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Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later

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In March 2005, the Remission in Schizophrenia Working Group (RSWG)[1] published a consensus definition of remission in schizophrenia, and developed operational criteria for its assessment (henceforth called the RSWG criteria). These criteria define remission as a level of core schizophrenia symptoms that does not interfere with an individual's behavior and is below that required for a diagnosis of schizophrenia to be made according to the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. The criteria consist of two elements:

• A symptom-based criterion, which includes seven diagnostically relevant items from the *DSM-IV*. The seven items specified in the *DSM* criteria were then cross-

In March 2005, the Remission in Schizophrenia Working Group (RSWG) proposed a consensus definition of symptomatic remission in schizophrenia and developed specific operational criteria for its assessment. They pointed out, however, that the validity and the relationship to other outcome dimensions required further examination. This article reviews studies on the validity, frequency, and predictors of symptomatic remission in schizophrenia and studies on patients' perspectives. These studies have demonstrated that the RSWG remission criteria appear achievable and sustainable for a significant proportion of patients, and are related to a better overall symptomatic status and functional outcome and, to a less clear extent, to a better quality of life and cognitive performance. However, achieving symptomatic remission is not automatically concurrent with an adequate status in other outcome dimensions. The results of the present review suggest that the RSWG remission criteria are valid and useful. As such, they should be consistently applied in clinical trials. However, the lack of consensus definitions of functional remission and adequate quality of life hampers research on their predictive validity on these outcome dimensions. Future research should therefore search for criteria of these dimensions and test whether the RSWG remission criteria consistently predict a "good" outcome with respect to functioning and quality of life.

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matched to three different rating scales (Positive and Negative Syndrome Scale [PANSS], the Scale for the assessment of negative symptoms and positive symptoms [SANS/SAPS], and the Brief Psychiatric Rating Scale [BPRS]). They correspond to eight items in the PANSS, all of which have to be scored with a symptom severity of ≤3 points ("mild" or better). The eight symptoms include: (i) delusions; (ii) unusual thought content; (iii) hallucinatory behavior; (iv) conceptual disorganization; (v) mannerisms/posturing; (vi) blunted affect; (vii) passive/apathetic social withdrawal; (viii) lack of spontaneity and flow of conversation *(Table I)*. The symptom-based criterion can also be assessed using the SANS/SAPS (severity ≤2 points). The BPRS (severity ≤3 points) does not contain adequate representation of negative symptoms and is therefore alone not satisfactory for evaluating remission. The two negative symptoms not included in the BPRS (ie, "social withdrawal" and "lack of spontaneity") need to be additionally assessed with PANSS or SANS when BPRS is used.

- A time criterion, which requires that an individual achieves the symptom-based criteria for a minimum of 6 months.[1]

According to the RSWG, these criteria represent an absolute threshold rather than a relative improvement from a predefined baseline, which can be applied to patients at all stages of the disease and that may facilitate cross-trial comparisons of interventions.[1-4] The corresponding European Working group concluded that this definition will enhance the conduct of clinical investigations and reset expectations for treatment outcome

Dimension of psychopathology	DSM-IV criterion	ICD-10 criterion	Proposed remission criteria items						
			Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS) items		Positive and Negative Syndrome Scale items		Brief Psychiatric Rating Scale (BPRS) items	
			Criterion	Global rating item number	Criterion	Item number	Criterion	Item number
Psychoticism	Delusions	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
(reality distortion)	Hallucinations	Hallucinations	Hallucinations (SAPS)	7	Hallucinatory behavior	P3	Hallucinatory behavior	12
Disorganization	Disorganized speech	Breaks in train of thought, incoherence or irrelevant speech	Positive formal thought disorder (SAPS)	34	Conceptual disorganization	P2	Conceptual disorganization	4
	Grossly disorganized or catatonic behavior	Catatonic behavior	Bizarre behavior (SAPS)	25	Mannerisms/ posturing	G5	Mannerisms/ posturing	7
Negative symptoms (psychomotor poverty)	Negative symptoms	Negative symptoms	Affective flattening (SANS)	7	Blunted affect	N1	Blunted affect	16
			Avolition-apathy (SANS)	17	Social withdrawal	N4	No clearly related symptom	
			Anhedonia-asociality (SANS)	22				
			Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

Table I. Proposed items for remission criteria of psychopathology dimensions and *DSM-IV* and *ICD-10* criteria for schizophrenia.[a]
[a] For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required. Rating scale items are listed by item number. [b] Use of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission.

at a higher level.[5] It is further essential to point out that the remission criteria can be applied only to patients who have previously been diagnosed using recognized diagnostic criteria and that fulfilling the remission criteria does not mean that the diagnosis is no longer applicable.[5] Finally, the application of the criteria does not imply or depend on any preconceptions about the causal mechanisms underlying the illness, or those that may have brought about remission.[5]

The present article aims to review the literature published since the introduction of the abovementioned RSWG criteria in March 2005. The review especially focuses on the validity of the applied remission criteria and frequencies and predictors of remission. Further, the patients' perspectives on the proposed remission criteria and implications for future research are discussed.

Since the publication of the remission criteria in March 2005, more than 50 articles on this topic have been published. Reviewing these articles brings about various problems: (i) many of the studies have used the symptom-severity remission criteria omitting the time criterion; (ii) some studies have used other outcome measures than the proposed PANSS, SANS/SAPS, or BPRS scales (eg, CGI-S); (iii) some studies using the BPRS have not assessed the two missing negative symptoms of the severity criteria; (iv) There is a huge variation with respect to duration of study period; (v) some studies suffered from high dropout rates, if reported at all; (vi) finally, there is a huge variation regarding sample selection (eg, acute inpatients vs stable outpatients, first-episode vs multiple episode patients, schizophrenia vs schizophrenia spectrum disorders, first-episode schizophrenia vs first-episode psychosis including affective psychosis, patients with comorbid substance use disorder in- or excluded, major differences in symptom severity at baseline, etc). Thus, comparability in terms of validity of criteria as well as frequencies and predictors of remission is limited.

Validity of the remission criteria

For validation of remission criteria two different approaches were used: (i) comparison of different definitions of symptomatic remission; and (ii) association of the remission criteria with various outcome dimensions including the overall symptomatic status, functional outcome, quality of life, or other outcome criteria.

Comparison of different definitions of symptomatic remission

To date, six post-hoc analyses have tested the proposed RSWG criteria against other remission criteria in schizophrenia.

In 2005 and 2006, Sethuraman et al[6] and Dunayevich et al[7] compared the RSWG criteria with the criteria proposed by Lieberman et al.[8] The latter require that a patient achieve 50% reduction in BPRS total score, BPRS scores of ≤3 concurrently on each of the following BPRS psychosis items (unusual thought content, suspiciousness, hallucinations, conceptual disorganization, mannerisms, and posturing), and a Clinical Global Impressions-Severity (CGI-S) score ≤3 for a minimum of 8 weeks. The first post-hoc analysis by Sethuraman et al[6] compared those two sets of criteria in 339 patients followed over 28 weeks. The percentage of cumulative time in remission was longer for the RSWG criteria. The authors concluded that the criteria by Lieberman et al are more stringent than the RSWG criteria. The second post-hoc analysis by Dunayevich et al[7] used pooled data from 6 double-blind, randomized trials including 2771 patients. The proportion of patients who met either remission criteria at any time during the study period (8 to 52 weeks) was 66% (n=1825; 902 patients met RSWG criteria and 923 patients Lieberman criteria). Mean reductions in PANSS total score at week 24 were significantly lower in those fulfilling RSWG criteria (-21.7 vs -42.6 in those fulfilling Lieberman criteria). Further, improvements of quality of life (QLS total score) were significantly lower with RSWG criteria (+15.4 vs +19.6 with Lieberman criteria). Regression analysis assessed the relative contribution of each of the components of the two remission criteria (severity thresholds) to improvements in QLS total score. BPRS change scores accounted for the greatest effect on QLS total score improvements. The authors concluded that the Lieberman criteria appeared more stringent than the RSWG criteria, as almost all patients achieving the Lieberman criteria also achieved the RSWG criteria, while the converse was not apparent.

In 2006, van Os and colleagues[9] assessed whether a change in remission status would be associated with changes in clinician-reported and patient-reported functional outcomes. A total of 317 patients with a median follow-up of 3.1 years were separated into patients with

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(n=145, 46%) or without (n=172, 54%) remission at baseline. These groups were followed up for change in remission status over time, and those who had changed were compared with nonchanged individuals for improvement in functional and quality of life outcomes. Within this study, the RSWG criteria were compared with RSWG criteria including the two PANSS items "depression" and "suicidality." Of the 145 patients, 35% moved out of remission and 31% moved into remission. When including depression and suicidality into the remission criteria these frequencies did not change considerably (37% and 29%). In both groups, change in remission status was associated with large differences in functional outcomes measured with the GAF and, to a lesser extent, in quality of life. This led the authors to conclude that the proposed remission criteria have "clinical validity."

In 2007, Leucht and colleagues reanalyzed 7 antipsychotic trials (n=1708) of patients with schizophrenia comparing three sets of remission criteria[10]: (i) the RSWG criteria; (ii) the Lieberman criteria; and (iii) the criteria by Liberman et al.[11] The latter require that the 9 BPRS items grandiosity, suspiciousness, unusual thought content, hallucinations, conceptual disorganization, bizarre behavior, self-neglect, blunted affect, and emotional withdrawal be rated at not more than "moderate" severity (score of ≥4). Comparable to the results by Sethuraman et al[6] and Dunayevich et al,[7] the Lieberman criteria were more stringent than the new RSWG criteria (pooled remission frequencies at 1 year using severity criteria only = 38% vs 48%; LOCF). The criteria proposed by Liberman et al[11] were less restrictive (pooled remission frequencies at 1 year severity criteria only: 69%; LOCF). The authors concluded that a high stringency does not mean the most adequate remission criteria and that a major advantage of the new criteria is that they have been conceptualized and are based on the *DSM-IV* criteria for schizophrenia.

In 2008, Beitinger and colleagues reanalyzed six antipsychotic trials (n=2463) of patients with schizophrenia comparing two sets of remission criteria[12]: the RSWG criteria (full criteria in the three mid-term to long-term studies; 28 to 52 weeks) using scores of ≤3 ("mild" or better), ≤2 ("very mild" or better) or 1 ("not present") and the Lieberman criteria. Applying the RSWG criteria to the mid-term studies with or without time criterion resulted in the following frequencies: scores ≤3 (LOCF): 42%/11%, ≤2 (LOCF): 16%/1.8%, 1 (LOCF): 3.4%/0%;

in the long-term studies with or without time criterion: scores ≤ 3 (LOCF): 42%/11%, ≤ 2 (LOCF): 13%/2%, 1 (LOCF): 5%/1%. Compared with the remission criteria by Lieberman, the RSWG remission criteria were less restrictive (week 28: 38% vs 60%). The authors concluded that the results of more stringent thresholds within the proposed remission criteria (scores of ≤2 or lower) show that a score of mild or better is a "realistic choice, more stringent thresholds yield remission frequencies are not realistic."

In 2009, Cassidy et al tested four sets of remission criteria in 141 first-episode psychosis (FEP) patients for prediction of functioning at the 2-year end point[13]: (i) all SAPS positive items (hallucinations, delusions, bizarre behavior, positive formal thought disorder) rated ≤2 (severity) for 3 consecutive months; (ii) all SAPS positive items rated ≤2 for 6 consecutive months; (iii) all SAPS positive and negative items (affective flattening, alogia, avolition-apathy, anhedonia-asociality) rated ≤2 for 3 consecutive months; (iv) all SAPS positive and negative items rated ≤2 for 6 consecutive months. Totals of 94% and 84% of subjects for 3 and 6 months achieved positive symptom remission, compared with 70% and 56% for positive and negative symptom remission, respectively. Linear regression analyses showed that only remission criteria containing both positive and negative symptom criteria independently predicted functional outcome. The authors concluded that consistent with the consensus definition of remission, severity of both positive and negative symptoms is necessary although a 3-month criterion had equal predictive validity to a 6-month criterion.

In summary, the following conclusions were able to be drawn:

- The new remission criteria by Andreasen et al[1] are less stringent than the remission criteria by Lieberman et al[8] and more stringent than the remission criteria by Liberman et al.[11] A higher stringency means that fewer patients will fulfill the remission criteria, but if fulfilled, the patients have a better clinical status. It is therefore likely that remission criteria with higher stringency will display a better predictive validity for a broader outcome. However, it should be subject to further discussion whether remission criteria with lower stringency and longer time criterion (Andreasen et al[1]) or remission criteria with higher stringency and shorter time criterion (Lieberman et al[8]) are to be preferred. The time criterion of 6 months

was judged to be an appropriate cutoff because "shorter cutoff periods would be insufficient to permit validation of sustained and stable improvement."[5] Additionally, the value of the inclusion of a change criterion is questionable (50% reduction in BPRS total score by Lieberman et al[8]) as remission rates across samples will highly dependent on BPRS baseline scores.

- The rationale for selecting positive and negative symptom items for the remission definition seems reasonable because only definitions of remission containing both positive and negative symptoms were predictive of functional outcome, and both are core dimensions of schizophrenia.
- The non-consideration of the symptom items depression and suicidality seems reasonable because there inclusion did not change remission frequencies considerably. This supports the assumption of van Os et al,[5] who judged the exclusion of not diagnostically specific symptoms as appropriate because "they are influenced by other factors, such as health care provision and cultural issues, which show great geographic and socioeconomic variability."
- Increasing the severity threshold to ≤2 ("very mild" or better) or 1 ("not present") means that hardly anybody will reach remission. This shows that a score of 'mild' or better is a realistic choice.[12]

Association of symptomatic remission to other outcome dimensions

To date, 21 articles have published data on the relation of RWSG remission status to other outcome dimensions including the overall symptomatic status, functional outcome, quality of life, or other outcome dimensions. Three publications have assessed differences between already remitted and nonremitted patients at baseline[14-16] and 14 publications within a follow-up period of 6 months to 5 years.[17-29] Additionally, four publications have presented data on the percentage of patients in symptomatic remission fulfilling other outcome criteria.[30-33] *Table II* gives an overview on these 21 studies. Data were only included if patients in actually remitted or nonremitted status were directly compared.

Overall, patients in symptomatic remission were found to have a better overall symptomatic status, a better functioning level, and, to a lesser clear extent, a better quality of life and a better cognitive performance.

Symptomatic status

All longitudinal studies which reported data on the relation of RSWG remission to the overall symptomatic status (n=11) have found significantly better symptom status at follow-up or greater psychopathology mean change scores from baseline in remitted vs nonremitted patients. Using the PANSS total score, the difference between remitters and nonremitters range between 8 points to 25 points at follow-up with a mean difference of approximately 18 points and a mean change score difference of 17 points (-32 vs. -17). The average PANSS total score in remitters of 47 points underlines the low psychopathology level related to RSWG remission, but also suggests that the proposed criteria encompass symptomatic remission and not complete absence of symptoms. Important data with respect to the relation of remission to overall psychopathology were published by Opler et al.[20] They statistically validate the criteria for remission using the PANSS scale in a 1-year trial assessing 675 patients. Using a PANSS total score of 60 points at time points > 6 months (8 and 12 months) the specificity of the remission criteria was 85%, ie, of the patients who had a total score >60, 85% were classified as not in remission. Sensitivity was also very high; 75% of patients with scores of <60 were classified as in remission. The authors concluded that these findings indicate that the remission criteria are both sensitive and specific indicators of the overall symptomatic status in schizophrenia.

Functional outcome

The five studies, which assessed the relation between remission and functional outcome, all found a significantly better functioning level in remitted vs nonremitted patients. However, three studies[30-33] assessed the proportion of patients in remission having a good functional level and found that only 30% to 38% of remitted patients at follow-up displayed an adequate functioning. For the interpretation of this result it is important to know that all three studies have set very stringent definitions of adequate functioning, ie, GAF >80 points[30,31] or adequate functioning in all 7 social roles in the GSDS scale[32] or fulfillment of vocational/occupation and independent living criteria for at least 6 months.[33] On the other hand it is arguable whether the chosen severity level "mild or better" is really not associated with impaired functioning as proposed in the original description of the criteria.[5] In

summary, it could be concluded that: (i) the fact of a significant difference in functioning between remitters and nonremitters does not necessarily mean that remitters are functioning well; (ii) that the stringency of the functioning criterion strongly influence the rates of patients who display an adequate functional outcome; and (iii) that

functioning in schizophrenia, in particular the vocational/occupational status, is probably determined by others factors independent from remission status, eg, common social and economic barriers of the general public in a given country. Besides, patients' functional outcome at follow-up is strongly influenced by the previous func-

Study	N	Assessment time-points (Baseline assessment [BA] and/or Follow-up [in months])	Remission criteria assessed (SC = only severity criteria; STC = severity AND time criteria)	Remitted vs nonremitted patients [1,2] (NA = Not assessed; NS = Not specified; mc = mean change; ns = not significantly different)			
				Overall symptomatic or clinical status	Functioning	Quality of life	Other outcome dimensions [3]
Studies comparing remitters with nonremitters							
Helldin et al[14,15]	211	BA	SC	NS	NS	NA	BC, LCHC, LUN
Ciudad et al[16]	1010	BA	SC	NS	SCOS: 8 vs 11	MCS-12: 37 vs 44	BSC
Dunayevich et al[7]	2771	6	SC	PANSS mc: -22 vs -11	NA	QLS mc: +15 vs +4	
Buckley et al[17]	184	6	SC	NS	NS	NS	NBC
Emsley et al[18]	462	12	STC	PANSS mc: -41 vs -23	NA	WQLS mc: 0.7 vs 0.3	NBC, LR
Kelly et al[19]	43	12	STC	BPRS: 28 vs 34	NA	QLS: 57 vs 53 (ns)	
Opler et al[20]	675	12	STC	PANSS: 52 vs 75	NA	NA	
Lasser et al[21]	578	12	STC	PANSS: 48 vs 67	NA	NS	
Kane et al[22]	1283	12	STC	CGI-I: 1.7 vs 3.7	NA	NA	
De Hert et al[23]	341	24	STC	PECC: 22 vs 38	GAF: 64 vs 44	NA	
Wunderink et al[24]	125	24	STC	PANSS: 44 vs 52	GSDS: 5 vs 7	WHOQoL: 98 vs 97 (ns)	
Emsley et al[25]	57	24	STC	PANSS: 41 vs 66	NA	NA	
Addington & Addington[26] (LOCF)	240	36	STC	PANSS pos & neg: 19 vs 35	NA	QLS: 85 vs 57	
Helldin et al[27]	211	60	SC	PANSS: 49 vs 66	NA	NA	LCHC
Eberhard et al[28]	115	60	STC	NS	GAF: 68 vs 52; SCOS: 8 vs 9	NA	NBC
Boden et al[29]	76	60	SC	NS	Good function (%): 73 vs 17	NS	
Studies assessing the percentage of patients in symptomatic remission fulfilling other outcome criteria							
Study	N	Assessment time-points	Assessed criteria	Patients with adequate functioning in %	Patients with adequate quality of life in %		
Bobes et al[30], San et al[31]	452	12	SC	30	NA		
Wunderink et al[32]	125	24	STC	37	NA		
Lambert et al[33]	2960	36	STC	38	67		

Table II. Relationship of symptomatic remission according to Andreasen et al[1] to other outcome criteria in schizophrenia (sorted according to assessment time points). (1) Data are only reported when already remitted patients were compared with nonremitters at baseline; data of baseline differences of patients who achieved remission or not at follow-up are not reported. (2) Scales: PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; CGI-I = Clinical Global Impression-Improvement Scale; SCOS = Strauss-Carpenter Outcomes Scale; GAF = Global Assessment of Functioning Scale; GSDS = Groningen Social Disability Schedule; QLS = Quality of Life Scale; WQLS = Wisconsin Quality of Life Scale; MCS-12 = Mental Component Score of the Medical Outcomes Study 12-item Short Form health survey. (3) Other outcome dimensions: LCHC = Less consumption of health care; LR = Less relapse; BC = Better cognition; NBC = No better cognition; BDA = Better drug attitude; LUN = Less unmet needs; BSC = Better social cognition

tioning level. For example, in a study by Catty et al,[34] assessing predictors of employment within an 18-month follow-up period in 312 patients with psychotic disorders, previous work history, and RSWG remission where significant predictors of the number of hours employed (*P*=0.001 and *P*<0.001, respectively).

Quality of life

With respect to quality of life, 2 of 6 studies have found no differences between remitted and nonremitted patients; the others found a significantly better quality of life in remitted patients. However, studies assessing the frequency of remitted patients being in adequate quality of life have found that only 60% to 70% of patients display a satisfying quality of life.

Other outcome criteria

With respect to other outcome dimensions, 6 studies have found that remitted vs nonremitted patients had less consumption of health care resources, fewer relapses in the respective follow-up period, and fewer unmet needs. However, cognitive performance or neuropsychological improvements were not related to remission status in two of three studies. Further, the respective studies on cognition do not answer the question whether patients with remission display better cognitive functioning or if patients with a higher level of cognitive performance are more likely to meet remission criteria.

Frequencies of remission

The reported frequencies of the RSWG criteria could be classified in following categories: (i) frequencies of the cross-sectional symptom-severity remission criterion; (ii) frequencies of patients fulfilling both the symptom-severity and the time criterion; (iii) frequencies on the stability of remission criteria over time. Studies were restricted to those with at least 6-month follow-up *(Table III)*. As many studies especially focused on first-episode patients they are reported separately in this section. Since March 2005, more than 30 publications have reported frequencies of fulfilled remission criteria in first- and multiple episode psychosis/schizophrenia, 17 in multiple episode and 15 in first-episode patients *(Table III)*. Follow-up periods vary between 6 months and 5 years. Completer frequencies (if reported) vary

between 40% and 80% with an average percentage of approximately 60% of patients who completed the respective follow-up remission assessment. The following conclusions could be drawn (numbers represent mean frequencies across studies):

- Many patients (45% to 70%) fulfill remission criteria at some point during the respective follow-up period with higher percentages when the time criterion is omitted (61% vs 47%).
- At follow-up in completers, more patients fulfill remission criteria when the time criterion is omitted (56% vs 44%).
- In first- and multiple episode completers, using the severity remission criteria only, there is an increase of remission frequencies between 6-month and 24-month follow-ups (6-month: 46%, 12-month: 52%, 24-month: 63%) with 51% fulfilling the criteria at longer follow-up periods. In first- and multiple episode completers, using the severity and time remission criteria, there also is an increase of remission frequencies over time (6-month: 24%, 12-month: 39%, 24-month: 47%, longer follow-up periods: 55%).
- Comparing first- and multiple episode completers, using the severity remission criteria only, first-episode patients display higher remission frequencies during follow-up (61% vs 52%). Comparing first- and multiple episode completers, using the severity and time remission criteria, first-episode patients display higher remission frequencies during follow-up (48% vs 43%).
- In approximately 75% of patients who reached remission (severity only or severity and time) at some point during follow-up remission remains stable.
- Remission frequencies are higher in patients completing the follow-up assessments compared to patients who dropped out of the study/treatment.

Predictors of remission

Attempts have been made to identify predictors of treatment outcome in schizophrenia since the introduction of effective treatment more than 50 years ago.[51] With respect to remission, identification of specific premorbid, demographic, early improvement, and treatment predictors could help to identify patients who will possibly achieve remission and to identify risk factors for nonremission.
With respect to the proposed remission criteria, 12 studies to date have assessed predictors of remission using

Study	N	CO (%)	Study duration (in months)	Only severity criteria (in %)					Severity AND time criteria (in %)					Stability of remission (duration, %) [1]
				At any time	6 months	12 months	24 months	Longer follow-up [2]	At any time	6 months	12 months	24 months	Longer follow-up [2]	
Multiple episode patients														
Dunayevich et al[7]	2771	1389 (50)	6	66	23	-	-	-	-	-	-	-	-	-
Buckley et al[17]	184	NS	6	-	55	-	-	-	-	-	-	-	-	6/84
Beitinger et al[12] (3)	903/201	NS	12	-	42/61	42/63	-	-	-	11/20	11/32	-	-	-
Opler et al[20]	675	427 (63)	12	-	-	39	-	-	-	-	-	-	-	-
Leucht et al[10] (3)	748	390 (52)	12	-	-	48/68	-	-	-	-	27/52	-	-	-
Kissling et al[35]	715	508 (71)	12	-	-	60	-	-	-	-	31	-	-	12/84
Lasser et al[21]	578	437 (76)	12	-	-	-	-	-	-	-	41	-	-	12/85
Bobes et al[30]	452	376 (83)	12	-	-	63	-	-	-	-	-	-	-	12/90
Rossi et al[36]	347	243 (70)	12	-	-	45	-	-	-	9	32	-	-	12/63
Kane et al[22]	1283	495 (39)	12	52	-	-	-	-	-	-	29	-	-	-
Caton et al[37] (5)	186	NS	12	-	-	-	-	-	-	-	50	-	-	-
Cohen et al[38]	198	NS	12	-	-	49	-	-	-	-	-	-	-	-
Lambert et al[39]	529	211 (40)	18	-	-	-	-	-	33	-	-	-	-	-
Lambert et al[33]	2960	2210 (75)	24	-	-	-	-	-	-	-	-	47	-	-
De Hert et al[23]	341		24	-	-	-	44	-	-	-	-	29	-	6/71; 24/63
Gasquet et al[40]	933	563 (60)	36	-	-	-	-	-	-	-	-	-	61	-
van OS et al[9]	317	NS	36 (3.1 y)	46	-	-	-	-	-	-	-	-	-	36/65
Eberhard et al[28] (6)	115	NS	60	-	-	-	-	-	59	-	54	62	59	-
Summary results [7]	-	62%	-	55	46	55	44	-	46	15	38	46	60	76
First-episode patients														
Boter et al[41]	498	NS	12	-	-	-	-	-	-	-	30	-	-	-
Emsley et al[18]	462	NS	12 (381 d)	70	-	-	-	-	24	-	-	-	-	-
Menezes et al[42]	200	153 (77)	12	-	-	-	-	-	-	-	74	-	-	-
Bachmann et al[43]	40	NS	14	-	-	68	-	-	-	-	-	-	-	-
Cassidy et al[13]	207	141 (68)	24	56	-	-	-	-	-	-	-	-	-	-
Petersen et al[44]	547	369 (67)	24	-	-	-	62	-	-	-	-	36	-	-
Malla et al[45]	107	NS	24	-	-	-	82	-	-	-	-	-	-	-
Wunderink et al[32]	125	NS	24	-	-	-	-	-	-	-	-	52	-	-
Emsley et al[25]	56	28 (49)	24	70	-	-	-	-	-	-	-	40	-	24 (83)
Novick et al[46]	1009	701 (69)	24	-	-	-	-	-	-	-	-	70	-	-
Addington & Addington[26]	240	147 (61)	36	-	-	-	-	-	-	-	-	37	-	-
Lambert et al[47]	392	NS	36	70	-	-	-	-	70	-	-	-	60	-
Boden et al[29]	76	NS	60	-	-	-	-	53	-	-	-	-	-	-
De Haan et al[48]	110	NS	60	-	-	-	-	-	-	44	-	-	38	-
Crumlish et al[49] (4)	118	67 (57)	96	-	-	-	-	49	-	-	-	-	-	-
Summary results	-	64%	-	67	-	68	72	51	47	44	52	47	49	83

Table III. Remission frequencies (in %) over various follow-up time-points in first- and multiple-episode patients (sorted according to duration of trial). LOCF = Last-observation-carried-forward; CO = Completers only; NS = Not specified. (1) Stability of remission shows duration in months and % of patients who reached remission and remained in remission within the study period; (2) Duration of follow-up is indicated by study duration; (3) Data report LOCF and CO frequencies; (4) Remission was fulfilled if all 30 PANSS items were Frequencyd ≤ 3; (5) 186 of 341 patients assessed had a primary psychosis diagnosis; (6) Remission time criterion 12 months instead of 6 months; (7) CO data were used

multivariate regression models *(Table IV)*. Multivariate regression takes into account several predictive variables simultaneously and controls for confounders, thus modeling the predictive value of interest with higher accuracy than univariate analyses.

Overall, 6 most relevant predictors of symptomatic remission were identified *(Table IV)*: (i) shorter duration of untreated psychosis (assessed in 6 of 12 studies, in 5 of 6 studies being a significant predictor of remission [SPR]); (ii) better premorbid adjustment (assessed in 5 of 12 studies, in 4 of 5 studies SPR); (iii) lower psychopathology or illness severity scores at baseline (assessed in 11 of 12 studies, in 10 of 12 studies SPR); (iv) better functioning level at baseline (assessed in 9 of 12 studies, in 7 of 9 studies SPR); (v) early improvement in symptoms or functioning (assessed in 7 of 12 studies, in 5 of 5 studies SPR); and (vi) medication adherence during treatment (assessed in 4 of 12 studies, in 3 of 4 studies SPR). Two other predictors were less clear related to remission: (i) female gender (assessed in 11 of 12 studies, in 2 of 11 studies SPR); and (ii) lack of substance use disorder at baseline or persistent substance use during

treatment (assessed in 6 of 12 studies, in only 3 of 6 studies SPR). Other previously identified predictors of outcome in schizophrenia such as insight,[52] cognitive performance,[53] age at onset,[54] biological variables,[54,55] or type of interventions[56] were not assessed in follow-up studies in the relation to the proposed remission criteria.

The 6 identified predictors were repeatedly found as relevant even for long-term outcome studies in first- and multiple-episode patients.[55,57-59] This finding underlines that predictors of remission are also relevant for the overall outcome in schizophrenia.[51] This conclusion is partly supported by studies, which assessed predictors of remission, functional remission, and adequate quality of life/subjective well-being simultaneously in a single patient cohort. Lambert et al[33,47] and Novick et al[60] analyzed predictors of these three outcome dimensions within the SOHO (Schizophrenia Outpatient Health Outcome) study at 2[33] and 3 years' follow-up.[47,60] Overall, symptomatic remission was mainly predicted by lower illness severity at baseline, better functioning level at baseline, early symptomatic improvement, medication adherence and remitted substance use; functional remis-

Study	Study duration (in months)	Premorbid, baseline, early improvement and treatment predictors related to symptomatic remission Significant (S) or not significant (NS) predictor of symptomatic remission in multivariate regression models - = Not assessed				
		Short(er) duration in untreated psychosis (DUP)	Better premorbid adjustment	Lower psychpathology or illness severity score at baseline	Better functioning level at baseline	Early symptomatic, functional or quality of life improvement/ remission	Medication nonadherence during treatment
Emsley et al[18]	12	S (2)	NS	S (neg symp)(3)	-	S (symptoms)**	-
Rossi et al[36]	12	-	-	S***	NS	-	-
Caton et al[37]	12	S(4)	S(4)	S(4)	-	-	-
Lambert et al[39]	18	S*	-	S***	S**	S (symptoms)***	-
Malla et al[45]	24	S**	S*	-	-	-	S***
Lambert et al[33 (1)]	24	-	-	S***	S**	S (symptoms)***	S**
Novick et al[46 (1)]	24	-	-	S**	S*	-	-
Emsley et al[25]	24	S(4)	S (education status)(4)	NS	S, (marital status)(4)	S (symptoms)(4)	-
Lambert et al[47 (1)]	36	-	-	NS	NS	S*** (symptoms)	NS
Gasquet et al[40 (1)]	36	-	-	S(4)	S, (employment)(4)	-	-
Novick et al[50 (1)]	36	-	-	S***	S***	-	S***
Addington & Addington[26]	36	NS	S*	S***	-	-	-

Table IV. Most relevant predictors of remission defined as severity and time criteria as proposed by Andreasen et al[1] (sorted according to duration of trial). (1) These studies used CGI-Schizophrenia criteria (CGI-SCH overall, positive, negative, cognitive and depressive subscores ≤ 3) instead of the PANSS severity items. (2) * for schizophreniform / schizoaffective disorder and ** for schizophrenia. (3) For schizophrenia only. (4) No *P* values provided for multivariate model, at least *P*<0.05. * = significant at *P*<0.05; ** = *P*≤0.01; *** = *P*≤0.001

sion by younger age, better functioning level at baseline and early functional remission; and adequate quality of life by younger age, lower illness severity at baseline, better functioning level at baseline, early symptomatic and quality of life remission, and medication adherence. Full remission (fulfilling all three dimensions for ≥6 months) and recovery (fulfilling all three dimensions for ≥24 months) was mainly predicted by younger age, better functioning level at baseline, and early improvement within all three outcome dimensions. Therefore, these results suggest that predictors of symptomatic remission are partly also predictors for the overall outcome in schizophrenia with baseline functioning playing an important predictive role.

Several limitations of these findings have to be addressed: (i) results are hampered by a large variation regarding aspects such as sample selection and collection, assessment methods used or duration of study period; (ii) aspects of type and intensity of treatment are rarely assessed. The meta-analysis of Menezes et al[56] of 37 longitudinal outcome studies of first-episode non-affective psychosis highlights the importance of these two aspects. They failed to confirm previously reported variables such as duration of untreated psychosis or age at onset as significant outcome predictors, and found that a favorable outcome were mainly related to combined pharmacotherapeutic and psychosocial interventions as well as lack of epidemiologic representativeness of the sample. These findings suggest that future studies on remission and its predictors should control for treatment aspects and should aim to assess cohorts as representative as possible.

Remission as perceived by patients, relatives, and psychiatrists

Patients, relatives and psychiatrists perspectives regarding the RSWG remission criteria have rarely been explored. In a study by Karow et al,[61] 44% of 131 patients were in symptomatic remission according to the RSWG symptom based remission criterion. However, only 39% of these remitted patients judged themselves as remitted, 32% were remitted according to their relatives, and 61% according to the psychiatrists. Only in 18% of all cases, patients, relatives and psychiatrists agreed in their assessment of patients' remission. Remission as assessed by the patients was most divergent from RSWG remission with only 43% accordance,

whereas remission as assessed by the psychiatrists showed the best accordance (80%). Relatives' estimates showed 52% accordance with the RSWG remission, yet the highest accordance with RSWG nonremission (84%).

Comparisons of the different assessments of remission with other clinical measures showed a preference on the patients' side for subjective well-being and on the psychiatrists' side for the level of symptoms of psychosis. The results indicated that patients, their relatives, and psychiatrists differ highly in their understanding what state of symptom reduction should be called "symptomatic remission."

Conclusions

The present review shows that the consensus RSWG remission criteria are clinically meaningful; they appear achievable for a significant proportion of patients in routine clinical practice and are applicable across the course of the illness. Further, validation studies have shown that they are related to a good overall symptomatic status with low levels of overall psychopathology or illness severity, to a better functional status compared with non-remitted patients and, to a less clear extent, to a better quality of life or cognitive performance. On the other hand, these studies have also consistently shown that patients in remission do not automatically have an "adequate" functional level or quality of life. Both results support the assumption that patients being in symptomatic remission display a better overall illness state, although it has to be acknowledged that being in symptomatic remission does not necessarily mean that the patient is doing well, because other components of the illness (such as enduring affective or cognitive symptoms) may lead to functional impairments or poor quality of life. Research in this field is among others hampered by the lack of consensus definitions of an "adequate" functional and quality of life status in schizophrenia. Future research should therefore search for such criteria and test whether the fulfillment of the RSWG remission criteria is consistently related to an "adequate" functional and quality of life status. In summary, results of this review supports the conclusion of van Os and colleagues, who stated that remission is a necessary (but not sufficient) step towards recovery.[5] With respect to the comparison of different remission definitions, there are considerably differences between

the RSWG remission criteria and other remission criteria (ie, Lieberman et al[8] or Liberman et al[11]) with respect to symptoms included, inclusion of an improvement criterion, severity thresholds and duration or inclusion of the time criterion. These differences hamper the populations these criteria could be applied for and the comparability of results. With respect to stringency of the criteria, data have shown that a realistic proportion of patients could fulfill the RSWG remission criteria and that more stringent criteria (eg, lower thresholds for the severity criteria of ≤2 or =1) are not realistic in clinical settings. The inclusion of an improvement criterion (eg, achievement of 50% reduction in BPRS total score from baseline), as applied in the criteria by Lieberman et al,[8] increases the stringency and thereby the predictive validity for other outcome dimensions; however, only a minority of patients could reach such on outcome. Further, such a criterion implicates that studies including varying patient populations regarding baseline psychopathology are difficult (if not impossible) to compare. Applying less stringent severity criteria as proposed by Liberman et al[11] ("moderately ill" or better) leads to higher frequencies of patients in remission, but lowers the predictive validity for other outcome dimensions; further, its validity was hitherto insufficiently studied.

Of note, the inclusion of other symptoms such as depression and suicidality in the set of remission items did not change the remission frequencies considerably. This result supports the conceptualization of the RSWG criteria, which used the most diagnostically specific items of the Positive and Negative Symptoms Scale (PANSS) to define remission.[5] Items such as depression or anxiety relate to symptoms that are not diagnostic for schizophrenia. Conceptually, it may be subject of further discussion, whether depression and anxiety should be included in the RSWG criteria, as these dimensions were linked to poor quality of life. It may, however, be argued that these dimensions play a more import role in the broader concept of recovery.

The applied 6-month time criterion of the RSWG remission criteria is still a matter of debate. The only available study to date has found that a 3-month criterion has a comparable predictive validity for the stability of remission over time.[13] Further, studies on early response and the proportion of patients with early response being in stable remission over time have shown that even shorter time periods are predictive for

the stability of remission.[62,63] Applying shorter time periods is additionally supported by the fact that approximately 75% of patients reaching the symptom severity-criteria threshold without fulfilling the 6-month time criterion remain in remission throughout a 6- to 60-month follow-up period. However, this result is possibly hampered by large assessment gaps facing the problem to investigate remission status retrospectively over a 6- to 12-month time period. Further, it contradicts the known high cumulative relapse rates in schizophrenia.[64] As such, the applicability of the 6-month criterion versus shorter time criteria should be assessed in future prospective studies with short, possibly 1- to 3-monthly follow-up intervals. Finally, the RSWG proposed PANSS, and SAPS/SANS for the assessment of the remission criteria. However, Leucht et al proposed that in pragmatic trials the Clinical Global Impression Scale (CGI) could also be used (scores ≤3).[4]

With respect to frequencies of fulfilled remission criteria in different patient populations, this review has shown that 40% to 60% of patients with schizophrenia can reach remission, that remission frequencies differ markedly between different patient populations (eg, acute versus stabilized at baseline), that more patients reaching remission when the time criterion is omitted, that cumulative frequencies of remission increase over time, that first-episode when compared with mainly multiple-episode cohorts display higher frequencies of remission and that patients who drop out of study and/or treatment are less likely to be in remission. These results have several implications for future research and clinical settings:

- In future research, patient remission frequencies should be presented in the following categories[3]: (i) patients who were not in remission at baseline and who achieved remission during the study; (ii) patients who were in remission at baseline and remained in remission during the study; (iii) patients who were in remission at baseline, which was not sustained during the course of the study. In studies with at least 6-month follow-up, frequencies 2 and 3 should be separated into patients who reached the symptom-severity criteria only and those who reached the symptom-severity and time criteria.

- Dropout rates should be reported and adequate measures taken to account for their clinical status at dropout, when remission rates are presented. As patients who drop out are less likely to be in remission,

effort should be made to follow up these patients for the subsequent course of illness. Studies on service disengagement have repeatedly shown that these patients are in a poor mental state at time of disengagement.[65,66] These results supports that studies presenting frequencies of remission on the full cohort should possibly count all or the majority of lost-to-follow-up patients as nonremitters (if not better known).

- As it is unclear how frequently assessments should be performed over the course of a study, a balance should be kept between gaining the optimal amount of clinical data and designing a practical clinical trial.[3] It would be interesting to see methodological studies on the congruence between shorter (monthly) versus longer (3-monthly or longer) interval assessments. It is certainly difficult to engage patients in monthly assessments and potentially unreliable to assess them only 3-monthly.

With respect to predictors of symptomatic remission, the present study revealed several modifiable and unmodifiable factors. Unmodifiable predictors comprise a shorter duration of untreated psychosis, a better premorbid functioning, lower psychopathology or illness severity levels at baseline, and a better functioning at baseline (all factors are indirectly modifiable by community education campaigns); modifiable predictors include early remission and medication adherence. Other predictors including comorbid substance use or female gender were less conclusively related or not tested for their predictive validity. Further, other known predictors of outcome in schizophrenia were rarely or not tested in multivariate analysis.

With respect to future research, Lasser and colleagues[3] proposed a set of modifiable and unmodifiable factors, which should be assessed in studies on remission in schizophrenia. Beside their proposal and the assessment of the abovementioned predictors some other important recommendations should be addressed:

(i) As the diagnosis of schizophrenia was linked to poor overall outcome compared with other schizophrenia-spectrum disorders, diagnosis should be optimally separated into the three most prevalent schizophrenia-spectrum *DSM-IV* diagnoses, ie, schizophrenia, schizophreniform disorder, and schizoaffective disorder. As the concept of remission is not applicable for bipolar I disorder or severe depression with psychotic features, they should be excluded from analysis if first-episode cohorts are assessed. In long-term studies assessing remission in first-episode psychosis, diagnostic stability testing is also needed.[67]

(ii) Beside the abovementioned predictors, the latest research has shown that baseline and early change scores of subjective wellbeing have a high predictive validity for symptomatic remission and recovery.[48,62,68] As such, the SWN-K scale at baseline and early follow-up may be an interesting predictor to consider.

(iii) As Menezes et al[56] highlighted the importance of combined pharmacotherapeutic and psychosocial interventions as well as lack of epidemiologic representativeness as predictors, these aspects should be assessed or clearly described.

(iv) Whenever possible the relation of symptomatic remission to functional status or quality of life and their predictors should be assessed simultaneously. Because of the lack of consensus criteria with respect to "adequate" functioning and quality life, researchers should replicate findings of studies already applying criteria for functional outcome and should use quality of life scales specific for schizophrenia.

In summary, more than 50 prospective or post-hoc studies to date have applied the RSWG remission criteria to different patient populations in different settings using the symptom-severity criteria only or the complete remission criteria. The result that 40% to 60% of patients can achieve symptomatic remission during various follow-up periods supports the hope of the RSWG that remission is an achievable objective for a significant proportion of patients with a diagnosis of schizophrenia. However, as only about 10 out of 50 studies assessed the relationship of symptomatic remission to functional outcome and cognition, the hope of the RSWG that the availability of a validated remission measure would stimulate new studies on cognition and functional outcomes has only partly been fulfilled. This also holds true for studies on the association of symptomatic remission with quality of life. It is further important to know that none of the 50 studies to date have assessed the influence of differing clinical services or different type of interventions on the proposed remission criteria. Finally, only one study to date has assessed the congruence between RSWG remission and remission as perceived by patients, relatives, and professionals. This is surprising considering the hope of the RSWG was that the development of remission criteria should facilitate the dialogue on treatment expectations among physicians, patients and carers, health care administrators, and policy makers. The authors hope that the present article supports future research in this area. ❏

La remisión en la esquizofrenia: validez, frecuencia, predictores y percepción de los pacientes después de cinco años

En marzo de 2005 el grupo de trabajo sobre remisión en esquizofrenia (GTRE) propuso una definición de consenso de la remisión sintomática en la esquizofrenia y desarrolló criterios operacionales para su evaluación. Sin embargo, se señaló que la validez y la relación con otras dimensiones de la evolución requerían de futuras revisiones. Este artículo reseña estudios acerca de la validez, frecuencia y predictores de la remisión sintomática en la esquizofrenia y estudios sobre la percepción de los pacientes. Estos estudios han demostrado que los criterios de remisión del GTRE parecen alcanzables y sustentables para un grupo importante de pacientes y se relacionan globalmente con un mejor estado sintomático y una mejor evolución funcional, y en menor medida con una mejor calidad de vida y un mayor rendimiento cognitivo. Sin embargo, el alcanzar la remisión sintomática no es simultánea en forma automática con un adecuado estado en otras dimensiones de la evolución. Los resultados de la presente revisión sugieren que los criterios de remisión del GTRE son válidos y útiles. Como tal, debieran ser aplicados sistemáticamente en los ensayos clínicos. Sin embargo, la obtención de una remisión sintomática no coincide en forma automática con una definición que satisfaga las otras definiciones pronósticas.. La investigación futura debiera, por lo tanto, buscar criterios de estas dimensiones y probar si los criterios de remisión del GTRE predicen sistemáticamente una "buena" evolución en relación con el funcionamiento y la calidad de vida.

La rémission dans la schizophrénie : validité, fréquence, prévisions et perspectives des patients à 5 ans

En mars 2005, le groupe de travail sur la rémission dans la schizophrénie (GTRS) a proposé une définition consensuelle de la rémission symptomatique dans la schizophrénie et développé des critères opérationnels spécifiques pour son évaluation. Ils ont souligné, cependant, que la validité de la définition et les relations avec les autres dimensions pronostiques nécessitaient une analyse plus vaste. Cet article passe en revue des études sur la validité, la fréquence et les prévisions d'une rémission symptomatique dans la schizophrénie ainsi que des études sur les perspectives des patients. Ces études ont démontré que les critères de rémission du GTRS semblaient réalisables et durables pour un nombre significatif de patients. Ces critères sont de plus liés à un état symptomatique globalement meilleur, ainsi qu'un meilleur état fonctionnel, et, dans une moindre mesure, à une qualité de vie et à une performance cognitive meilleures. Cependant, l'obtention d'une rémission symptomatique ne coïncide pas automatiquement avec une définition satisfaisante pour les autres dimensions pronostiques. Les résultats de cette analyse suggèrent que les critères de rémission du GTRS sont valables et utiles. Ils devraient donc être systématiquement appliqués dans les études cliniques. Cependant, le manque de définition consensuelle pour la rémission fonctionnelle et pour une qualité de vie satisfaisante entrave la recherche sur la validité prédictive de ces dimensions pronostiques. Il faudrait donc faire des recherches pour déterminer l'importance de ces dimensions et voir si les critères de rémission du GTRS prévoient de façon fiable une « bonne » évolution respectant le fonctionnement et la qualité de vie.

Clinical research

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