Published in final edited form as:

J Psychopharmacol. 2009 June ; 23(4): 436–441. doi:10.1177/0269881108093883.

Remission in schizophrenia: the relationship to baseline symptoms and changes in symptom domains during a one-year study

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Abstract

The concepts of partial recovery and remission have become increasingly important for the evaluation of the effectiveness of schizophrenia therapeutics. The relationship of baseline symptoms and changes in symptoms to remission of psychosis was evaluated. Fifty-six outpatients with residual schizophrenia completed a double-blind trial of olanzapine versus haloperidol and were then enrolled into a one-year open-label trial of olanzapine. Out of these 56 subjects, 13 (23%) met remission criteria at the beginning of the open-label treatment and were excluded. During the one-year study, 7/43 (16%) subjects met remission criteria. These subjects had significantly lower baseline ratings for tardive dyskinesia (TD) than subjects who did not achieve remission (1.8 ± 1.5 vs. 4.2 ± 4.6 , $P = 0.03$). As expected, remitted subjects had significantly greater improvements in Brief Psychiatric Rating Scale total scores, positive subscale scores and scale for the Assessment of Negative Symptoms total scores. Remitted subjects also experienced a significantly greater improvement in depressive symptoms ($P = 0.001$), activation ($P = 0.005$), and Clinical Global Impressions scores ($P < 0.001$), as well as greater improvements in extrapyramidal symptoms ($P = 0.007$) and TD ($P < 0.001$). These results suggest that the relationship of depressive symptoms and improved side effects to the construct of remission in schizophrenia may deserve special attention. Future studies should aim to relate remission criteria to functional outcomes, cognition, and other important symptom domains.

Keywords

depression; extrapyramidal side effects; remission; schizophrenia; tardive dyskinesia

Background

In the past, schizophrenia has been conceptualised as a chronic, recurrent disease that leads to a significant residual morbidity occurring through a process of behavioural deterioration (Lieberman, *et al.*, 1996). However, advances in treatments and earlier attention to diagnosis may lead to improved longer-term outcome potential, and a broader focus on effectiveness has led to increased attention to the overall health and well being of people with schizophrenia. In conjunction, there has been an increase in emphasis on clinical outcomes that are meaningful to people with schizophrenia, their family members, and clinicians, as well as a greater focus on remission and partial functional recovery. This shift in focus is due, in part, to new understanding of the etiology and course of schizophrenia, new treatments, and increased interest in improving outcomes among people with schizophrenia, families, advocates, and professionals (Bellack, 2006).

To date, many definitions have been used to describe remission (Amminger, *et al.*, 1997; Auslander and Jeste, 2004; Curtis, *et al.*, 2001; Eaton, *et al.*, 1998; Harrow, *et al.*, 2005; Ho, *et al.*, 2000; McIntyre, *et al.*, 2006; Liberman, *et al.*, 2002; Liberman and Kopelowicz, 2005; Yen, *et al.*, 2002). Standardisation of the concept of remission may help to set higher goals for treatment, improve documentation of clinical status, facilitate dialogue on treatment expectations, and enhance the conduct and reporting of clinical investigations (Van Os, *et al.*, 2006). The Schizophrenia Working Group, consisting of schizophrenia experts, recently developed expert consensus criteria to define remission in schizophrenia. They defined remission as a state in which a person with schizophrenia experienced an improvement in core signs and symptoms such that the remaining psychiatric symptoms (positive and negative) are of low intensity and no longer interfere significantly with behaviour and are below the threshold that is typically used in justifying the initial diagnosis of schizophrenia (Andreasen, *et al.*, 2005). The purpose of this study was to compare baseline symptoms and changes in symptom domains in people with schizophrenia who met the Schizophrenia Working Group definition of remission and those who did not meet these criteria during a one-year open-label olanzapine study.

Methods

Subjects included in this study were outpatients with chronic schizophrenia who participated in a 12-month open-label trial of olanzapine following completion of a randomized, double-blind, 16-week trial of olanzapine versus haloperidol (Buchanan, *et al.*, 2005). Subjects were all outpatients at the Maryland Psychiatric Research Center Outpatient Research Program and the VA VISN 5 Mental Illness Research, Education and Clinical Center Psychopharmacology Clinic in Baltimore, Maryland. Subjects were entered into the double-blind study if they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and had residual positive and/or negative symptoms, which were defined as a minimum Brief Psychiatric Rating Scale (BPRS) positive symptom level of 8 or a score of 4 on any positive item (thought content, suspiciousness, hallucinations, and unusual thought content) or a minimum negative symptom score on the Scale for the Assessment of Negative Symptoms (SANS) of 20 or a score of 2 in at least one of four SANS global items (affective flattening, alogia, avolition/apathy, or anhedonia/asociality), despite two previous adequate antipsychotic treatment trials. Subjects with current drug use or alcoholism, organic brain disorder, or mental retardation were excluded. Subjects who completed the 16-week double-blind trial were then offered an opportunity to enter a 12-month trial of open-label olanzapine. Olanzapine dose was flexible between 10 and 30 mg/day. Weekly pill counts were performed to measure medication adherence. If subjects were less than 75% compliant, they were dropped from the study. Assessments included: the BPRS (18 item, scored 1–7; Overall and Gorham, 1962), the SANS (Andreasen, 1989), the Clinical Global

Impressions (CGI; ECDEU, 1976), the Quality of Life Scale (QLS; Heinrichs, *et al.*, 1984), the Level of Functioning Scale (LOF; Hawk, *et al.*, 1975), Hamilton Depression Rating Scale (HAM-D; Hamilton, 1976), Simpson-Angus Scale (SAS; Simpson and Angus, 1970), and the Maryland Psychiatric Research Center Tardive Dyskinesia (MPRC TD) Scale (Cassidy, *et al.*, 1997). All raters were master level or doctoral level clinicians. The Interrater Correlation Coefficient (ICC) for these instruments ranged from 0.76 to 0.90. Assessments were performed monthly.

Baseline demographic and clinical variables and changes over time were compared for subjects who did and did not achieve remission criteria during the 12-month study. Remission was defined as a rating of 'mild' or less on all the following symptom domains and the subjects who meet these symptom criteria for at least 6 months (Andreasen, *et al.*, 2005). The domains included were as follows: psychoticism (BPRS items: grandiosity, suspiciousness, unusual thought content, and hallucinatory behaviour), disorganisation (BPRS items: conceptual disorganisation and mannerisms/posturing), and negative symptoms (SANS global items: affective flattening, avolition/apathy, anhedonia/asociality, and alogia). Subjects who met the symptom severity remission criteria at baseline of the open-label study were not included in the analysis because their inclusion would not permit the determination of predictive variables or associated changes during treatment. The four BPRS positive symptom items were used to assess positive symptom change, the SANS total score was used to assess negative symptom change, the HAM-D total score was used to assess change in depressive symptoms, and the BPRS hostility and activation factors were used to assess change in the hostility and activation symptom domains (Buchanan, *et al.*, 2005).

Student's *t*-test and chi-square test were used for univariate analyses, and repeated measures mixed modeling, controlling for baseline, was used to evaluate symptom differences in remitters and nonremitters during the study (group by time effect interactions). Last observation carried forward (LOCF) was used for univariate analysis. All tests were two-tailed and significance was an $\alpha < 0.05$.

Results

In all, 56 subjects who completed either the haloperidol or olanzapine double-blind treatment arm were enrolled in the one-year open-label trial. At initiation of the open-label trial (baseline), 13 of 56 subjects (23%) met the remission criteria (other than the 6 month time component) and were not included in further analyses. Remission at baseline was not associated with previous treatment assignment in the double-blind phase and demographic variables were not different between those who did and did not meet remission criteria at baseline. Out of 13 remitters at baseline, 69% (9/13) were still in remission at the end of the one-year open-label study.

Thus, 43 subjects were included in the analysis of remitters and nonremitters in the one-year open-label olanzapine study. During the year of study, 16.3% ($N = 7$) of the subjects met remission criteria. The demographic and clinical characteristics between those who did and did not achieve remission are listed in Tables 1 and 2. There were no significant differences in baseline demographic variables and measures of symptomatology, except for TD. Subjects who achieved remission had significantly lower baseline MPRC TD scale total scores ($t = 2.32$, $df = 26.1$, $P = 0.03$). In the remission group, there were no subjects who discontinued in the one-year study (0/7), whereas 6/36 (16.7%) of the nonremitters discontinued at some point during the one-year study (fisher exact = 0.57, $df = 1$, $P = 0.32$). The mean time in the study was 329.9 ± 75.0 days for the nonremitters and 365 days for remitters ($t = 2.81$, $df = 35$, $P = 0.008$).

Least square means for baseline and endpoint values for symptom, side effect, and functional outcomes are presented in Table 3. Using mixed models for repeated measures, adjusting for baseline differences, we found that those who achieved remission had significantly greater improvements in symptomatology; BPRS total score ($F = 3.61$, $df = 13,412$, $P = 0.001$), positive symptoms ($F = 4.95$, $df = 13,422$, $P = 0.003$), activation ($F = 2.33$, $df = 13,425$, $P = 0.005$), and SANS total score ($F = 6.73$, $df = 13,425$, $P = 0.01$). In addition, remitted subjects had significantly greater improvements on the CGI ($F = 5.66$, $df = 13,431$, $P < 0.001$). Subjects who met remission criteria had significantly greater improvements in HAM-D total score, ($F = 5.03$, $df = 13,435$, $P = 0.001$), in SAS total score ($F = 2.24$, $df = 13,447$, $P = 0.007$), and in MPRC TD total score ($F = 101.6$, $df = 6,45$, $P < 0.001$), but there were no significant differences in LOF and QLS total scores. Antidepressant use was 17% (6/36) in the group not achieving remission and 14% (1/7) in those who attained remission ($P = \text{NS}$).

Discussion

In our study, approximately 17% of people with schizophrenia, with documented residual symptoms and not considered remitted at baseline successfully, achieved remission during the one-year open-label study even after 16 weeks of prior treatment with olanzapine or haloperidol and a documented history of only partial response. The only baseline measure that significantly distinguished remitters from nonremitters was higher dyskinetic movement scores in nonremitters. Otherwise, subjects who developed remission were clinically indistinguishable at baseline from those who did not achieve remission. Tardive dyskinesia has been identified previously as a risk factor for poor outcomes in schizophrenia (Lieberman, *et al.*, 1996; Murray and Van Os, 1998). Poor response to drug treatment in first-episode schizophrenia has been linked to a greater risk for the development of TD (Chakos, *et al.*, 1996). Neurodegenerative processes may be involved in the pathogenesis of TD and thus, may contribute to a poorer likelihood of achieving symptomatic remission (Tan, *et al.*, 2005).

Subjects who achieved remission had significantly greater improvements in extrapyramidal symptoms and scores on the TD rating scale during the one-year study. This was not due to the switch from haloperidol to olanzapine as 16% of those previously treated with haloperidol and 17% of those treated previously with olanzapine achieved remission during this one-year open-label study (Table 1). Another recent study also found that achieving remission was associated with improvements in extrapyramidal side effects (Emsley, *et al.*, 2007). These findings suggest that treatments with better neurological side effect profiles may be more likely to be associated with long-term illness improvements.

As expected and not surprisingly, based upon the criteria for remission, we found significant improvements in positive and negative symptoms in the subjects who achieved remission than those who did not. However, remission was also associated with significant improvements in depressive symptoms and activation symptoms. Depressive symptom resolution may be an important factor in achieving remission. In a recent report (Ascher-Svanum, *et al.*, 2005), remission of depressive symptoms in schizophrenia was related to better mental health functioning, greater life satisfaction, better family relationships, greater medication adherence, lower likelihood of seeking emergency psychiatric services, fewer alcohol-related problems, and a lower risk of suicidal behaviours. This relationship to functional outcomes suggests that more attention should be focused on depressive symptoms in schizophrenia.

Changes in the LOF and quality of life scores were not significantly different in remitters and nonremitters. However, QLS scores were numerically higher at baseline in remitters (60

vs. 46) and tended to improve more in remitters than non-remitters (6 vs. 3.7; $P = 0.09$). Others have reported that higher quality of life scores at baseline and greater improvements in life quality during treatment are predictive of remission (Ascher-Svanum, *et al.*, 2005; Dunayevich, *et al.*, 2006; Lasser, *et al.*, 2005). Our findings were not statistically significant possibly because of the relatively small sample size and due to the large variance and standard error of the mean QLS scale scores. The small sample size is a limitation of the study, yet with significant findings in depressive symptoms and side effects, the results are encouraging and should encourage future investigations to replicate these findings and examine remission in relation to the improvements in quality of life in a larger sample.

Remission is differentiated from the concept of recovery, which generally implies the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology (Andreasen, *et al.*, 2005; Bellack, 2006; Leucht and Lasser, 2006). The movement in mental health care to promote recovery is in due, in part, to the President's New Freedom Commission on Mental Health (2006). Unfortunately, the field has not developed a standardised definition or criteria for recovery (Bellack, 2006; Leucht and Lasser, 2006; Resnick, *et al.*, 2005). Thus, remission is a more defined and achievable goal and is a necessary but not a sufficient step toward recovery (Lieberman, *et al.*, 2002). Remission does not imply the same symptomatic improvements as recovery but serves as a standardised way to measure symptoms that are remained at a low level for a period of time. However, the current definition of remission implies symptoms that do not interfere with function, and this is not necessarily true. Because of the way remission is currently defined, people with schizophrenia in remission may continue to be cognitively impaired, socially isolated, unemployed, and marginalised, all of which has led some experts to recommend that 'symptomatic remission' may be a better term (Kopelowicz, *et al.*, 2005; Remington and Kapur, 2005). Also, it should be noted that remission is not a static process. Remission criteria typically require that subjects meet the symptom criteria for six consecutive months to be considered in remission. Therefore, minor symptom fluctuations, which commonly occur, may prevent some subjects from meeting remission criteria. Nonetheless, until a more widespread consensus on appropriate rating methods for other aspects of schizophrenia are developed, the use of positive and negative symptom criteria will remain our best measures of remission.

Our study is limited by the small sample of subjects who achieved remission. Although the small number of remitters did not preclude us from detecting significant differences in motor side effects and depressive symptoms, the small number of remitters may have precluded us being able to identify other clinical correlates of remission. Another limitation is the fact that all subjects had a chronic, treatment-resistant form of the illness, and the previous illness stability of the subjects is unknown. Therefore, these results may not be generalisable to first episode or treatment-responsive people with schizophrenia. Nonetheless, the results are applicable to a significant proportion of people with schizophrenia who suffer from this illness and are encouraging in that, even in this cohort of chronic subjects, achieving remission within one year is possible. Finally, we did not measure cognition in this study. Cognitive functioning has been found to be improved in people with schizophrenia who are considered to be in full recovery (Kopelowicz, *et al.*, 2005; Robinson, *et al.*, 2004); however, its relationship to remission criteria is not yet clarified (Auslander and Jeste, 2004; Lieberman and Kopelowicz, 2005; Emsley, *et al.*, 2007; Barbarotto, *et al.*, 2001; Gold *et al.*, 2002; Smith, *et al.*, 2002; Harvey, *et al.*, 2007; Helldin, *et al.*, 2006).

In conclusion, our findings show that it is difficult to predict which people with schizophrenia may achieve remission. The best predictor of remission is low levels of dysknetic movements, whereas symptom severity does not necessarily predict remission. During treatment, those who achieve remission are more likely to also have improvements

in depressive symptoms and symptoms of activation and may have a tendency to improve in quality of life measures and important areas of focus for improving long-term outcomes. In addition, those people achieving remission had significantly greater improvements in both ratings of extrapyramidal side effects and TD. However, the question regarding the domains of neurocognition which improve in people with schizophrenia undergoing remission, as well as the question whether psychosocial functioning can be improved, remain unanswered. Future studies should address these issues and, thereby, develop better ways of defining, operationalising, and measuring remission and recovery.

Acknowledgments

This project was supported by the Advanced Center for Intervention and Services Research (P50 MH40279, Buchanan, RW, PI) and (R01 MH45074, Buchanan RW, PI). The authors would like to thank Yang Yu, MS for data analysis. Preliminary results of this manuscript were presented at the 9th Annual College of Psychiatric and Neurologic Pharmacists Meeting, Baltimore, Maryland, April 2006.

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Table 1

Demographic characteristics

	No remission (<i>N</i> = 36)	Remission (<i>N</i> = 7)
Age (years)	43.8 ± 8.4	45.8 ± 8.2
Sex (%)	72M (26/36)	71M (5/7)
Race (%)	61W (22/36)	71W (5/7)
Age of onset (years)	22.0 ± 7.3	22.1 ± 8.1
Duration of illness	21.8 ± 8.9	23.7 ± 7.1
Previous treatment	21 haloperidol (58%) 15 olanzapine (42%)	4 haloperidol (57%) 3 olanzapine (43%)

Table 2

Clinical characteristics at baseline

	No remission (<i>N</i> = 36)	Remission (<i>N</i> = 7)	Statistics
LOF	16.6 ± 6.4 (<i>N</i> = 32)	19.5 ± 2.6 (<i>N</i> = 6)	<i>t</i> = -1.08, <i>df</i> = 38, <i>P</i> = 0.28
HAM-D total	10.3 ± 7.9	8.9 ± 6.1	<i>t</i> = 0.44, <i>df</i> = 41, <i>P</i> = 0.66
BPRS total	35.6 ± 9.8	36.0 ± 10.2	<i>t</i> = -0.10, <i>df</i> = 41, <i>P</i> = 0.92
Positive	8.6 ± 4.0	7.4 ± 2.6	<i>t</i> = 0.73, <i>df</i> = 41, <i>P</i> = 0.47
Hostility	5.4 ± 2.4	6.4 ± 3.4	<i>t</i> = -0.93, <i>df</i> = 41, <i>P</i> = 0.36
Activation	4.7 ± 1.8	5.0 ± 2.9	<i>t</i> = -0.37, <i>df</i> = 41, <i>P</i> = 0.71
SANS total	33.8 ± 11.4	25.5 ± 5.1 (<i>N</i> = 6)	<i>t</i> = 1.75, <i>df</i> = 40, <i>P</i> = 0.09
CGI	4.8 ± 0.9	4.6 ± 0.5	<i>t</i> = 0.76, <i>df</i> = 41, <i>P</i> = 0.45
QLS total	46.1 ± 21.2 (<i>N</i> = 32)	58 ± 10.9 (<i>N</i> = 6)	<i>t</i> = -1.33, <i>df</i> = 36, <i>P</i> = 0.19
MPRC TD score	4.2 ± 4.6 (<i>N</i> = 32)	1.8 ± 1.5 (<i>N</i> = 6)	<i>t</i> = 2.32, <i>df</i> = 26.1, <i>P</i> = 0.03
SAS score	2.1 ± 3.0 (<i>N</i> = 34)	3.1 ± 3.2	<i>t</i> = -0.79, <i>df</i> = 41, <i>P</i> = 0.47

LOF, Level of Functioning Scale; HAM-D, Hamilton Depression Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; CGI, Clinical Global Impressions; QLS, Quality of Life Scale; MPRC TD, Maryland Psychiatric Research Center Tardive Dyskinesia Scale; SAS, Simpson-Angus Scale.

This table represents unadjusted scores for baseline characteristics in the study groups.

Table 3

Baseline and endpoint least squares means (standard error)

	Remitters baseline	Nonremitters baseline	Remitters endpoint	Nonremitters endpoint	Statistics
LOF	17.1 (0.1)	17.1 (0)	17.8 (1.7)	17.9 (0.8)	$F = 2.67$, $df = 260$, $P = 0.08$
BPRS total ^a	35.6 (1.3)	35.5 (0.6)	27.5 (2.3)	34.4 (1.1)	$F = 3.61$, $df = 13,412$, $P = 0.001$
Positive ^a	8.3 (0.2)	8.4 (0.1)	5.4 (0.7)	8.0 (0.4)	$F = 4.95$, $df = 13,422$, $P = 0.003$
Hostility	5.9 (0.5)	5.4 (0.2)	3.7 (0.6)	5.2 (0.4)	$F = 1.49$, $df = 13,422$, $P = 0.12$
Activation ^a	4.8 (0.5)	4.7 (0.1)	3.4 (0.4)	4.5 (0.2)	$F = 2.33$, $df = 1425$, $P = 0.005$
SANS total ^a	31.5 (0.6)	32.8 (0.3)	24.0 (2.1)	31.5 (1.3)	$F = 6.73$, $df = 13,425$, $P = 0.001$
CGI ^a	4.7 (0.1)	4.8 (0)	3.7 (0.3)	4.7 (0.1)	$F = 5.66$, $df = 13,431$, $P < 0.001$
HAM-D ^a	9.6 (0.8)	10.1 (0.5)	5.6 (2.2)	8.6 (0.9)	$F = 5.03$, $df = 13,435$, $P = 0.001$
QLS total	49.0 (0.6)	48.4 (0.2)	57.0 (5.9)	52.8 (2.2)	$F = 2.52$, $df = 261$, $P = 0.09$
MPRC TD Score ^a	3.2 (0.3)	3.6 (0.1)	2.6 (1)	3.2 (0.8)	$F = 101.6$, $df = 645$, $P < 0.001$
SAS ^a	2.7 (0.4)	2.4 (0.2)	0.8 (0.3)	1.6 (0.3)	$F = 2.24$, $df = 13,447$, $P = 0.007$

LOF, Level of Functioning Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; CGI, Clinical Global Impressions; HAM-D, Hamilton Depression Rating Scale; QLS, Quality of Life Scale; MPRC TD, Maryland Psychiatric Research Center Tardive Dyskinesia Scale; SAS, Simpson-Angus Scale.

LS means adjusted for baseline.

^aMixed modeling time by group interactions-significant results.