Depressive Symptoms in Schizophrenia Outpatients—Prevalence and Clinical Correlates

Oliver Freudenreich [1,3,4], Constantin Tranulis [2,4], Cori Cather [1,3,4], David C. Henderson [1,3,4], A. Eden Evins [1,3,4], Donald C. Goff [1,3,4]

Abstract

Background: Depressive symptoms are common in schizophrenia and can occur during any phase of the illness. Our goal was to establish the prevalence and correlates of depressive symptoms in a cohort of schizophrenia outpatients at varying stages of their illness who were receiving first- and second-generation antipsychotics. **Method:** In a cross-sectional study, we comprehensively assessed psychopathology in 131 schizophrenia outpatients. Correlations and multiple linear regressions were used to explore correlates of depression, specifically illness course variables, residual positive symptoms, insight and treatment. **Results:** Using a cutoff threshold of fourteen on the Hamilton Depression Rating Scale (HAM-D), 14% of patients experienced clinically significant depression, regardless of age of illness onset or duration of illness. While 22% of the cohort received antidepressants, the treated subgroup was not different from the untreated cohort with regard to depressive symptoms. Patients treated with first-generation antipsychotics did not exhibit more depression compared to those receiving second-generation antipsychotics. A multiple linear regression model that included positive symptoms, insight, meeting schizophrenia criteria in the past month, and being treated with mood stabilizers explained 33.6% of the variance of the HAM-D. **Conclusions:** Our results confirm significant depressive symptoms in a notable proportion of schizophrenia outpatients. Effective treatments are urgently needed to reduce the psychopathology burden beyond psychosis.

Key Words: Schizophrenia, Depression, Insight, Antipsychotics

Introduction

Depression is common among patients with schizophrenia and is associated with a wide range of poor outcomes, including psychotic relapse and suicide (1). Depression may occur at any phase of the illness, including in first-episode patients (2) and in elderly schizophrenia patients (3). The literature shows significant heterogeneity regarding the prevalence of depression in schizophrenia ranging from 7 to 75% (modal depression rate of 25%), depending on the definition of depression (4). Indeed, depression may be used to describe a mood, a syndrome (a cluster of cognitive, affective and neurovegetative symptoms) or a disorder (namely, a major depressive disorder). While generally patients suffering from schizophrenia do not fulfill all criteria for a major depressive disorder, they often present clinically significant depressive symptoms (i.e., the syndrome). Thereafter, we will refer to the syndrome when using the term depression, unless specifically stated otherwise.

Motivated by the hope of reducing the depression burden in schizophrenia with atypical antipsychotics, Siris (4)

[1] Massachusetts General Hospital Schizophrenia Program
[2] Department of Social Medicine, Harvard Medical School
[3] Massachusetts General Hospital
[4] Harvard Medical School

Address for correspondence: Oliver Freudenreich, MD, MGH Schizophrenia Program, Freedom Trail Clinic, 25 Staniford Street, 2nd Floor, Boston, MA 02114
Phone: 617-912-7835; Fax: 617-723-3919;
E-mail: ofreudenreich@partners.org

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suggested a stepwise algorithm for evaluating and treating depression in schizophrenia, beginning with excluding organic etiologies, then increasing support and surveillance given the possibility that the symptoms were prodromal manifestations of relapse or reactions to stress. Symptoms could be treated by reducing typical antipsychotic dosage (if neuroleptic-induced dysphoria, akinesia or akathisia are suspected), or by adding an antiparkinsonian or a benzodiazepine. Persistent symptoms could be addressed by switching to an atypical compound, using antidepressants or mood stabilizers (e.g., lithium). Siris concluded by stressing the need of additional investigations of depressive symptoms in schizophrenia.

One important correlate of depression is the presence of positive symptoms. In a seminal cohort study, Koreen and colleagues (5) followed seventy first-episode patients suffering from schizophrenia for five years with monthly psychopathology ratings. Using *Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III)* criteria, 22% of patients were suffering from major depression at baseline, but with the addition of depression diagnosed by rating scales scores, this percentage increased to 75%. Depression was temporally related to psychotic symptoms, with only 4% of subjects suffering from depression while not psychotic. Consistent with the observed association of depression and psychosis is the earlier finding that depression in the acute phase of schizophrenia decreases in severity with neuroleptic treatment alone (6). One older study suggested that resolution of psychosis was retarded if tricyclic antidepressants were added during the acute illness phase (7). Positive symptoms have also been linked to depression in stable schizophrenia outpatients with residual, persistent psychosis (8).

Complicating the etiology of depressive symptoms in schizophrenia is the effect of antipsychotics. Harrow observed that depression in schizophrenia was correlated with first-generation antipsychotic treatment and suggested that depression was related to anhedonia and mesolimbic dopaminergic reward dysfunction, which can be worsened by the dopaminergic blockade by typical antipsychotics (9). By contrast, second-generation antipsychotics may have some efficacy for depressive symptoms over and above improvement in positive and negative symptoms (10), perhaps due to direct antidepressant effects not mediated by antipsychotic efficacy (11).

In this cross-sectional study, we explored the prevalence and correlates of depressive symptoms in a well-characterized sample of outpatients with schizophrenia, spanning a wide spectrum of illness stages (including first-episode and chronic patients), symptom severity (remitted, partially remitted and ill at the syndromal level) and antipsychotic treatment choice (first- and second-generation antipsychotics, including clozapine). We aimed to answer the following three questions: 1) how common are depressive symptoms in schizophrenia outpatients across the entire life course of the illness? 2) do depressive symptoms persist along with residual psychosis in chronic patients? and, 3) is the prevalence of depression lower in patients treated with second-generation antipsychotics compared to first-generation antipsychotics?

Materials and Methods

Patients

The study cohort consisted of 131 outpatients with schizophrenia who were participating in the Massachusetts General Hospital Schizophrenia Genetics Study. In the genetics study, patients are comprehensively assessed with regard to diagnosis, treatment history and psychopathology. All patients meet *DSM-IV* diagnostic criteria for schizophrenia or schizoaffective disorder, depressed type based on clinical records and confirmed by a Structured Clinical Interview for DSM-III-R (SCID) interview (12). Patients were evaluated in the Freedom Trail Clinic, an urban mental health center that serves as the base for the Massachusetts General Hospital Schizophrenia Program. The study was approved by the responsible institutional review boards, and all study participants provided written, informed consent.

Ratings

Clinical ratings were made by experienced research psychiatrists and symptom raters who established and maintained satisfactory interrater reliability for all measures. From the comprehensive battery used for clinical characterization of subjects in the genetics study, we decided to use the following scales to test our hypotheses:

Depressive symptoms were measured with the Hamilton Depression Rating Scale (HAM-D) (13), items scored on 0 to 2 or 0 to 4 scales, with the sum of the first 17 items used as a global measure of depressive symptoms (range between 0 and 52). We chose the following cutoffs: a HAM-D score below 7 as an indication of insubstantial symptoms (this cutoff is often used to define remission in depressive disorders [14], including the STAR*D trial [15]); and a score of 14 or more as an indication of clinically significant symptoms (based on the work by Leentjens et al. [16] and the choice of a minimum score of 14 to indicate sufficient depression severity to be eligible for participation in the aforementioned STAR*D trial [15]). Given the confounding risks of antidepressants when studying depressive symptoms, antidepressant treatment was used as a variable in the multiple regression models given its potential relationship with depression. This does not imply that prescription of antidepressants equals depression, given that antidepressants, in a small number of cases, clearly have alternative indications, such as obsessive-compulsive symptoms or negative symptoms.

Table 1 Demographic Characteristics of the Sample (total N=131)

Demographic Characteristics	N (%)	Mean	SD	Range
Age		44.2	9.3	22–69
Male	94 (72%)			
Education (years)		11.9	2.5	3–18
Marital status:				
Single	99 (76%)			
Married	7 (5%)			
Divorced/Separated/Widowed	17 (13%)			
Missing information	8 (6%)			
Employed	31 (24%)			
Age of onset		24.3	7.5	9–49
Duration of illness (years)		20.0	9.6	1–45
Antipsychotic medication:				
Only 1st generation	28 (21%)			
At least one is clozapine	31 (24%)			
At least one is 2nd generation (clozapine excluded)	36 (27%)			
>1 antipsychotic (polypharmacy)	29 (22%)			
Antidepressant treatment	29 (22%)			
Anticonvulsant treatment	27 (21%)			
Other psychotropic	48 (37%)			

Psychosis was measured with the positive subscale of the Positive and Negative Syndrome Scale (PANSS) (17), and negative symptoms with its negative subscale. Given a previously reported relationship between insight and depression (e.g., 18, 19), we included the Scale to Assess Unawareness of Mental Disorder (SUMD) (20). The SUMD is a 20-item, semi-structured interview that allows flexible rating of several key aspects of insight. For our study, we used the first three general items: general awareness of suffering from a mental illness (SUMD-illness), awareness of beneficial effect of medication (SUMD-medications) and awareness of negative consequences of the illness (SUMD-consequences). These three items represent separate dimensions of insight and, thus, are considered individually in our study.

Besides psychopathology ratings, we considered two indicators of the specific stage of the illness: the duration of illness and the presence of schizophrenia criteria during the last month (dichotomous variable obtained from SCID). In addition to antidepressants, treatment with mood stabilizers and first- and second-generation antipsychotics was examined. Antipsychotic treatment was classified in three groups: typical antipsychotics, atypical antipsychotics and a clozapine group. Given the proposed definition of atypicality as a higher 5-HT2A than D2 blockade (21), and the clinical consensus that adding a typical antipsychotic does not remove the atypicality of the antipsychotic treatment, we considered that receiving at least one atypical antipsychotic warrants inclusion into the atypical group. We also considered that the unique effectiveness of clozapine is not hindered by co-administered antipsychotics, thus the clozapine group is defined regardless of concomitant medication.

Statistical Analysis

Data were collected and manipulated in Microsoft Access® and Excel®. All statistical tests were performed in SPSS version 15.0 for Windows XP®.

Before conducting correlational analysis, all data were examined with regard to deviation from the normal distribution and for outliers. Because SUMD items distribution was asymmetrical, we computed Spearman rho correlation coefficients between them and HAM-D, PANSS-positive score and PANSS-negative score. As these correlations were performed in an exploratory manner, no correction for multiple comparisons was made and level of significance was set at 0.05, two-tailed.

Two linear regressions were performed using different algorithms in order to minimize the likelihood of suboptimal selection of the predictors of HAM-D total score. The potential variables were PANSS-positive, PANSS-negative, the three SUMD items, the antidepressant treatment status (yes/no), the antipsychotic class (first generation, second generation and clozapine), the mood stabilizer treatment status (yes/no) and meeting schizophrenia criteria in the last month (a proxy measure for recent psychotic relapse that

could be missed if psychotic symptoms are already treated). All variables were introduced in the first linear regression model. Secondly, a multistep selection was performed using a stepwise algorithm to enter or reject variables: variables entered the model with $p<0.15$ and were rejected if at subsequent steps $p>0.30$ (22).

Results

Demographic information about the cohort of 131 subjects is summarized in Table 1, and clinical characteristics are described in Table 2.

Table 2 Psychopathological Characteristics of the Sample

Clinical Characteristics	Mean	SD	Range
PANSS Total	63	14	38–99
PANSS-Positive	15	5.7	7–30
PANSS-Negative	19	4.2	9–35
HAM-D	9.5	4.2	0–29
SUMD-Illness	1.8	1.2	1–5
SUMD-Medications	1.8	1.2	1–5
SUMD-Consequences	2.1	1.4	1–5

PANSS: Positive And Negative Syndrome Scale
HAM-D: Hamilton Depression scale, score of the 17 first items
SUMD: Scale to Assess Unawareness of Mental Disease
(with three items: awareness of mental disorder, awareness of effects of medication and awareness for social consequences of disease)

Twenty-two percent of subjects were receiving antidepressants and 14% had a HAM-D score of 14 or higher (i.e., indicating at least moderate depression). Moreover, 71% of the sample had HAM-D scores over 7 (i.e., indicating some level of depressive symptoms as opposed to being remitted).

In our naturalistic sample, depressive symptoms were prevalent and represented a significant clinical dimension, regardless of age of onset and duration of illness as seen in Figures 1 and 2, respectively.

There was no difference in depressive symptoms between the different classes of antipsychotics used (see Figure 3), HAM-D scores being 9.0±3.5 for first-generation antipsychotics, 9.3±3.7 for the second-generation, 9.9±3.7 for the clozapine group, and the ANOVA test being not significant ($F=.475$, $p=.623$). HAM-D scores did not vary between the group receiving antidepressant therapy (9.3±4.3) and the rest of the sample (9.9±4.1), nor did PANSS scores (results not shown).

Spearman rho correlations between the clinical variables are shown in Table 3. HAM-D was positively correlated with PANSS-positive scores (Spearman rho=.426, $p<0.001$, $N=116$), and with SUMD-consequences item (Spearman rho=0.228, $p=0.028$, $N=93$). The SUMD items were intercorrelated (Spearman rho 0.405–0.540, $p<0.001$).

It is noteworthy that depressive symptoms were not correlated with negative symptoms, as measured by the negative syndrome subscale of the PANSS, suggesting that depressive symptoms as measured by HAM-D are a dimension of psychopathology independent of negative symptoms.

In order to further explore the correlates of depression in our sample, we performed two multiple linear regressions. In the first model, we included all potential variables. This model had an adjusted R-squared of 0.16 (i.e., explained 16% of the variance of HAM-D).

A second multiple linear regression was performed using a stepwise algorithm: a six-variable solution performed better than the previous model, with PANSS-positive, receiving mood stabilizers, meeting schizophrenia criteria in the last month and the three SUMD items (illness, medications and consequences) explaining 33.6% of the variance (adjusted). The standardized beta coefficients described in Table 4 show that PANSS-positive has a positive correlation and the strongest relationship with HAM-D. Receiving mood stabilizers was associated with lower HAM-D scores, and meeting schizophrenia criteria in the last month with increased HAM-D scores. Finally, the SUMD had a more complex behavior, with more awareness of mental disorder being correlated to higher depressive symptoms, and an inversed relationship for the awareness of benefit from medication and for the awareness of social consequences of the illness.

Discussion

We confirm a substantial depressive comorbidity burden across the life of patients with schizophrenia. Few patients, however, met full criteria for a major depressive disorder. Depressive symptoms were not limited to patients early in the course of their illness. Combining antidepressant treatment and HAM-D scores above 14 as indicators of clinically relevant depression, the resulting rate of 31% of patients is broadly consistent with the aforementioned modal rate of depression in 25% of schizophrenia patients (4) and with a 12-year follow-up study that found for any given month 30 to 35% of patients experienced at least one of the core symptoms of the depressive syndrome (23).

Similar to other studies (8, 24-26), we also found that residual positive symptoms were associated with depressive symptoms. The lack of association of HAM-D scores with negative symptoms suggested that HAM-D might be less likely to be confounded by negative symptoms than previously thought. This could be at least partly related to the diminished use of typical antipsychotics and diminished prevalence of their extrapyramidal side effects. The multiple regression analysis revealed the positive psychopathology subscale of the PANSS to be the principal predictor of HAM-D scores. The presence of recent schizophrenia criteria in the

Figure 1 Average HAM-D Total Score (horizontal trait), Standard Deviation (bin) and Range (vertical bars) as a Function of Age of Onset of Schizophrenia

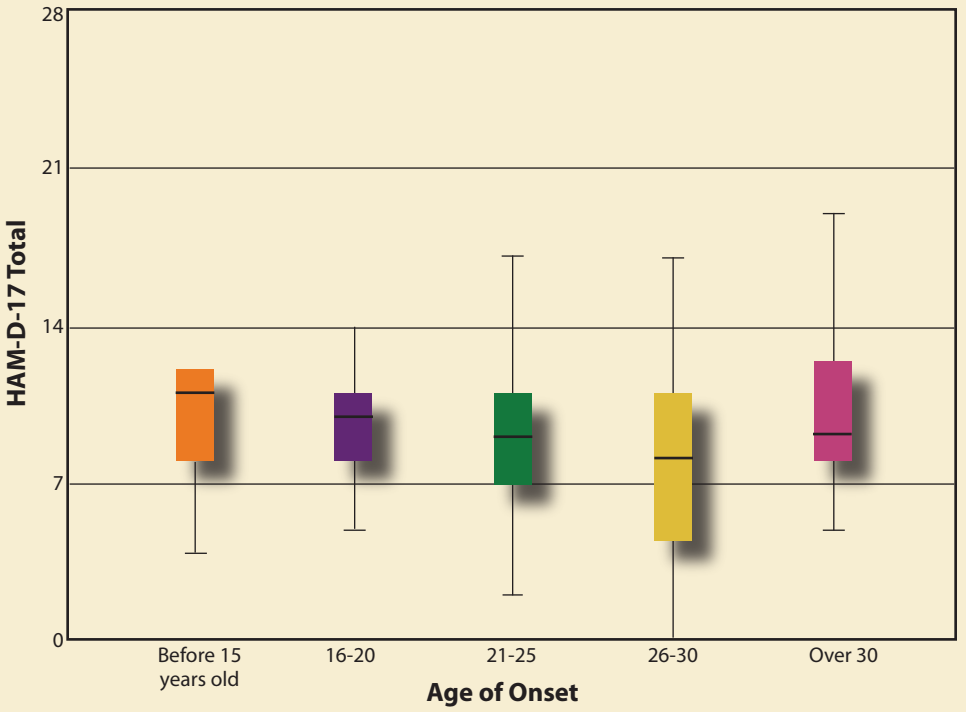


Figure 2 Average HAM-D Total Score (horizontal trait), Standard Deviation (bin) and Range (vertical bars) as a Function of the Duration of Illness

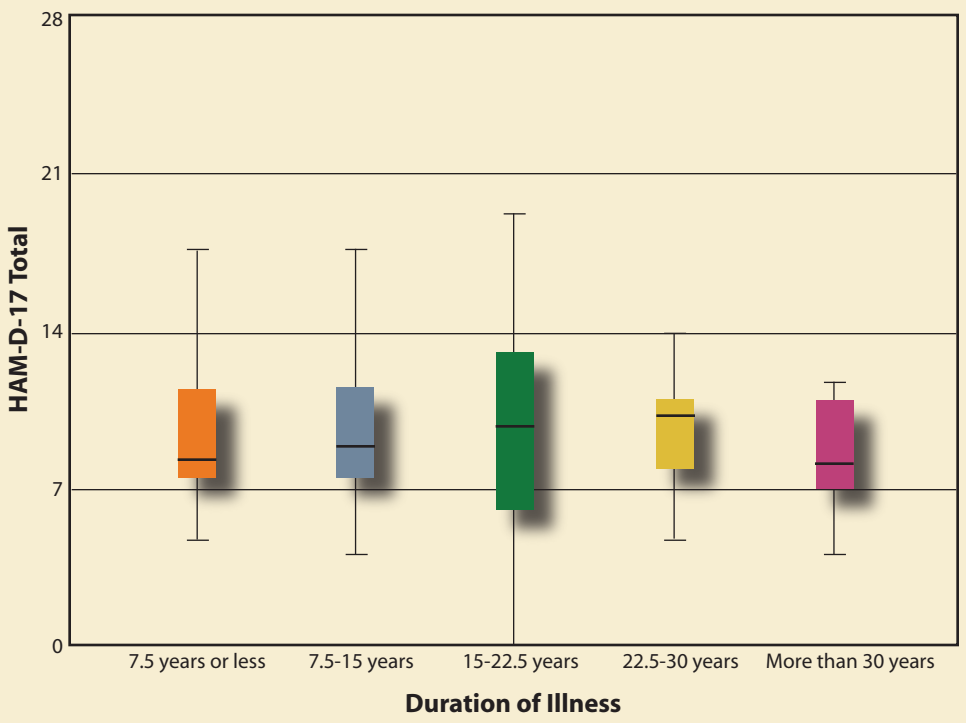
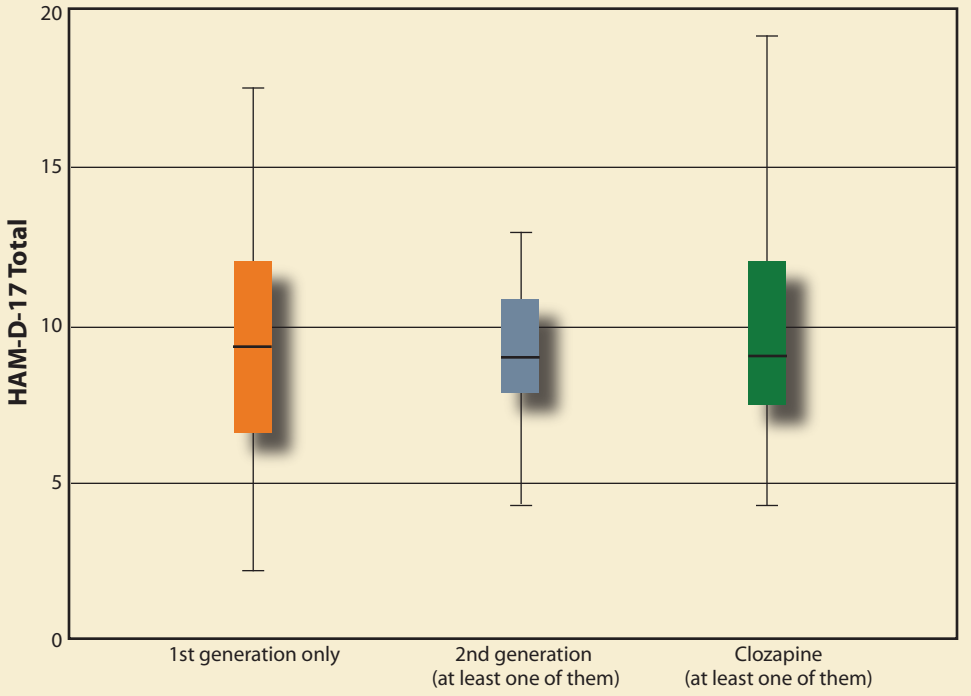


Figure 3 **Average HAM-D Total Score (horizontal trait), Standard Deviation (bin) and Range (vertical bars) as a Function of the Class of Antipsychotic Received**



model supports the notion that depression is not only associated with active psychosis, but depression can persist into the postpsychotic period even if psychosis has already receded. In our sample with a fairly good level of insight (mean item scores between 1.8 and 2.1), we saw a small relationship between the awareness of social consequences of the illness and the HAM-D total score. Our cross-sectional findings of insight and positive symptoms being associated with depression are consistent with a recent longitudinal study by Drake and colleagues (27) who discovered a complex and dynamic picture of the relationship between insight, depression and paranoia. Early in the course of illness, insight was predictive of depression, while later paranoia became the strongest predictor of depression.

In our cohort, treatment with second-generation antipsychotics did not confer benefit compared to first-generation antipsychotics with regard to depressive symptoms and neither did the addition of antidepressants, at least by nonrandomized, cross-sectional assessment. Mood stabilizers (valproate in 17, gabapentin in 5, lithium in 3, carbamazepine in 3 patients; one patient received phenytoin and one patient lamotrigine) were associated with less depression.

While some dysphoria may be an adverse medication effect from conventional neuroleptics (and the hypothetical mesolimbic reward dysfunction would aggravate this), and some psychological, depressive reactions may follow resolution of a psychotic episode (28) or represent demoralization, recent work suggests that depression can be an unspecific early sign of brain dysfunction (as supported by its high incidence during the prodromal phase of schizophrenia) that evolves into more severe patterns (i.e., psychosis) in vulnerable individuals (29). This model posits depressive symptoms as an important but unspecific feature of several neuropsychiatric disorders and would explain the high prevalence of depressive symptoms in other neuropsychiatric illnesses (e.g., early Alzheimer's disease or delirium). Understanding the pathophysiology of such cosyndromal depression could lead to more effective treatments.

Our study has several limitations. First, our cross-sectional design is prone to the usual bias and does not capture the dynamic aspect of fluctuations in individual patient's depressive symptoms; only a longitudinal study (for example, 23, 29) can do this. Second, since we started sample collection prior to the widespread adoption of the Calgary Depression Scale for Schizophrenia (CDSS) (30), we did not measure depression with what could be viewed as the gold standard (31). Nevertheless, at least in our sample, the HAM-D performed well and was not correlated with the main confounder, negative symptoms. A direct comparison

between the CDSS and HAM-D concluded that both scales were useful, although the CDSS was more sensitive to detect mild and severe depression (32). Last, our study was not randomized with regard to antipsychotics, mood stabilizers or antidepressants, and so any conclusions about efficacy or lack of efficacy of these medications for depression are only suggestive. Also, some patients might have received antidepressants for symptoms other than depression, such as negative symptoms or obsessive-compulsive symptoms.

Our cross-sectional analysis of depressive symptoms in typical, community-dwelling schizophrenia patients suggests that the affective symptom cluster is clinically important and yet treatment is insufficient; the advent of second-generation antipsychotics has not remedied the problem as initially hoped (4), and antidepressants are not broadly effective. Despite the prevalence and clinical relevance of depressive symptoms in schizophrenia, there is a paucity of controlled studies specifically designed to treat depression. Only two studies have used a randomized design to examine the value of adding selective serotonin reuptake inhibitors (SSRIs) to antipsychotics (33, 34), and neither showed significant benefit from the added antidepressant, sertraline. Clearly, more research into the pathophysiology and treatment of affective symptoms in schizophrenia is needed.

Author Disclosures

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Contributors

Dr. Freudenreich, Dr. Tranulis and Dr. Goff designed this study together. Dr. Freudenreich wrote the first manuscript draft. Dr. Tranulis analyzed the data. Drs. Cather, Henderson and Evins helped with the overall study design and with subject recruitment. All authors contributed to, and have approved, the final manuscript.

Conflict of Interest

Dr. Freudenreich has received support from the Sidney Baer Foundation, Primedia and Cephalon, and Dr. Cather has received support from the Sidney Baer Foundation, Primedia, Eli Lilly and Wyeth. Dr. Henderson reports having received lecture fees from Pfizer, Inc., Eli Lilly, Janssen, Solvay, Wyeth, Bristol-Meyers Squibb and Otsuka Pharmaceuticals, and research funding from Eli Lilly, Bristol-Meyers Squibb and Pfizer. Dr. Evins reports having received research supplies from Janssen Pharmaceutica and GlaxoSmithKline, a research grant from Janssen Pharmaceutica, expects a research grant from Sanofi-Aventis and has applied for a research grant from Pfizer, Inc. She has not received any consulting fees or lecture fees, and owns no biomedical-related equities. She also receives funding from NIDA on a collaborative project with GlaxoSmithKline. Dr. Goff has received compensation within the past three years from:

Table 3 Correlations between Psychopathological Variables

		PANSS Positive	PANSS Negative	SUMD Illness	SUMD Medications	SUMD Consequences
HAM-D	Spearman rho	.426†	.114	-.011	.064	.228*
	Sig. (2-tailed)	<.001	.226	.911	.515	.028
	N	116	115	104	105	93
PANSS-Positive	Spearman rho	1	.142	.193	.150	.236*
	Sig. (2-tailed)		.126	.050	.128	.011
	N		118	103	104	92
PANSS-Negative	Spearman rho		1	0.129	.272†	.178
	Sig. (2-tailed)			0.197	.006	.092
	N			102	103	91
SUMD-Illness	Spearman rho			1	.540†	.493†
	Sig. (2-tailed)				<.001	<.001
	N				104	93
SUMD-Medications	Spearman rho				1	.405†
	Sig. (2-tailed)					<.001
	N					93

*correlation significant for p<0.05, 2-tailed
†correlation significant for p<0.01, 2-tailed

Table 4 Multiple Linear Regression Model for HAM-D

	Partial Correlation Coefficients				
	Unstandardized Coefficients		Standardized Coefficients		
	B	Std. Error	Beta	t	Sig.
(Constant)	2.558	1.415		1.808	.076
PANSS-Positive	.293	.077	.437	3.789	.000
Treatment with mood stabilizers	-2.156	.869	- .266	-2.481	.016
SUMD-Consequences	.911	.327	.373	2.784	.007
SUMD-Illness	-1.073	.460	-.376	-2.335	.023
Meeting schizophrenia criteria last month	2.127	1.158	.202	1.836	.071
SUMD-Treatment	.722	.434	.247	1.662	.102

Dependent variable: HAM-D total score (first 17 items)
Stepwise algorithm with probability-of-F-to-enter ≤.150 and probability-of-F-to-remove ≥.300

AstraZeneca, Cephalon, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutica, Merck, Organon, Pfizer, Inc., Solvay, Wyeth, XenoPort, Vox, DiMedix, SG Cowen, Advanced Health Media, American Psychiatric Association, Primedia, Behavioral Options, Axio, VerusMed, the Nelson Group, Letters and Science, Centron, Imedex, Oakstone Publishing, Synapse, NARSAD, NIMH and the Sidney Baer Foundation. Dr. Tranulis reported no biomedical financial interests or potential conflicts of interest.

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