

Empirical Validation of Primary Negative Symptoms: Independence From Effects of Medication and Psychosis

Mary E. Kelley, M.S., Daniel P. van Kammen, M.D., Ph.D., and Daniel N. Allen, Ph.D.

Objective: Recent studies of negative symptoms in schizophrenia—specifically, those involving the deficit syndrome—have focused on uncovering the symptoms that are primary to the disease rather than secondary to the psychotic process. One of the foremost concerns in this effort is establishing whether the negative symptoms observed are the result of medication effects. **Method:** This study used negative symptom ratings obtained in a drug withdrawal paradigm to compare symptom profiles in the same schizophrenic patients when they were on and off antipsychotic drug treatment. The study group consisted of 93 physically healthy male patients with DSM-III-R-defined schizophrenia. Principal components analysis was performed on negative symptom data obtained separately during haloperidol treatment and again when the patients were drug free to determine whether there were meaningful factor scores that were consistent across medication conditions. Drug withdrawal effects on negative symptom factors were then tested for associations with secondary sources of variance including extrapyramidal side effects, anxiety/depression, and psychosis. **Results:** Two factors, termed affective flattening and diminished motivation, exhibited similar loadings when the patients were both on and off medication. Changes in motivation were associated with changes in anxiety/depression and psychosis, while changes in affective flattening were associated with changes in extrapyramidal side effects. **Conclusions:** The documented secondary sources of negative symptoms are related to different and distinct aspects of negative symptoms; this finding will aid in the identification of primary negative symptoms.

(*Am J Psychiatry* 1999; 156:406–411)

The study of negative symptoms in schizophrenia is receiving renewed attention because of the possible effects of the new “atypical” antipsychotic drugs on what were once proposed to be refractory symptoms (1). Although negative symptoms have since been shown to be influenced by both medication and exacerbation, it is clear that some patients have residual negative symptoms (2, 3) that have not responded satisfactorily to traditional pharmacological treatment and may not respond to the new serotonin/dopamine antagonists either (4).

Recent attempts to incorporate the idea of secondary versus primary negative symptoms include categorization by longitudinal presentation (e.g., the deficit syn-

drome [2] and Kraepelinian classifications [5–7]), as well as statistical adjustment for secondary sources (8–10). The focus of evaluations of the deficit syndrome has been to distinguish primary or enduring negative symptoms from those that are the result of medication, exacerbation, or the psychotic process (11), while Kraepelinian classification focuses on continued inability (for at least 5 years) to function independently.

Additional studies have specifically addressed the hypothesis that negative symptoms remain stable over time. Despite differences in follow-up time and scale measurements, most studies support the idea that negative symptoms, while less variable than psychotic symptoms, do change over time (12–17). However, there is also some indication that there is less change in negative symptoms as the illness progresses (15, 18).

Negative symptom syndrome classifications have also been studied for temporal stability. While more liberal classifications show more stability than the symptoms themselves, direct assessment of consistency over time has shown only mild to moderate stability

Received Jan. 26, 1998; revision received Aug. 26, 1998; accepted Sept. 1, 1998. From the VA Pittsburgh Healthcare System, Highland Drive Division; and the Department of Psychiatry and the Department of Neurology, University of Pittsburgh School of Medicine. Address reprint requests to Ms. Kelley, GIM (130U), VA Pittsburgh Healthcare System, University Drive C, Pittsburgh, PA 15240.

Supported by a VA Merit Review Board grant to Dr. van Kammen and NIMH grant MH-44841.

(19–21). In contrast, the deficit syndrome has demonstrated more adequate stability (2, 20, 22, 23).

Specific pharmacological intervention paradigms have shown direct treatment and withdrawal effects on negative symptoms (24–27). Our group (28) has previously studied symptom profiles (29) in drug-free patients without exacerbation of symptoms in an attempt to empirically identify primary negative symptoms by controlling for level of positive symptoms as well as medication effects. The assessment of negative symptoms in drug-free patients at the time of relapse, combined with a matching assessment when they are on medication, provides a unique opportunity for determining medication and exacerbation effects on negative symptoms. A study by Miller et al. (8) used a paired assessment with a fixed 3-week drug washout and evaluated the secondary effects of extrapyramidal side effects, psychosis, disorganization, and depression. These investigators concluded that negative symptoms increased following drug withdrawal and that the change was also associated with changes in positive symptoms and symptoms of disorganization. However, in a competing model, there were no significant stand-alone predictors of the change in negative symptoms.

Since the effect of atypical antipsychotic agents on negative symptoms has been suggested to be their advantage over traditional antipsychotics, it is important to define the concept of negative symptoms more clearly with respect to which symptoms respond to treatment, how often they respond, and to what extent. The purpose of the present study was to use a double-blind drug withdrawal paradigm to determine whether meaningful factors that are similar when patients are both on and off medication are present and to evaluate possible secondary sources of negative symptoms.

METHOD

The study group consisted of 93 physically healthy male patients with schizophrenia or schizoaffective disorder who were participating in a relapse prediction/drug withdrawal protocol. All subjects were screened with complete physical, neurological, and psychiatric evaluations conducted by board-certified psychiatrists. Trained staff obtained the diagnostic data from a structured interview in which the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (30) or the Structured Clinical Interview for DSM-III-R (SCID) (31) and a DSM-III-R checklist were used. Patients who met the DSM-III-R criteria for alcohol or substance abuse/dependence were excluded at the time of the study unless they had been in remission for at least 6 months. Diagnostic, clinical, and demographic data were examined at a consensus conference. After complete description of the study to the subjects, written informed consent for the protocol was obtained from each subject and reviewed by the institutional review board.

All subjects were put on a low-monoamine and caffeine- and alcohol-free diet at admission, and their medication was converted to haloperidol for at least 3 months if they were not already being treated with haloperidol. Benztropine was administered in doses of 1–4 mg/day if necessary during stabilization but was withdrawn at least 2 weeks before the preliminary evaluation; thus, no pharmacological control over extrapyramidal side effects was used that could

TABLE 1. Characteristics of 93 Schizophrenic Patients in a Study of Negative Symptoms

Variable	Mean	SD	Range
Age (years)	37.1	8.0	20–63
Age at onset (years)	23.6	4.9	13–35
Duration of illness (years)	13.5	7.2	0.5–30
Dose of haloperidol (mg/day)	10.6	6.5	1–40
Days drug free	37.7	12.4	14–67

affect the data presented. No other medications were given. Identical-looking placebo capsules replaced the haloperidol capsules overnight after baseline procedures were performed. The drug-free period was a maximum of 6 weeks before follow-up procedures. Patients who met criteria for relapse within 6 weeks of drug withdrawal (N=41) were given neurochemistry evaluations and behavioral ratings at that time; the remaining patients (N=52) were evaluated at the end of the 6-week period. Patients remained in the hospital for the duration of the study. Characteristics of the patients are shown in table 1.

Negative symptoms were measured with the Scale for the Assessment of Negative Symptoms (SANS) (32) on a weekly basis by therapists who were blind to medication status. Secondary sources of negative symptoms were evaluated with use of the Bunney-Hamburg global psychosis scale (33), the Brief Psychiatric Rating Scale (BPRS) (34), and a modified version of the Simpson-Angus Rating Scale (35) for extrapyramidal side effects that contained eight of the original 10 items, excluding leg pendulousness and head dropping, which are commonly not rated. Extrapyramidal side effects were approximated by the mean of all eight scores on the Simpson-Angus scale; anxiety/depression was assessed as the mean of scores on the anxiety, depression, and guilt items from the BPRS. Relapse was defined as a 3-point increase in the Bunney-Hamburg global psychosis rating from the baseline psychosis rating established the last week the patients were taking haloperidol. The increase had to be sustained for 3 days before the relapse criterion was considered to have been met.

Principal components analysis (varimax rotation) was performed on the haloperidol-treatment and drug-free SANS items separately to determine whether there were meaningful factor scores that were consistent across medication conditions. Linear regression was then used to determine the relation between the negative symptom factors and possible secondary sources.

RESULTS

Of the 20 SANS items (eliminating global and subjective ratings), a factor including most of the items contained in the affective flattening subscale as well as poverty of speech accounted for 34.5% of the total variance when the patients were taking haloperidol and 42.3% of the variance when they were drug free (table 2). The next highest factor included similar items when the patients were on and off medication, consisting of mostly anhedonia and apathy items; this similar factor was observed in a combination of medicated and unmedicated patients by Keefe et al. (6). The haloperidol condition and drug-free condition factor loadings were compared across all 20 variables for these two factors; the resulting Pearson correlation coefficients were 0.923 and 0.927 for the affective and anhedonia/apathy factors, respectively (in each case, $df=18$, $p<0.0005$). The remaining factors included what have been found to be disorganization/positive symptom items, which are considered to be dimensions independent of negative symptoms and thus were not pursued in further analysis (table 3).

TABLE 2. Loadings on Two Factors of Symptoms of Schizophrenic Patients Both On and Off Medication With Haloperidol

Factor and Item	Loading		Percent of Variance	
	Haloperidol	Drug Free	Haloperidol	Drug Free
Affective flattening			34.5	42.3
Unchanging facial expression	0.891	0.835		
Decreased spontaneous movements	0.787	0.748		
Paucity of expressive gestures	0.896	0.884		
Affective nonresponsivity	0.752	0.749		
Lack of vocal inflections	0.883	0.794		
Poverty of speech	0.733	0.571		
Diminished motivation			14.6	12.4
Grooming and hygiene	0.758	0.709		
Lack of persistence at work or school	0.772	0.802		
Physical anergia	0.678	0.681		
Recreational interests and activities	0.797	0.777		
Sexual interests and activity	0.725	0.634		
Ability to feel intimacy	0.450	0.594		
Relationships with friends and peers	0.632	0.700		

For use in further analysis, means of the individual items with high loadings (>0.50)—all items listed in table 2—were used as approximate scores for the factors; these factors were termed affective flattening and diminished motivation. To test the “primary” nature of the factors, effects of withdrawal on secondary sources such as psychosis, extrapyramidal side effects, and anxiety/depression were tested for significant associations with the effect of withdrawal on negative symptoms (table 4). While changes in motivation were correlated with changes in psychosis and anxiety/depression, the effect of withdrawal on affective flattening was associated only with change in extrapyramidal side effects.

DISCUSSION

This study used an evaluation of patients’ symptoms when they were on and off medication to discriminate primary from secondary negative symptoms associated with pharmacological treatment (i.e., drug-responsive, drug-induced) (36) and those secondary to or intensified by psychotic exacerbation (27, 37). The fact that factor structures of negative symptoms were similar with and without medication lends support for the idea that the relationships among the symptoms are independent of both medication and exacerbation. This result is unique to this study and particularly relevant for the further understanding of the primary/secondary distinction in the study of negative symptoms.

TABLE 3. Disorganization Factors for Schizophrenic Patients On and Off Medication With Haloperidol

Variable	Percent of Variance
On haloperidol	
Third factor: blocking, social inattentiveness, and latency of response	10.2
Fourth factor: poverty of content	5.4
Fifth factor: inattentiveness during mental status testing and inappropriate affect	5.1
Drug free	
Third factor: blocking, social inattentiveness, latency of response, lack of eye contact, and inattentiveness during mental status testing	7.6
Fourth factor: poverty of content and inappropriate affect	5.7

In schizophrenia research, use of factor analysis to determine clusters of symptoms is well documented. Most studies have attempted to verify the original positive/negative symptom dichotomy proposed by Crow (1). Considerable evidence has shown that a third syndrome, loosely termed disorganization, exists separately from both the positive and negative dimensions (38–40). However, the factor analysis of negative symptoms along with positive symptoms will emphasize their similarities, relative to psychotic symptoms, and minimize their differences. This is true because principal components analysis and further extensions to factor analysis account only for the variance in the data at hand.

Factor analyses of negative symptoms only are more clearly able to aid in the distinction among patterns of negative symptoms that may be different in their etiology and course. Despite differences in study populations and severity of illness among study groups, the studies thus far, including the current one, have shown strikingly similar results in regard to underlying negative symptom factors (6, 39, 41–44). In particular, these studies also showed a wide variation in sample sizes (range=40–549). The factors emerging from these studies have consistently included ones that represent affective flattening and diminished motivation (anhedonia and apathy) and various numbers of factors representing disorganization (e.g., attentional impairment, alogia, poverty of content).

Further analysis indicated that the negative symptom factors are also differentiated by their secondary correlates. Specifically, diminished motivation was associated with exacerbation and mood effects, while affective flattening showed only medication effects. This would indicate that the motivation factor represents the aspect of negative symptoms that is responsive to traditional antipsychotic treatment; i.e., it parallels changes in psychosis. The affective flattening factor would in turn represent those negative symptoms that do not respond to antipsychotic treatment and may in fact be drug-induced. Thus, it appears that in the search for primary negative symptoms, a first step would be to focus on this affective cluster of symptoms rather than lack of motivation. In cases where the

TABLE 4. Regression Results: Predicting the Effect of Withdrawal of Medication on Negative Symptoms in Schizophrenic Patients^a

Variable	Beta	SE	t	p	Model R ²	F (df=3, 88)	p
Dependent variable: change in affective flattening ^b					0.19	6.76	<0.0005
Change in extrapyramidal side effects ^c	0.867	0.243	3.56	0.001			
Change in anxiety/depression ^d	0.092	0.118	0.78	n.s.			
Change in psychosis ^e	0.082	0.049	1.69	n.s.			
Constant	0.103						
Dependent variable: change in motivation ^b					0.30	12.60	<0.0005
Change in extrapyramidal side effects ^c	0.149	0.194	0.77	n.s.			
Change in anxiety/depression ^d	0.209	0.094	2.23	0.03			
Change in psychosis ^e	0.162	0.039	4.18	<0.0005			
Constant	-0.006						

^a Change scores computed as score when taking haloperidol minus score when drug free.

^b Calculated as the mean of the scale items indicated for each factor in table 2.

^c Mean of all Simpson-Angus scale scores.

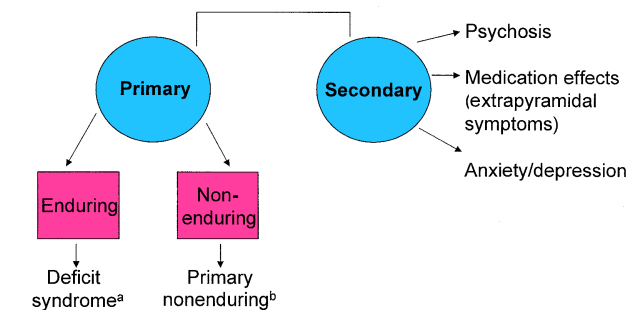
^d Cluster from BPRS scores.

^e Bunney-Hamburg global psychosis scale score.

newer antipsychotics (i.e., those with fewer extrapyramidal side effects) are being used or in the case of a drug-free evaluation, we suggest that these symptoms may be a relatively good measure of primary negative symptoms, which could then be tested over time for longitudinal stability. In addition, this cluster of symptoms may be specific targets for future improvements in pharmacological treatment.

While it may be tempting to control statistically for the effects of extrapyramidal symptoms in order to eliminate these effects, we suggest that this approach be used with caution. It is clear to a certain extent that these two observational concepts, negative symptoms and extrapyramidal side effects, overlap considerably, and that drug-induced negative symptoms may in fact be a component of extrapyramidal side effects and vice versa. In addition, it is likely that patients with affective flattening are more susceptible to medication effects and extrapyramidal side effects, which would indicate that neither process is more "primary" but that these behavioral manifestations may have a similar source. Thus, we suggest that the two syndromes may not be statistically independent but are conceptually independent, and that controlling for the variance in negative symptoms associated with extrapyramidal side effects would be inappropriate if the two syndromes are indeed caused by the same mechanism. The only way to assess the natural course of these two syndromes is by removing or reducing the causes of extrapyramidal side effects pharmacologically, through evaluation of patients when they are drug free or evaluation of the newer antipsychotics, combined with careful and rigorous longitudinal observation.

The idea that affective flattening and poverty of speech may be more stable over time and less responsive to treatment has been demonstrated through previous longitudinal studies (12) and was discussed in Crow's reevaluation of the two-syndrome concept (45). Mueser et al. (14) noted time effects for anhedonia and avolition, but not affective flattening or alogia, in a 1-year follow-up. McGlashan and Fenton (22) also showed changes over time for all subscales of the SANS except affective flattening in an extended (ap-

FIGURE 1. The Search for Primary Negative Symptoms in Schizophrenia: A Two-Stage Process

^a Carpenter et al. (2).

^b Tandon et al. (3).

proximately 5-year) follow-up study. In addition, Fenton and McGlashan (20) noted that among the six prominent cross-sectional subtype classification systems, affective flattening and poverty of speech are the only symptoms shared by all. These authors had previously proposed (15) that these symptoms be added as a criterion for a diagnosis of schizophrenia, which has become a reality with DSM-IV.

The terms "primary" and "secondary" need clarification at this time. Specifically, the differentiation must be made between primary enduring negative symptoms (i.e., the deficit syndrome) and what may be termed primary nonenduring negative symptoms (3), i.e., those that may be primary to the illness but still fluctuate with exacerbation. We propose that the empirical differentiation of primary negative symptoms is a two-stage process. Medication and exacerbation effects, as well as effects of other secondary sources, must first be uncovered and, if necessary, controlled statistically. The aspects of negative symptoms that are not associated with secondary effects must then be tested for longitudinal stability (figure 1). While these two stages may be evaluated retrospectively with appropriate analytic techniques, it is not clear that the secondary nature of symptoms can be determined reli-

ably by using clinical judgment at the time of assessment (46). In addition, it is not clear what frequency of longitudinal assessment should be used to prove stability; if the primary/secondary distinction is valid, it should hold up under the more rigorous scrutiny of monthly or weekly assessments. Future research on independent samples is needed to validate both the findings of the current study and the possible longitudinal stability of these measures.

REFERENCES

1. Crow TJ: Molecular pathology of schizophrenia: more than one disease process? *Br Med J* 1980; 280:66-68
2. Carpenter WT Jr, Heinrichs DW, Wagman AMI: Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry* 1988; 145:578-583
3. Tandon R, Jibson MD, Taylor SF, DeQuardo JR: Conceptual models of the relationship between positive and negative symptoms, in *Contemporary Issues in the Treatment of Schizophrenia*. Edited by Shriqui CL, Nasrallah HA. Washington, DC, American Psychiatric Press, 1995, pp 109-124
4. Carpenter WT Jr, Conley RR, Buchanan RW, Breier A, Tamminga CA: Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995; 152:827-832
5. Keefe RSE, Mohs RC, Losonczy MF, Davidson M, Silverman JM, Kendler KS, Horvath TB, Nora R, Davis KL: Characteristics of very poor outcome schizophrenia. *Am J Psychiatry* 1987; 144:889-895
6. Keefe RSE, Harvey PD, Lenzenweger MF, Davidson M, Apter SH, Schmeidler J, Mohs RC, Davis KL: Empirical assessment of the factorial structure of clinical symptoms in schizophrenia: negative symptoms. *Psychiatry Res* 1992; 44:153-165
7. Keefe RSE, Frescka E, Apter SH, Davidson M, Macaluso JM, Hirschowitz J, Davis KL: Clinical characteristics of Kraepelinian schizophrenia: replication and extension of previous findings. *Am J Psychiatry* 1996; 153:806-811
8. Miller DD, Flaum M, Arndt S, Fleming F, Andreasen NC: Effect of antipsychotic withdrawal on negative symptoms in schizophrenia. *Neuropsychopharmacology* 1994; 11:11-20
9. Möller H-J: The negative component in schizophrenia. *Acta Psychiatr Scand* 1995; 91(suppl 388):11-14
10. Tollefson GD, Sanger TM: Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *Am J Psychiatry* 1997; 154:466-474
11. Kirkpatrick B, Buchanan RW, McKenney PD, Alphas LD, Carpenter WT Jr: The schedule for the deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Res* 1989; 30:119-123
12. Pogue-Geile MF, Harrow M: Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. *Schizophr Bull* 1985; 11:427-439
13. Johnstone EC, Owens DGC, Frith CD, Crow TJ: The relative stability of positive and negative features in chronic schizophrenia. *Br J Psychiatry* 1986; 150:60-64
14. Mueser KT, Douglas MS, Bellack AS, Morrison RL: Assessment of enduring deficit and negative symptom subtypes in schizophrenia. *Schizophr Bull* 1991; 17:565-582
15. McGlashan TH, Fenton WS: The positive-negative distinction in schizophrenia: review of natural history validators. *Arch Gen Psychiatry* 1992; 49:63-72
16. Arndt S, Andreasen NC, Flaum M, Miller D, Nopoulos P: A longitudinal study of symptom dimensions in schizophrenia: prediction and patterns of change. *Arch Gen Psychiatry* 1995; 52:352-360
17. Häfner H, Maurer K: Epidemiology of positive and negative symptoms in schizophrenia, in *Contemporary Issues in the Treatment of Schizophrenia*. Edited by Shriqui CL, Nasrallah HA. Washington, DC, American Psychiatric Press, 1995, pp 125-154
18. Eaton WW, Thara R, Federman B, Melton B, Liang K-Y: Structure and course of positive and negative symptoms in schizophrenia. *Arch Gen Psychiatry* 1995; 52:127-134
19. Häfner H, Maurer K: Are there two types of schizophrenia? true onset and sequence of positive and negative syndromes prior to first admission, in *Negative Versus Positive Schizophrenia*. Edited by Marneros A, Andreasen NC, Tsuang MT. Berlin, Springer-Verlag, 1991, pp 134-159
20. Fenton WS, McGlashan TH: Testing systems for assessment of negative symptoms in schizophrenia. *Arch Gen Psychiatry* 1992; 49:179-184
21. Marneros A, Deister A, Rohde A: Validity of the negative/positive dichotomy for schizophrenic disorders under long-term conditions. *Schizophr Res* 1992; 7:117-123
22. McGlashan TH, Fenton WS: Subtype progression and pathophysiological deterioration in early schizophrenia. *Schizophr Bull* 1993; 19:71-84
23. Fenton WS, McGlashan TH: Antecedents, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. *Am J Psychiatry* 1994; 151:351-356
24. Tandon R, Goldman RS, Goodson J, Greden JF: Mutability and relationship between positive and negative symptoms during neuroleptic treatment in schizophrenia. *Biol Psychiatry* 1990; 27:1323-1326
25. Tandon R, Ribeiro SCM, DeQuardo JR, Goldman RS, Goodson J, Greden JF: Covariance of positive and negative symptoms during neuroleptic treatment in schizophrenia: a replication. *Biol Psychiatry* 1993; 34:495-497
26. Addington J, Addington D: Positive and negative symptoms of schizophrenia: their course and relationship over time. *Schizophr Res* 1991; 5:51-59
27. van Kammen DP, Peters JL, Yao JK, van Kammen WB, Neylan T, Shaw D, Linnoila M: Norepinephrine in acute exacerbations of chronic schizophrenia: negative symptoms revisited. *Arch Gen Psychiatry* 1990; 47:161-168
28. Kelley ME, Gilbertson M, Mouton A, van Kammen DP: Deterioration in premorbid functioning in schizophrenia: a developmental model of negative symptoms in drug-free patients. *Am J Psychiatry* 1992; 149:1543-1548
29. Andreasen NC, Flaum M, Swayze VW II, Tyrell G, Arndt S: Positive and negative symptoms in schizophrenia: a critical reappraisal. *Arch Gen Psychiatry* 1990; 47:615-621
30. Spitzer RL, Endicott J: *Schedule for Affective Disorders and Schizophrenia—Lifetime Version*, 3rd ed. New York, New York State Psychiatric Institute, Biometrics Research, 1979
31. Spitzer RL, Williams JBW, Gibbon M, First MB: *Instruction Manual for the Structured Clinical Interview for DSM-III-R (SCID)*. New York, New York State Psychiatric Institute, Biometrics Research, 1989
32. Andreasen NC: Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry* 1982; 39:784-788
33. Bunney WE Jr, Hamburg DA: Methods for reliable longitudinal observation of behavior. *Arch Gen Psychiatry* 1963; 9:280-294
34. Overall JE, Gorham DR: *The Brief Psychiatric Rating Scale*. *Psychol Rep* 1962; 10:799-812
35. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; 212:11-19
36. van Kammen DP, Mouton A, Kelley M, Breeding W, Peters J: Explorations of dopamine and noradrenaline activity and negative symptoms in schizophrenia: concepts and controversies, in *Negative Versus Positive Schizophrenia*. Edited by Marneros A, Andreasen NC, Tsuang MT. Berlin, Springer-Verlag, 1991, pp 317-340
37. Rosen WG, Mohs RC, Johns CA, Small NS, Kendler KS, Horvath TB, Davis KL: Positive and negative symptoms in schizophrenia. *Psychiatry Res* 1984; 13:277-284
38. Bilder RM, Mukherjee S, Rieder RO, Pandurangi AK: Symptomatic and neuropsychological components of defect states. *Schizophr Bull* 1985; 11:409-419

39. Liddle PF: The symptoms of chronic schizophrenia: a re-examination of the positive-negative dichotomy. *Br J Psychiatry* 1987; 151:145-151
40. Andreasen NC, Arndt S, Alliger R, Miller D, Flaum M: Symptoms of schizophrenia: methods, meanings, and mechanisms. *Arch Gen Psychiatry* 1995; 52:341-351
41. Mueser KT, Sayers SL, Schooler NR, Mance RM, Haas GL: A multisite investigation of the reliability of the Scale for the Assessment of Negative Symptoms. *Am J Psychiatry* 1994; 151: 1453-1462
42. Gibbons RD, Lewine RRJ, Davis JM, Schooler NR, Cole JO: An empirical test of a Kraepelinian vs a Bleulerian view of negative symptoms. *Schizophr Bull* 1985; 11:390-396
43. Stuart GW, Malone V, Currie J, Klimidis S, Minas IH: Positive and negative symptoms in neuroleptic-free psychotic inpatients. *Schizophr Res* 1995; 16:175-188
44. Toomey R, Kremen WS, Simpson JC, Samson JA, Seidman LJ, Lyons MJ, Faraone SV, Tsuang MT: Revisiting the factor structure for positive and negative symptoms: evidence from a large heterogeneous group of psychiatric patients. *Am J Psychiatry* 1997; 154:371-377
45. Crow TJ: The two-syndrome concept: origins and current status. *Schizophr Bull* 1985; 11:471-486
46. Flaum M, Andreasen NC: The reliability of distinguishing primary versus secondary negative symptoms. *Compr Psychiatry* 1995; 36:421-427