subjects with one of the above mentioned diagnosis were then randomly selected using a randomization software (Jager et al., 2008; Seemuller et al., 2010).

2.2. Assessments

Sociodemographic and course-related variables such as age at onset or episodes of illness were collected using a standardized documentation system (Cording, 1998) during interviews with patients, relatives and care providers. To assess symptom severity the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1988) was used in the schizophrenia patients, and the Hamilton Depression Rating Scale, 17-item version, for the depressed patients (Hamilton, 1960). As an external criterion for overall illness severity the Clinical Global Impression Severity Scale (CGI-S) was applied (Guy, 1976). The patient's global functioning was evaluated applying the Global Assessment of Functioning Scale (GAF) (American Psychiatric Association, 1994). Ratings were assessed by trained clinicians at baseline and subsequently every two weeks until discharge and at the one-year follow-up. All raters had been trained using the applied scales. A high inter-rater reliability was achieved (ANOVA-ICC > 0.8).

2.3. Statistical analysis

Aim was to evaluate remission in schizophrenia patients using the consensus criteria for remission and to develop a definition of remission mirroring a state of being asymptomatic/"normal". Patients achieving the consensus remission criteria and the asymptomatic criterion where then compared regarding sociodemographic and clinical variables. In a third step, we compared both schizophrenia remitter subgroups to patients achieving remission suffering from major depression as a potential reference value.

The definitions for remission were as follows:

1. The consensus remission criteria in schizophrenia

The consensus criteria by Andreasen et al. (3) were applied in the schizophrenia patients defining remission as a PANSS score of three or less of the following items: delusions (P1), unusual thought contents (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerism/posturing (G5), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6). Results of the acute inpatient treatment phase refer to remission only by applying the symptom-severity component, the time component was considered at the one-year follow-up assessment.

2. Defining asymptomatic remission in schizophrenia

Defining remission in schizophrenia following the definition of remission in other psychiatric disorders is hampered by the fact that until today no PANSS ratings are available in healthy controls. Therefore, we followed a previous analysis of our working group finding that remission (as a state of being asymptomatic/with only minimal symptoms) is mirrored by having an overall CGI-S of 1 (normal) (Riedel et al., 2010). This CGI based definition for remission in schizophrenia was then calculated using sensitivity and specificity for each PANSS value using receiver operating curves (ROC). The optimal cut-off values were found with the unweighted addition of sensitivity and specificity. Confidence intervals were calculated covering the optimal cut-off values using non-parametric bootstrap samples. Therefore, the cut-

offs' variances were estimated using 10,000 resamples of the original data by random sampling with replacement.

3. Remission in major depression

In the depressed patients remission was defined as a HAMD-17 total score ≤ 7 (Frank et al., 1991).

The three remitter subgroups (schizophrenia consensus remitters, schizophrenia asymptomatic remitters, depressed remitters) were compared regarding the overlap in terms of concurrent treatment response (defined as a 50% improvement from baseline to discharge) (Leucht et al., 2007b) with regard of the score correction proposed by Obermeier et al. (2010) for PANSS measures, the degree of illness severity in remission, the level of functioning as well as the association between remission and the risk to relapse after discharge from hospital using univariate tests (Fisher-Wilcoxon- and *t*-tests). Relapse was defined via two items from the above mentioned standardized documentation system following Schennach et al. (2012). The first item evaluates an acute exacerbation of the illness, and the second item explicitly examines rehospitalisation because of a worsened psychopathological condition. A positive rating for either item was defined as a relapse and was assessed retrospectively by a study clinician at the one year follow-up study examination interviewing the patient. All statistical analyses were performed using the statistical software environment R 2.11.1 (25).

2.4. Treatment

In brief, all patients were treated at the discretion of the psychiatrist in charge under consideration of the international clinical guidelines for the treatment of schizophrenia and depression (Bauer et al., 2007; Falkai et al., 2005), for further description see (Jager et al., 2008; Seemuller et al., 2010). During the study schizophrenia patients were treated under naturalistic conditions as follows (multiple answers possible): 81% of the patients received typical antipsychotic, 80% of patients atypical antipsychotic treatment and 65% of the patients were treated with typical well as atypical antipsychotics. Mean relative antipsychotic doses were estimated in the schizophrenia subgroup from Defined Daily Doses (DDD) (WHO Collaborating Centre for Drug Statistics Methodology, 2010). The DDD is defined as the average maintenance dose of the drug when used on its major indication in adults and was found to be 1.42 (±1.08).

Tranquilizers were administered in 79% of patients and mood stabilizers in 16%. A total of 27% of the patients were treated with antidepressants. The depressed patients received tricyclic antidepressants in 66%, selective-serotonin-reuptake-inhibitors in 49% and monoamino-oxidase inhibitors in 8% of the cases. 37% of the patients were furthermore treated with lithium and mood stabilizers. 40% of the patients additionally received typical and 28% atypical antipsychotics and 73% of the patients also tranquilizers.

3. Results

3.1. Patients

3.1.1. Schizophrenia sample

Of the 474 patients enrolled 239 patients (128 male/111 female) were available for this analysis. 46 patients dropped out for different reasons in the beginning of the study, 28 were discharged from hospital within 7 days after admission. 161 patients dropped out until follow-up. Patients with/without a study drop-out are compared in Table 2.

The mean age was 35.84 years (±10.34), the mean duration of illness was 7.14 years (±8.92) and the mean duration of the current hospitalization was 63.26 days (±49.11). 32% of these patients suffered from their first illness episode with a mean age at onset of 28.17 (±9.51) years. At admission, 18% of the patients suffered from suicidality. The mean PANSS total score at admission was 69.69 (±17.91), the mean CGI-S 5.4 (±0.84) and the mean GAF score 41 (±10.55) with a significant improvement in all scales resulting in a mean PANSS total score of 48.06 (±13.72), a mean CGI-S of 3.36 (±1.06) and a mean GAF score of 65.3 (±12.05) points at discharge.

3.1.2. Depression sample

Of the 1014 patients enrolled 529 patients (183 male/346 female) were available for this analysis. Patients with/without a study drop-out are compared in Table 2. The mean age was 45.61 years (±11.65), the mean duration of illness was 7.48 years (±9.58) and the mean duration of the current hospitalization 66 days (±46.77). 20% of these patients suffered from their first illness episode with a mean age at onset of 37.71 (±12.67) years. At admission, 43% of the patients suffered from suicidality. The mean HAMD total score at admission was 21.53 (±6.15), the mean CGI-S 5.19 (±0.69) and the mean GAF score 48.49 (±11.33) with a significant improvement in all scales resulting in a mean HAMD total score of 7.71 (±5.6), a mean CGI-S of 2.92 (±1.23) and a mean GAF score of 70.48 (±11.13) at discharge.

3.2. Assessments

3.2.1. Remission rates

3.2.1.1. Defining asymptomatic remission — a CGI based definition. ROC analysis identified a cut-off of ≤34 points in the PANSS total score when defining remission as a CGI score of 1. For sensitivity and specificity of the ROC analysis please see Table 1.

3.2.1.2. Schizophrenia sample. Following the consensus criteria 150 patients (63%) were identified to be in remission at discharge. Of the 150 schizophrenia consensus remitters 71% were still in remission 1 year after discharge. When applying the asymptomatic criterion 43 patients (18%) achieved remission at discharge and 50% of the asymptomatic discharge remitters were still in remission at follow-up.

3.2.1.3. Depression sample. In the patients suffering from depression 301 patients (57%) were remitters at discharge. 70% of the depressed remitters were also remitters at the time-point of follow-up.

The mean time of remission in both patient samples was 21.85 (± 26.88) days.

3.2.2. Comparing remitters/non-remitters at discharge

A comparison of the sociodemographic and clinical characteristics of the three remitter subgroups is shown in Table 3a. In order to analyse between group differences of the two schizophrenia remitter subgroups we had to exclude those patients achieving asymptomatic remission from the subgroup of the consensus remitters given that all 43 asymptomatic remitters achieved the consensus remission criteria at the same time, please see Table 3b.

3.2.2.1. Regarding response to antipsychotic treatment. Generally, the schizophrenia patient sample comprised 59% of responders at discharge. Schizophrenia consensus remitters also achieved the response

Table 1
ROC analyses for identifying the cut-off of the PANSS total score for the definition of remission based on the CGI.

	Value
Correlation CGI/PANSS at discharge	0.66
AUC of predicting CGI <2 by PANSS	0.96
Optimal PANSS cut-off for predicting CGI < 2	≤34
Bootstrap confidence interval of the cut-off	[30;34]
Sensitivity for the cut-off	1
Specificity for the cut-off	0.84

Table 2
Comparison of relevant sociodemographic and clinical variables between patients with/without a study drop-out.

	Schizophrenia patient sample			Depressed patient sample		
	Drop-out 40%	Included 60%	*p*-Value	Drop-out 48%	Included 52%	*p*-Value
Age (years)	34.91 (±11.99)	35.79 (±10.40)	0.261	44.64 (±12.26)	45.61 (±11.65)	0.157
Age at onset (years)	27.12 (±9.31)	28.18 (±9.51)	0.205	37.93 (±12.83)	37.71 (±12.67)	0.871
Duration of illness (years)	7.09 (±9.35)	7.08 (±8.91)	0.987	6.17 (±8.62)	7.48 (±9.58)	0.008
Number of previous hospitalizations	2.90 (±6.09)	2.98 (±4.87)	0.732	1.29 (±2.32)	1.60 (±2.68)	0.065
Gender (male)	61%	53%	0.121	42%	35%	0.193
First illness episode	44%	47%	0.321	49%	52%	0.341
Duration of current episode <6 months	60%	63%	0.174	63%	67%	0.602
Diagnostic subtype			0.221			0.005
Schizophrenia	85%	81%				
Schizoaffective disorder	12%	12%				
Brief psychotic disorder	3%	17%				
Depressive episode				45%	37%	
Recurrent depressive episode				50%	53%	
Bipolar disorder				4.5%	9%	
Dysthymia				0.5%	1%	
PANSS total score study admission	72.99 (±20.54)	69.85 (±17.99)	0.152			
HAMD total score study admission				22.86 (±6.00)	21.53 ± 6.15	0.132

criterion in 81% of the cases whereas in schizophrenia asymptomatic remitters the rate of patients being responders at the same time was 98%. Similarly, in the depressed patients 98% of the remitters were treatment responders at the same time, see Fig. 1. Comparing the schizophrenia consensus and the depressed remitters significantly more depressed remitters were concurrent treatment responders ($p < 0.0001$), yet no significant difference was found when comparing the response rate between schizophrenia asymptomatic and depressed remitters ($p = 1$).

3.2.2.2. Regarding illness severity (Clinical Global Impression Scale). The mean CGI-S in schizophrenia patients achieving the consensus criteria was 2.95 (±0.97), 2.23 (±0.84) for the schizophrenia asymptomatic remitters and 2.33 (±0.95) for the depressed remitters. The schizophrenia consensus remitters scored significantly higher on the CGI-S compared to the depressed remitters ($p < 0.0001$), no significant difference could be observed when comparing the schizophrenia asymptomatic and the depressed remitters ($p = 0.4924$), see Fig. 2.

3.2.2.3. Regarding the level of functioning. When comparing the degree of functioning between schizophrenia remitters according to the consensus criteria (mean GAF 70.25 (±11.03)) and the remitted depressed patients (mean GAF 75.36 (±9.44)) a significantly better functioning was found in the depressed patient subgroup ($p < 0.0001$). Schizophrenia asymptomatic remitters had a mean GAF score of 78.63 (±9.27) which was even higher than the mean GAF score of the depressed patients ($p = 0.0358$), Fig. 3.

3.2.3. Achieving remission and the risk to relapse during follow-up

30% of the schizophrenia consensus remitters and 26% of the schizophrenia asymptomatic remitters suffered from a relapse within the year after discharge. In comparison 20% of the remitted depressed patients had a relapse during the follow-up period, see Fig. 4. Comparing the risk to relapse between the different remitter groups showed that the risk to relapse was 1.8 times higher for the schizophrenia consensus remitters compared to the depressed remitters ($p = 0.0174$) and 1.4 times higher for the asymptomatic schizophrenia remitters compared to the depressed patients ($p = 0.4172$).

Table 3a
Comparing schizophrenia consensus remitters, schizophrenia asymptomatic remitters and depressed remitters regarding sociodemographic and clinical variables (*p*-values were adjusted for the respective diagnosis in terms of illness-related and sociodemographic variables using a linear model).

	Schizophrenia consensus remitters	Schizophrenia asymptomatic remitters	Depressed remitters	*p*-Value consensus vs depression	*p*-Value asymptomatic vs depression
Age (years)	36.03 (±10.06)	37.18 (±10.05)	45.7 (±11.78)	0.8288	0.4459
Age at onset (years)	30.05 (±9.46)	32.42 (10.35)	38.47 (±12.79)	0.0035	0.0211
Duration of illness (years)	5.54 (±7.6)	4.3 (±7.42)	6.81 (±9.51)	0.0374	0.1421
Number of previous hospitalizations	2.23 (±4.01)	1.53 (±3.92)	1.34 (±2.35)	0.9237	0.6762
Gender (male)	49%	56%	32%	0.5057	0.36
First illness episode	40%	58%	26%	0.8395	0.3593
Duration of current episode <6 months	75%	84%	71%	0.8957	0.3527
Living with partner	19%	26%	57%	0.1084	0.1369
Having a job/occupation	59%	68%	74%	0.0859	0.0859
Diagnostic subtype			Depressive episode: 39%	n.a.	n.a.
Schizophrenia	80%	65%	Recurrent depressive episode: 51%		
Schizoaffective disorder	10%	9%	Bipolar disorder: 8%		
Brief psychotic disorder	10%	26%	Dysthymia: 1%		
Treatment with atypical antipsychotics	16%	12%	n.a.	n.a.	n.a.
Treatment with typical antipsychotics	20%	23%			
Treatment with both	62%	63%			
CGI-S discharge	2.95 (±0.97)	2.23 (±0.84)	2.33 (±0.95)	<0.0001	0.4924
PANSS total score discharge	41.07 (±8.77)	31.77 (±1.43)	n.a	n.a.	n.a.
PANSS positive subscore discharge	8.85 (±2.19)	7.23 (±0.53)	n.a	n.a.	n.a.
PANSS negative subscore discharge	10.8 (±3.8)	7.49 (±0.77)	n.a	n.a.	n.a.
PANSS general psychopathology subscore discharge	21.43 (±4.65)	17.05 (±1.11)	n.a	n.a.	n.a.
GAF discharge	70.25 (±11.72)	78.63 (±9.27)	75.95 (±10.56)	<0.0001	0.0358

Table 3b
Comparing the two schizophrenia remitters groups regarding sociodemographic and clinical variables (*p*-values were adjusted for the respective diagnosis in terms of illness-related and sociodemographic variables using a linear model).

	Schizophrenia consensus remitters[1]	Schizophrenia asymptomatic remitters	*p*-Value
Age (years)	35.57(± 10.07)	37.18 (±10.05)	0.364
Age at onset (years)	29.09 ± 8.95	32.42 (10.35)	0.0106
Duration of illness (years)	6.04 ± 7.64	4.3 (±7.42)	0.055
Number of previous hospitalizations	2.51 ± 4.04	1.53 (±3.92)	0.068
Gender (male)	47%	56%	0.408
First illness episode	38%	58%	0.789
Duration of current episode <6 months	72%	84%	0.375
Living with partner	17%	26%	0.121
Having a job/occupation	56%	68%	0.0852
Diagnostic subtype			<0.0001
Schizophrenia	86%	65%	
Schizoaffective disorder	10%	9%	
Brief psychotic disorder	4%	26%	
Treatment with atypical antipsychotics	13%	12%	0.231
Treatment with typical antipsychotics	21%	23%	
Treatment with both	64%	63%	
CGI-S discharge	3.01 (±0.91)	2.23 (±0.84)	<0.0001
PANSS total score discharge	43.12 (±8.97)	31.77 (±1.43)	<0.0001
PANSS positive subscore discharge	8.81 (±2.13)	7.23 (±0.53)	0.512
PANSS negative subscore discharge	11.84(±3.9)	7.49 (±0.77)	<0.0001
PANSS general psychopathology subscore discharge	23.61 (±4.8)	17.05 (±1.11)	0.001
GAF discharge	68.01 (±11.51)	78.63 (±9.27)	<0.0001

[1] Patients within the consensus remitters achieving asymptomatic remission at the same time were excluded from this subgroup in this analysis in order to allow between group comparison.

4. Discussion

4.1. Remission in schizophrenia and general aspects on the consensus criteria

In line with previous study reports we found a considerable number of schizophrenia patients being in remission at discharge (63% of the patient sample) when applying the consensus criteria for remission (Bobes et al., 2009; Kane et al., 2007; Kissling et al., 2005; Leucht et al., 2007a) and significantly fewer patients (18%) fulfilling a stricter remission criterion. It is well known that the rate of patients achieving remission considerably depends on the respective definition applied and remission rates in schizophrenia vary between 3%–80% in the literature (Leucht and Lasser, 2006). A major problem when comparing remission rates in schizophrenia using the consensus criteria is the question of whether or not the time criterion of the proposed definition has been applied (Lambert et al., 2010). Regarding the acute treatment, in the present study only the symptom-severity component of the consensus criteria was applied due to the fact that the mean duration of hospitalization was >60 days. Many authors have applied solely the symptom-severity component of the criteria due to a short-term design of their study (van Os et al., 2006; Wunderink et al., 2007), yet this approach

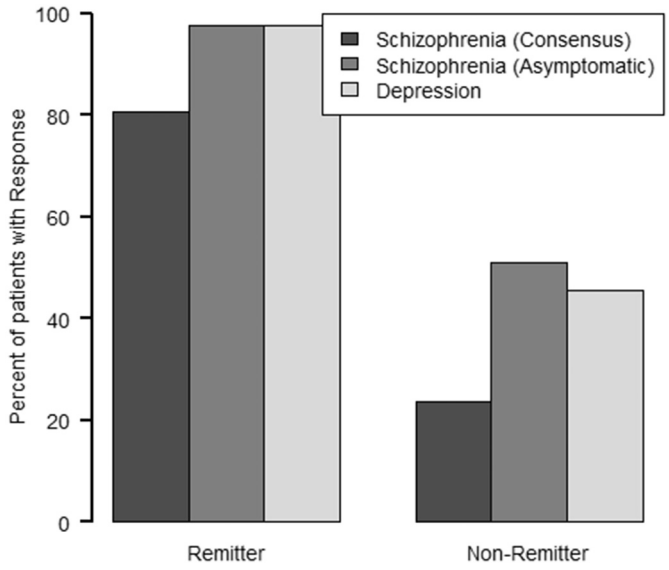

Fig. 1. Schizophrenia remitters (consensus criteria and asymptomatic criterion) and depressed remitters and the degree of concurrent treatment response at discharge.

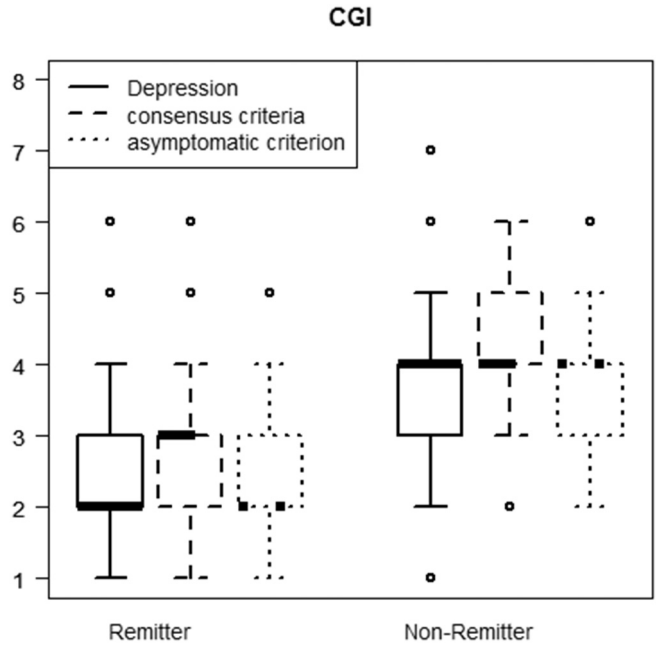

Fig. 2. Schizophrenia remitters (consensus criteria and asymptomatic criterion) and depressed remitters and the mean CGI at discharge.

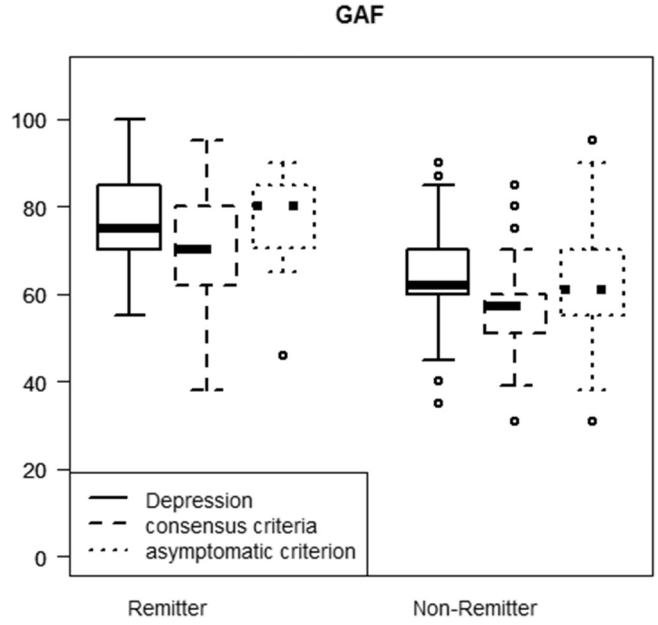

Fig. 3. Schizophrenia remitters (consensus criteria and asymptomatic criterion) and depressed remitters and the level of functioning (mean GAF score) at discharge.

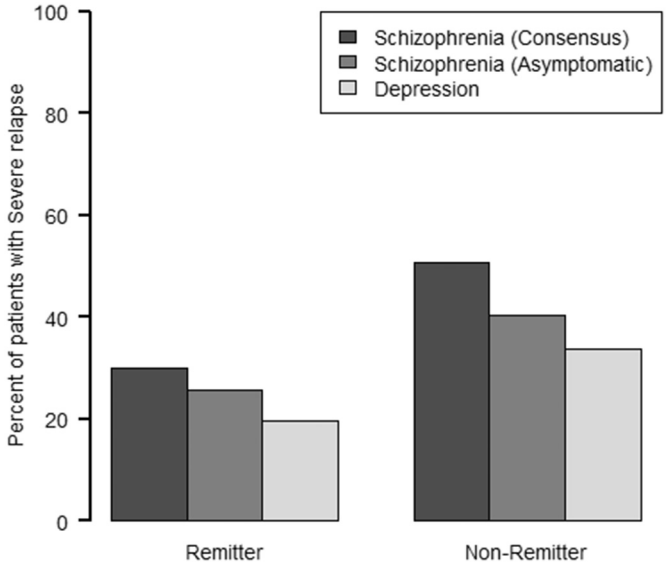

Fig. 4. Schizophrenia remitters (consensus criteria and asymptomatic criterion) and depressed remitters and the likelihood of relapse during the 1-year follow-up after discharge.

raises the question if these patients fulfilling only the symptom-severity component are really "true" remitters. There have been reports finding that most patients achieving the symptom-severity component of the consensus criteria are very likely to also achieve them after 6 months or even longer time-periods therefore suggesting that the symptom-severity component can adequately identify "true" remitters in short-term assessments (Schennach-Wolff et al., 2010). And just very recently, Johansson et al. showed that the consensus criteria discriminate between being stable, unstable, or never being in remission in their five year exploratory follow-up study also suggesting that these criteria are applicable over time (Johansson et al., 2017).

In terms of the adequacy of the symptom-severity threshold, the consensus criteria have generally been found to be less stringent than other established definitions of remission e.g. the remission criteria by Lieberman (= 50% reduction in the total score of the Brief Psychiatric Rating Scale (BPRS), BPRS scores of ≤3 in the BPRS psychosis items and a CGI severity rating of ≤3 for a minimum of 8 weeks) (Sethuraman et al., 2005). When reanalyzing six antipsychotic drug trials of schizophrenia patients Beitinger et al. compared different sets of definitions of remission changing the severity threshold of the consensus criteria (Beitinger et al., 2008). Interestingly, when applying the consensus criteria with the usually proposed threshold (≤3) at week 28 the authors identified 61% of the patients being in remission, yet after scaling the value of the symptoms down from "mild" to a "very mild/questionable" degree the remission rate was 16.3% similar to the 63% consensus remitters and 18% asymptomatic remitters in our sample (Beitinger et al., 2008).

When comparing the schizophrenia consensus remitters to the depression remitters less depressed patients were found to achieve remission (57%) compared to the 63% schizophrenia consensus remitters. We want to emphasize that the aim of comparing the three subgroups in this analyses was not to compare the patients' symptoms and likelihood of achieving remission, but to underline the euphemistic definition of remission by the consensus criteria when e.g. there are more remitters in schizophrenia than in depression when traditionally patients with schizophrenia are believed to show a poorer outcome than patients with affective disorders (Moller et al., 1988).

4.2. The consensus criteria and the patient's illness severity and level of functioning

Generally, when comparing the schizophrenia consensus and asymptomatic remitters the asymptomatic remitters were the ones with a later onset and shorter duration of illness as well as with a greater proportion of first-episode patients suggesting less illness chronicity in these patients achieving a very strict definition for remission. This is not very surprising keeping in mind, that the remission criterion of asymptomatic remission is based on a CGI rating of 1. Variables like the duration of illness (short) or numbers of episodes (few) have consistently been associated with a more favourable course of schizophrenia and better chances to respond to treatment as well as to achieve remission and recovery (Haro et al., 2008; Marshall et al., 2005). It should be kept in mind though, that clinical analyses like the one at hand do not allow to draw definite causal conclusions between the different variables. Patients with less illness episodes might more likely be remitters but it can also be the other way around that patients in remission are the ones will less episodes.

Schizophrenia consensus remitters were treatment responders at the same time in 81% of the cases, whereas the rate of remission and response overlapped in 98% of depressed remitters and also in the schizophrenia asymptomatic remitters. Again, this discrepancy can easily be explained by the respective definitions for remission because the consensus criteria allow a mild illness severity whereas the other two definitions ask for a state of having less than mild symptoms. Leucht et al. were able to show that the consensus criteria adequately mirror a general state of being "mildly ill" (Leucht et al., 2007a) which is in line with present results.

In line with this, schizophrenia consensus remitters were found to have a significantly lower level of functioning compared to the schizophrenia asymptomatic remitters. There are also some comparative studies showing that when applying the consensus criteria and rather strict definitions of adequate functioning (e.g. a GAF score of >80 points) only 30% to 38% of consensus remitters display an adequate functioning (Bobes et al., 2009; San et al., 2007; Wunderink et al., 2009).

4.3. The consensus criteria and the likelihood of having a favourable course of schizophrenia

Along with our previous results we found significantly more schizophrenia consensus remitters to have a relapse during the one-year follow-up after discharge compared to the schizophrenia asymptomatic remitters.

Comparative research consistently states that remitters suffer from less relapses than non-remitters (Lambert et al., 2010). To our knowledge this is the first study comparing the consensus remitters and their risk to relapse to other remitter classes. As Helldin et al. stated remission is believed to be an important goal in order to reduce future treatment needs (Helldin et al., 2009) which makes remission a benchmark of a favourable versus unfavourable course of schizophrenia. Also Lambert et al. believe that a higher stringency of a definition for remission means that fewer patients will fulfil the respective criteria, but if fulfilled, the patients have a better clinical status and the criteria with higher stringency might display a better predictive validity for a broader outcome (Lambert et al., 2010). Also Johannson et al. found that remission duration was significantly longer for the cut-off score 2 rather than 3 in their evaluation of the consensus remission criteria (Johansson et al., 2017). This mirrors to a certain degree results on persistent residual symptoms in remitted patients which have consistently been associated with a higher risk to relapse and a more unfavourable course of the illness (Schennach-Wolff et al., 2011).

Therefore, it seems to be inevitable to re-discuss the appropriateness of the consensus criteria given that they allow persistent core symptoms of schizophrenia with mild severity when this is a condition where impairments in functioning and a rather high risk to relapse are prominent. Besides, given that researchers have distinguished between the cognitive, affective, negative and psychotic domains of schizophrenia, the question arises if different remission criteria for each of the domains would also be needed (van Os et al., 2010). This should be discussed by researchers and clinicians, for as van Os questions in his

comment on the assessment of remission in schizophrenia, shouldn't we generally make sure that we are talking about the same thing when speaking of remission (Haro et al., 2007)?

4.4. Strengths and limitations

The strength of this study is that it is among the first to compare remission rates in schizophrenia patients applying different definitions of remission. Both studies were naturalistic studies. On the one hand such a design does not allow a sufficient control of study results for the effect of different pharmacological treatments. But on the other hand a naturalistic design resembles the real-world situation allowing to draw reliable clinical implications. Due to the exclusion of patients with drug and alcohol dependency and the inclusion of only inpatients findings of this study might be less generalizable, however might still exhibit higher external validity than results from randomized-controlled trials. Due to the study design, the time criterion of the consensus criteria could not be considered at discharge, which might have biased current results. Also, the remission status of the examined patients might have fluctuated over time given that examination time-points were at admission and then only at follow-up.

5. Conclusions

Schizophrenia consensus remitters were found to have greater illness severity, less functioning and a significantly higher risk to relapse during a one-year follow-up period compared to schizophrenia patients achieving a state of being asymptomatic. This raises the question of whether or not the proposed severity threshold of the consensus criteria still allowing mild symptoms adequately mirrors what is understood to be remission. If remission in schizophrenia is supposed to be a clinical state of being asymptomatic or suffering from only minimal symptoms in order to identify patients with satisfying functioning and a negligible risk to relapse then the currently proposed consensus criteria need to be revised.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

The German Research Network on Schizophrenia and the German Research Network and Depression designed the study and wrote the protocol. Author Rebecca Schennach managed the literature searches and analyses and wrote the first draft of the manuscript. Author Michael Obermeier undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

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