CME

Association of Depressive Symptoms With Worse Functioning in Schizophrenia: A Study in Older Outpatients

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Background: Subsyndromal depressive symptoms are highly prevalent and associated with substantial impairments of daily function in the general population. Depressive symptoms are common in schizophrenia. However, few studies have examined the relationship of functioning and well-being to the presence of depressive symptoms in schizophrenia.

Method: 202 middle-aged or elderly outpatients with schizophrenia (DSM-III-R or DSM-IV criteria) were categorized by severity of depressive symptoms on the Hamilton Rating Scale for Depression (HAM-D) using previously validated cutoff points, i.e., HAM-D total score ≤ 6 (low), from 7 to 16 (medium), and ≥ 17 (high). We also assessed severity of positive and negative symptoms, movement disorders, neurocognitive performance, daily functioning, and health-related quality of well-being with standardized measures.

Results: A total of 11.4% of patients had HAM-D scores ≥ 17, and 56.4% had HAM-D scores from 7 to 16. Even after adjusting for severity of other psychopathology, patients with more severe depressive symptoms had significantly worse everyday functioning ($p < .02$), except for physical functioning, and health-related quality of well-being ($r = –.365$, $p < .001$) than did those with lower HAM-D scores. These differences were unrelated to those in demographics, extrapyramidal symptoms, tardive dyskinesia, neurocognitive performance, or number of physical illnesses.

Conclusion: The results suggest the importance of evaluating schizophrenia patients for the presence of depressive symptoms. Effectiveness of adjunct treatment of depressive symptoms with antidepressants and psychosocial management in improving functioning of schizophrenia patients deserves further study.

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Depressive symptoms are common among schizophrenia patients, with prevalence estimates ranging from 20% to 80%.[1–4] There is considerable evidence that persons with depressive disorder, or even those with subsyndromal depressive symptoms in the general population, experience impairment of daily functioning and an increased number of disability days.[5–10] Depression comorbid with medical conditions such as myocardial infarction or cancer is associated with an increased risk of physical complications and mortality.[11,12] Yet, the impact of depressive symptoms on functioning and quality of life in schizophrenia has not been evaluated adequately. This is a particularly important issue to study in older patient populations, since aging itself is a risk factor for certain types of functional decline.

Some studies have suggested that depressive symptoms could be a core component associated with a favorable course and outcome in acute schizophrenia,[13] while others have noted that depressive symptoms are associated with a greater risk of suicide and relapse in chronic schizophrenia.[3,14–16] Siris[17] postulates that a depression-like syndrome can play a disastrous role in the long-term course of the illness in at least some patients with schizophrenia. In prior reports involving smaller samples of middle-aged and elderly patients, we found significant associations between depressive symptoms and functional deficits on some measures,[18] but not on others.[19] Our investigations also suggested that cognitive deficits, severity of negative

symptoms (but not of positive symptoms), duration of psychosis, use of anticholinergic medications, and severity of extrapyramidal symptoms (EPS) were each associated with greater impairment in functional capacity and quality of well-being in schizophrenia.[19–23] To fully assess the independent impact of depressive symptoms on functional status in schizophrenia, it is necessary to consider other patient and clinical characteristics that may contribute to patients' functional impairment.

In the present investigation, we examined the relationship of depressive symptoms, as well as other psychopathology, cognitive deficits, and other patient characteristics, to everyday functioning and health-related quality of well-being in a well-characterized large sample of middle-aged and elderly outpatients with schizophrenia. We hypothesized that functioning and health-related quality of well-being would be significantly lower in schizophrenia patients with more severe depressive symptoms than in those with less severe depressive psychopathology. Furthermore, we postulated that the impact of depressive symptoms on functioning would be independent of other relevant patient characteristics.

METHOD

Subjects

Subjects were 202 middle-aged or elderly outpatients with schizophrenia participating in ongoing research at the University of California at San Diego (UCSD) Intervention Research Center (IRC) for Psychosis in Older Adults. Diagnoses were established with the Structured Clinical Interview[24] for DSM-III-R or DSM-IV[25] administered by trained Ph.D. or M.D. fellows and confirmed by consensus at a subsequent staff meeting attended by at least 2 board-certified psychiatrists. A number of these patients have contributed data to prior reports.[4,18,19,26] Patients with schizoaffective disorder and those with a history of major depressive episodes were specifically excluded from the study. The protocol was approved by the UCSD Institutional Review Board, and all subjects (and their legal conservators, if relevant) provided informed written consent prior to participation.

Measures

Sociodemographic information and medical, psychiatric, and pharmacologic history were obtained at intake. Trained geriatric psychiatry fellows conducted neurologic and other physical examinations, and necessary laboratory tests were performed. Other assessments were as follows.

Psychopathology and movement disorders. Severity of depressive symptoms was rated with the 17-item Hamilton Rating Scale for Depression (HAM-D).[27] Patients were categorized into 3 groups by the severity of their depressive symptoms based on previously reported HAM-D cutoff points[4,28,29]: (1) low-severity (HAM-D total score ≤ 6), (2) medium-severity (HAM-D total score from 7 to 16), and (3) high-severity (HAM-D total score ≥ 17).

Global psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS),[30] and positive and negative symptoms were measured with the Scale for the Assessment of Positive Symptoms (SAPS)[31] and the Scale for the Assessment of Negative Symptoms (SANS).[32] EPS were evaluated with the modified Simpson-Angus Scale[33] and tardive dyskinesia, with the Abnormal Involuntary Movement Scale (AIMS).[34,35]

Neurocognitive function. The patients were administered the Mini-Mental State Examination (MMSE)[36] and the Mattis Dementia Rating Scale (DRS).[37] The subjects also completed a comprehensive neuropsychological evaluation consisting of an expanded Halstead-Reitan Battery,[38] selected subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[39] and the California Verbal Learning Test.[40] Using previously published norms,[38,41–43] raw scores on each measure were converted to age-, gender-, and education-corrected T-scores having a mean of 50 and standard deviation of 10 within the normal population. Test scores were grouped into 7 neuropsychological ability areas: (1) verbal, (2) psychomotor/processing speed, (3) abstraction/cognitive flexibility, (4) attention/working memory, (5) learning, (6) retention, and (7) motor skills. These ability areas were defined as described previously.[26] Mean T-scores were calculated for each ability area as well as across the entire neuropsychological battery.

Functioning and well-being. Health-related well-being was measured with the Quality of Well-Being (QWB) scale, which classifies subjects according to 3 subscales of observable functioning (mobility, physical activity, and social activity) and 1 subscale of subjective symptoms.[44] QWB total scores were expressed in terms of an overall rating ranging from 0.0 ("dead") to 1.0 ("perfect health"). The mean for age-comparable healthy adults is 0.71 (SD = 0.09).[18]

We also used the Pfeffer Outpatient Disability scale (POD),[45] a 10-item scale designed to assess patients' level of disability in terms of instrumental activities of daily living (IADLs), such as managing personal finances, and mobility around the community. The information for rating POD items was generally obtained via patient self-report; higher POD scores represent greater disability in IADLs.

Patients' levels of functioning and well-being were also assessed with the 36-Item Short Form Health Survey (SF-36).[46] The SF-36 measures physical functioning, social functioning, role limitations due to physical and emotional problems, mental health and general health perception, bodily pain, and vitality. SF-36 raw scores were transformed to a scale ranging from 0 to 100 using a standard formula,[46] with higher scores indicating better health and functional status.

Table 1. Comparison of Patient Characteristics By Severity of Depressive Symptoms[a]

Characteristics	Severity of Depressive Symptoms[b] Low Severity (A) (N = 65)	Medium Severity (B) (N = 114)	High Severity (C) (N = 23)	F[c]	χ^2	df	p	Significant Group Differences
Continuous variables; mean (SD)								
Age, y	56.1 (9.0)	58.3 (10.2)	55.6 (7.2)	1.51		2,198	.222	
Education, y	12.3 (2.5)	12.3 (2.4)	12.9 (3.5)	0.62		2,198	.537	
Age at onset of schizophrenia, y	30.5 (13.8)	29.7 (13.5)	29.1 (14.6)	0.11		2,192	.897	
No. of physical illnesses[d]	1.7 (1.7)	1.9 (1.4)	2.2 (1.7)	0.64		2,154	.528	
SAPS total score	12.7 (5.0)	16.6 (5.9)	20.8 (6.1)	18.5		2,182	< .001	A < B < C
SANS total score	14.2 (6.2)	16.7 (5.8)	17.7 (5.9)	4.03		2,182	< .019	A < B, C
AIMS total score	4.9 (3.3)	5.1 (3.6)	3.9 (3.6)	1.14		2,171	.321	
Simpson-Angus Scale score	17.5 (4.3)	19.3 (5.4)	19.3 (5.1)	2.14		2,158	.121	
MMSE total score	26.8 (3.4)	26.4 (3.1)	26.0 (2.8)	0.67		2,197	.512	
DRS total score	131.0 (13.8)	130.1 (11.7)	130.3 (10.5)	0.08		2,145	.927	
Overall neuropsychological T-score	42.9 (5.6)	42.3 (6.4)	40.1 (6.4)	1.02		2,121	.363	
Categorical variables, N (%)								
Male	44 (68)	76 (67)	14 (61)		0.37	2	.832	
Non-white	21 (32)	21 (18)	7 (30)		4.88	2	.087	
Currently single	22 (33)	36 (32)	11 (47)		2.27	2	.321	
History of previous psychiatric hospitalization	55 (85)	91 (80)	19 (83)		0.65	2	.723	
Family history of psychosis	10 (15)	18 (16)	6 (26)		1.59	2	.451	
Family history of mood disorder	12 (18)	19 (17)	8 (35)		4.07	2	.130	
Receiving atypical antipsychotics	14 (21)	27 (24)	5 (22)		0.47	2	.977	
Receiving anticholinergic drugs	29 (44)	49 (43)	13 (56)		1.45	2	.483	
Receiving antidepressants	14 (21)	31 (27)	13 (56)		10.5	2	< .01	A, B < C

[a]Abbreviations: AIMS = Abnormal Involuntary Movement Scale, DRS = (Mattis) Dementia Rating Scale, MMSE = Folstein Mini-Mental State Examination, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms.
[b]Low severity: HAM-D 0–6, medium severity: HAM-D 7–16, high severity: = HAM-D ≥ 17; 17-item HAM-D.
[c]Analysis of variance.
[d]Number of DSM-IV Axis III diagnoses (0 to 6).

Procedures

Through patient interviews, trained staff administered the functional measures, and these raters were kept unaware of the patients' scores on psychopathology scales and of their cognitive assessments. We have established high inter-rater reliability for all of these scales, e.g., intraclass correlation coefficients (ICCs) for the QWB and SF-36 were 0.95 and 0.94, respectively (Patterson et al.[18] and A. Sciolla, M.D.; T.L. Patterson, Ph.D.; L.A. McAdams, Ph.D.; et al., manuscript submitted, 2000). The neuropsychological battery has been shown to have excellent test-retest reliability (ICC for 1-year test-retest performance on the overall neuropsychological score was 0.93 in the patients[26]).

Statistical Analysis

Continuous variables were assessed for normality of distribution within groups and for homogeneity of variance across groups, and appropriate transformations were employed when necessary. The Pearson correlation was used to test for correlations among continuous variables. Overall group comparisons were performed on continuous variables with analysis of variance (ANOVA) and appropriate covariates (ANCOVA). In variables showing significant differences among the 3 groups, we performed post hoc pairwise comparisons with Bonferroni corrections to determine which pair of groups had significant differences. Comparisons on categorical variables were performed using chi-square tests. All comparisons were 2-tailed, with p values < .05 being considered significant.

RESULTS

Among the 202 outpatients with schizophrenia, 65 (32.2%) had HAM-D scores ≤ 6 (low-severity depressive symptoms), 114 (56.4%) had HAM-D scores from 7 to 16 (medium-severity depressive symptoms), and 23 (11.4%) had HAM-D scores ≥ 17 (high-severity depressive symptoms) (Table 1). (In general, individual patients with higher HAM-D scores did not have the necessary number of symptoms to meet DSM-III-R or DSM-IV criteria for major depression.) No significant differences were found among these 3 groups in demographic characteristics, marital status, number of physical illnesses, age at onset of schizophrenia, history of at least 1 psychiatric hospitalization, severity of motor symptoms (EPS or tardive dyskinesia), or degree of cognitive impairment.

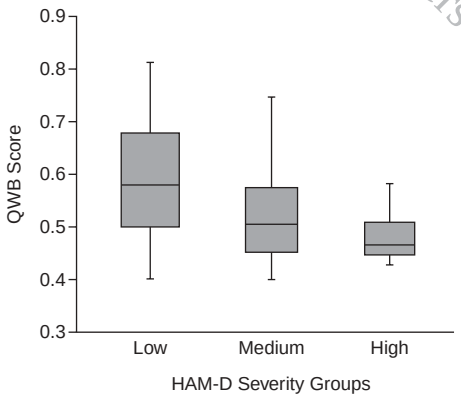
The high-severity patients had more severe positive symptoms (per SAPS total score) than the medium-severity patients, and the latter group had more severe positive symptoms than the low-severity patients. There were no significant differences in severity of negative symptoms (per SANS total score) between the high-

Table 2. The Quality of Well-Being (QWB) Scale Scores and Functioning Measures by Severity of Depressive Symptoms[a]

QWB and Functioning Measures, mean (SD)	Severity of Depressive Symptoms[b] Low Severity (A)	Medium Severity (B)	High Severity (C)	F[c]	df	p	Significant Group Differences
QWB score[d]	0.59 (0.11)	0.52 (0.09)	0.49 (0.06)	10.98	2,160	< .001	A > B, C
POD score[e]	1.5 (2.5)	2.2 (3.2)	4.0 (4.8)	3.64	2,136	.028	A < C
SF-36 factors[f]							
Physical functioning	73.7 (23.5)	65.2 (26.8)	55.5 (20.5)	2.34	2,91	.106	...
Role limitations due to physical problems	69.3 (33.4)	55.8 (36.2)	31.8 (38.9)	4.64	2,91	.012	A > C
Role limitations due to emotional problems	82.8 (30.5)	62.8 (38.8)	33.3 (36.5)	8.01	2,92	< .001	A, B > C
Vitality	63.1 (24.6)	56.5 (22.7)	38.6 (17.9)	4.63	2,91	.012	A > C
Mental health	75.1 (16.4)	66.2 (18.4)	43.6 (17.5)	12.94	2,91	< .001	A, B > C
Social functioning	76.6 (25.4)	68.6 (27.1)	37.5 (32.1)	8.58	2,92	< .001	A, B > C
General health	72.3 (19.2)	65.5 (19.6)	48.0 (22.8)	6.17	2,91	.003	A, B > C
Bodily pain	76.5 (23.3)	70.8 (28.4)	34.5 (17.2)	11.34	2,92	< .001	A, B > C

[a]Abbreviations: HAM-D = Hamilton Rating Scale for Depression, POD = Pfeffer Outpatient Disability scale, SF-36 = 36-item Short Form Health Survey.
[b]Low severity: HAM-D 0–6; medium severity: HAM-D 7–16, high severity: HAM-D ≥ 17; 17-item HAM-D.
[c]Analysis of variance.
[d]A: N = 53; B: N = 92; C: N = 18.
[e]A: N = 45; B: N = 77; C: N = 17.
[f]A: N = 32; B: N = 52; C: N = 11.

Figure 1. Quality of Well-Being (QWB) Scores Among Schizophrenia Patients With Depressive Symptoms of Low, Medium, and High Severity[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression. Box plots represent median and quartiles for the QWB total scores among patients with low- (HAM-D total score ≤ 6; N = 53), medium- (HAM-D total score from 7–16; N = 92), and high-severity (HAM-D total score ≥ 17; N = 18) depressive symptoms.

severity and medium-severity groups; however, both of these groups had more severe negative symptoms than the low-severity group. As expected, the proportion of patients who had been prescribed antidepressant medications was higher among the high-severity patients than among the medium-severity and low-severity patients. However, there were no group differences in percentages of patients receiving typical versus atypical antipsychotics or anticholinergic agents.

The high-severity and medium-severity patients had lower QWB scores than the low-severity patients, with the high-severity group reporting the lowest mean score on the QWB (Table 2). Similarly, the high-severity patients reported worse performance on the IADLs (POD total) relative to the levels reported by the low-severity patients.

Because the SF-36 health functioning assessment was started later in the project, only 95 of the 202 patients received it at baseline. All SF-36 subscale scores, with the exception of the physical functioning subscale score, were lower in the high-severity patients compared with the medium-severity and low-severity patients (see Table 2). The largest group differences were found in the mental health, bodily pain, social functioning, and role limitations due to emotional problems subscales of the SF-36.

There was a significant, but modest, correlation between HAM-D and QWB scores ($r = -.365$, $p < .001$). The relationship between depressive symptoms and QWB score can be more clearly understood by considering the patterns of QWB scores within the 3 patient groups formed on the basis of HAM-D scores. There was no significant relationship between HAM-D and QWB scores at the lower ends of the HAM-D scale; some patients in the low-severity group had high QWB scores while others had low QWB scores (Figure 1). In contrast, the high-severity patients had consistently low QWB scores; the highest QWB score among the high-severity patients was 0.62, which is 1 SD below the mean of healthy subjects.[18]

The severity of depressive symptoms was significantly correlated with severity of positive symptoms ($r = .499$, $p < .001$) and with severity of negative symptoms ($r = .195$, $p < .01$). Since positive and negative symptoms might contribute to a decline of health-related well-being and functioning, we reconducted the above analyses, covarying for SAPS and SANS scores. The pattern of findings remained essentially the same, i.e., the high-severity

patients had lower QWB and SF-36 scores compared with the low-severity patients. The group differences in the POD score, however, became nonsignificant.

DISCUSSION

Sixty-eight percent of the patients in the present study had HAM-D total scores of 7 or higher, suggesting that at least mild depressive symptoms are common in middle-aged and elderly outpatients with schizophrenia even when patients with schizoaffective disorder and those with a past history of a major depressive episode are excluded. This study supports the hypothesis that functioning and health-related quality of well-being are significantly worse in schizophrenia patients with more severe depressive symptoms than in those with minimal or mild depressive symptoms and that this functional impairment cannot be explained on the basis of other differences between these groups in terms of demographic characteristics, positive and negative symptoms, movement disorder, or cognitive deficits.

The present findings extend our previous results with smaller samples (which had also included patients with schizoaffective disorder) suggesting that among older patients with schizophrenia, severity of depressive symptoms correlates with certain measures of functioning such as health-related quality of well-being (Patterson et al.[18] and A. Sciolla, M.D.; T.L. Patterson, Ph.D.; L.A. McAdams, Ph.D.; et al., manuscript submitted, 2000). Since major depression,[47–49] general medical illnesses,[50] cognitive deficits,[51,52] and severity of psychotic symptoms[53,54] are all associated with depressive symptoms as well as with impaired functioning and well-being, it is important to consider the potential impact of each of these factors on our results. Major depression was not likely to be a factor since patients with a current or past history of major depressive episodes and those with schizoaffective disorder were specifically excluded. General medical comorbidity was also unlikely to be a factor, since there were no significant differences in the mean numbers of Axis III diagnoses (medical conditions) among the high-severity, medium-severity, and low-severity patients. Similarly, the 3 groups were comparable on all cognitive measures whether examined in terms of global scores or specific cognitive ability areas. (All 3 groups had mild-to-moderate cognitive deficits, consistent with the levels expected in schizophrenia patients in general.) While positive and negative symptoms as measured with the SAPS and SANS did differ significantly among the 3 depressive-level groups, the pattern of results was still the same when we reconducted the analyses using the SAPS and SANS scores as covariates.

Strengths of the present study include a large sample size, carefully diagnosed and characterized clinically stable outpatients, and use of standardized rating scales for depressive symptoms as well as for functional status and health-related quality of well-being. Furthermore, ratings of depression and other psychiatric symptoms were obtained independent of the assessments of functional status and the cognitive assessments. Different staff members, who were unaware of the results of the other assessments, completed each of these evaluations, minimizing the risk of spurious associations attributable to rater biases.

In a Finnish study by Hintikka et al.,[55] depressive symptoms in patients with schizophrenia were associated with significantly worse performance in only 2 of 6 domains of functioning. There are several important differences between their study and ours. Foremost, their classifications of functional status were done in terms of dichotomous grouping of patients for each domain, whereas we employed functional measures with continuous scales. Also, Hintikka et al. measured depressive symptoms with a self-report/self-administered scale (the Beck Depression Inventory), whereas in the present study, trained staff members based the HAM-D ratings on interviews. Finally, our study was restricted to middle-aged and elderly patients.

One of the limitations of the current study is that we did not include performance-based objective measures of functioning. As noted in the Introduction, some of our prior studies found little relationship between severity of depressive symptoms and level of functioning evaluated by an examiner under laboratory conditions using performance-based measures such as the Direct Assessment of Functional Status[19] and the UCSD Performance-Based Skills Assessment.[56] It is conceivable that depressive symptoms are associated with subjectively reported but not objectively measurable functional deficits. There may be at least 2 possible explanations for the differential impact of depressive symptoms on different types of measures: (1) a depressive response bias may impact self-reports of functioning, i.e., patients with depressive symptoms may be more likely to complain of functional deficits irrespective of their actual everyday functioning,[57] or (2) depressive symptoms may adversely impact patients' ability to motivate or organize themselves in routinely performing functional tasks in everyday living, even though the patients retain their abilities to perform those tasks of everyday living when explicitly prompted by someone else (such as an examiner in the laboratory). The lack of a relationship between depressive symptoms and neuropsychological test performance observed in the present study is consistent with the latter explanation. Thus, the patients' depressive symptoms (at mild-to-moderate levels present in our sample) did not appear to impact their capacity to perform behaviorally based cognitive tasks under laboratory conditions wherein an examiner was prompting them for performance of a task. Whichever of these 2 possibilities explains the observed relationship between depression and functioning, the implications are similar: improving patients' self-perceptions of their quality of well-being and ability to function inde-

pendently might conceivably be achieved through treatment of their depressive symptoms.

Given the cross-sectional design of the present study, we cannot definitively establish the presence of a causal link between depressive symptoms and functional impairment, nor the direction of such a link if there is one. Nonetheless, these results at least suggest the possibility that patients' everyday functioning and quality of well-being might be improved by more direct treatment of their depression symptoms. On the other hand, any link between depressive symptoms and functional status may be bidirectional, and efforts to directly improve patients' functional status could result in a decrease in depressive symptoms. The latter possibility is consistent with behavioral treatments for unipolar depression, e.g., unipolar depression appears to improve when patients are encouraged to engage in more pleasant activities.[58] In her recent review of the relevant literature for older adults, Bruce[59] notes that the evidence strongly suggests a reciprocal and perhaps spiraling relationship between depression and disability. The possibility that improvements in functioning may be obtained from direct treatment of depression and the possibility that depression may be improved from direct behavioral/environmentally based treatments are not mutually exclusive; rather, each is a testable hypothesis worthy of further investigation.

Other limitations of this study include the following: (1) Physical comorbidity was assessed as the number of conditions rather than the type of medical illnesses. This may hinder the discovery of specific medical conditions that could lead to more dysfunction than others. (2) The patients in the present study were recruited from outpatient clinics and were consequently less impaired than those typically seen in institutionalized settings. Thus, the findings may not be generalizable to the latter settings; some investigators have reported that depressive symptoms may be more common among community-dwelling patients.[60] It is worth stressing that today most patients with schizophrenia live in community settings rather than in long-term institutions. Similarly, our study sample included schizophrenia patients in mid-to-late life. We do not know whether our results are applicable to younger patients with schizophrenia. (3) Due to the large number of comparisons, there is an elevated risk of type I error. In part, we controlled for the latter by employing Bonferroni corrections in the specific group comparisons. It should also be noted that the observed significant differences were generally consistent with our a priori hypotheses.

It should be noted that the relationship between HAM-D scores and indices of functioning was not linear. Only the high-severity patients had consistently low levels of functioning; among the low-severity patients, some had very low QWB scores, while others had QWB scores within the normal range. It is apparent that factors other than depressive symptoms must be responsible for the wide differences in functional status in the low-severity group.

In conclusion, the present results extend the literature on depression and functioning by showing that even in the context of a serious mental disorder such as schizophrenia, for which there are many other salient aspects of the disorder that can potentially impact everyday functioning and quality of life (such as positive and negative symptoms or cognitive deficits), depressive symptoms seem to have an independent impact on patients' functioning. Depressive symptoms in this population should, therefore, be evaluated carefully. Depression may also be considered an important target of treatment in patients with schizophrenia. Yet even in the high-severity group (HAM-D total score ≥ 17), over 40% of the patients were not receiving antidepressant medications. There is some evidence that SSRIs are an effective adjunct to antipsychotic medications in improving the depressive symptoms in schizophrenia patients, yet most of the research has been limited to samples of predominantly young adults.[17] While existing treatment guidelines recommend antidepressants for major depressive episodes when they occur in schizophrenia patients, there are few data on the benefits versus risks of adjunct treatment with antidepressants for subsyndromal depressive symptoms.[61] Whether and to what degree antidepressant medication and/or psychotherapy may help restore a more satisfying quality of life and daily functioning in the schizophrenia patients with subsyndromal depressive symptoms remain to be evaluated through carefully controlled intervention studies. In such trials, it will be important to consider not only symptomatic improvement, but also improvement in the domains of everyday functioning and quality of life.

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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