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The Burden of Depressive Symptoms in the Long-Term Treatment of Patients With Schizophrenia

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Abstract

Objective—To prospectively measure the link between depressive symptoms and functional outcomes in the long-term treatment of people with schizophrenia.

Methods—Data were drawn from a large, multi-site, 3-year, prospective, naturalistic, observational study, in which subjects with schizophrenia were assessed at enrollment and at 12-month intervals thereafter. Individuals who were “Depressed” (defined as a total score ≥ 16 on the Montgomery-Asberg Depression Rating Scale) at enrollment were compared to those “Non-depressed” on functional outcomes, using self-report measures, clinicians’ ratings, and information from medical records. Statistical analyses included Generalized Estimation Equation and mixed regression analyses adjusted for individual characteristics. Longitudinal group comparisons across the 3-year study were augmented with a cross-sectional group comparison at enrollment.

Results—At enrollment, 39.4% (877/2228) of the participants were deemed Depressed. Across the 3-year study, the depressed cohort was significantly more likely than the Non-depressed to use relapse-related mental health services (emergency psychiatric services, sessions with psychiatrists); to be a safety concern (violent, arrested, victimized, suicidal); to have greater substance-related problems; and to report poorer life satisfaction, quality of life, mental functioning, family relationships, and medication adherence. Furthermore, changes in depressed status were associated with changes in functional outcomes.

Conclusions—People with schizophrenia and concurrent depressive symptoms have poorer long-term functional outcomes compared to the Non-depressed. Their poorer quality of life, greater use of mental health services, and higher risk of involvement with law enforcement agencies underscore a need for special treatment interventions. Treatment of the non-psychotic dimensions of schizophrenia is a critical part of recovery.

Keywords

schizophrenia; depressive symptoms; depression; outcomes

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1. INTRODUCTION

Depressive symptoms are recognized as an important and distinct symptom domain in schizophrenia (Siris et al., 2001) and may occur at any time during the course of the illness (Sands and Harrow, 1999). Although concurrent depressive symptoms were previously considered a good prognostic indicator (Stephens et al., 1966), research that is more recent has demonstrated that depressive symptoms serve as a poor prognostic indicator of recovery and reintegration into the community (Resnick et al., 2004). Depressive symptoms worsen quality of life (Reine et al., 2003) and increase the risk of suicide (Siris, 2001), psychotic relapse, and psychiatric hospitalization (Tollefson et al., 1999).

The prevalence of depressive symptoms among people with schizophrenia has been reported to range from 25% to 81% (Siris, 2001), depending on the treatment setting, phase of the illness, and the definition of depression. It is currently unclear what proportion of people with schizophrenia treated in usual practice settings experience at least a moderate level of depressive symptoms, whether the rates of depressive symptoms change over time, or which specific functional outcomes are more adversely affected by depressive symptoms during the course of the illness.

Prospective longitudinal data on depressive symptoms among people with schizophrenia in usual care are sparse (Sands and Harrow, 1999; Ritsner et al., 2003; an der Heiden et al., 2005), as studies have typically monitored a few outcome measures in a relatively small sample of inpatients following discharge from hospitalization, thus focusing on a vulnerable patient subgroup. The objectives of this study were to prospectively assess the prevalence of concurrent depressive symptoms in a large and diverse group of people with schizophrenia treated in usual practice settings across the U.S., and to focus on the relationships between baseline depressive symptoms and long-term functional outcomes. We used data from a large, 3-year, prospective, observational, study of schizophrenia in which depressive symptoms and functional outcomes were assessed at enrollment and at 12-month intervals thereafter. Participants who were depressed at enrollment were compared on the trajectory of their functional outcomes during the first year of the study, and across the 3-year follow-up. The study also assessed whether change in depressive status is accompanied by changes in functional outcomes.

2. METHODS

2.1. Data Source

We used data from the U.S. Schizophrenia Care and Assessment Program (US-SCAP), a large (N=2327), 3-year, naturalistic, prospective, non-randomized, multi-site study in the U.S. conducted between July 1997 and September 2003. US-SCAP aimed to improve understanding of the treatment provided to people with schizophrenia in usual care. Briefly, participants were enrolled from 6 regional sites and diverse systems of care. Participants were diagnosed with schizophrenia, or schizoaffective or schizophreniform disorder, based on DSM-IV criteria, and were at least 18 years of age. Individuals were excluded from the study if they were unable to provide informed consent or had participated in a clinical drug trial within 30 days prior to enrollment. Institutional Review Board (IRB) approval was received at each regional site, and informed consent was received from all participants. Further details regarding US-SCAP are available elsewhere (Ascher-Svanum et al., 2004; Faries et al., 2005; Swanson et al., 2004).

The present study included US-SCAP participants who were assessed with the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) at enrollment and had at least 1 outcome measure following enrollment.

2.2. Measures

Assessments were performed at enrollment and at 12-month intervals thereafter with clinical and functional measures that were administered by trained and annually certified examiners. Participants were classified into “Depressed” or “Non-depressed” cohorts based on the MADRS total score at enrollment. Consistent with prior schizophrenia research (Tollefson et al., 1999), a score of ≥ 16 on the MADRS was defined as “Depressed” and a score < 16 as “Non-depressed.”

The Depressed and Non-depressed cohorts were compared on 32 functional variables that were measured with 4 instruments: The Quality of Life Scale (QLS) (Heinrichs et al., 1984); the Global Assessment of Functioning scale (GAF, Endicott et al., 1976); patients’ medical records, which provided information about mental health resource utilization for each previous 6-month interval; and the SCAP-Health Questionnaire (SCAP-HQ), a 102-item, patient-reported measure developed and validated for the US-SCAP study (Lehman et al., 2003). SCAP-HQ items were drawn from existing measures, such as Lehman’s Brief Quality of Life Interview (Lehman, 1988), the Arkansas Schizophrenia Outcomes Module (Cuffel et al., 1997), the Medical Outcomes Study Short Form 12 (SF-12) (Ware et al., 1996), and the CAGE (Ewing, 1984), a screening tool for the assessment of alcohol-related and drug-related problems.

The functional outcome variables were conceptually assigned to 6 general domains: mental health resource utilization, safety in the community, substance use, productivity, activities and relationships, and quality of life. Definitions of the functional outcome variables and their measures are presented in Table 1.

We also identified patients who have changed their depressive status and those who did not, during any 2 consecutive depression assessments across the 3-year study. This resulted in 4 mutually exclusive groups, based on patients’ depressed status at any of the first 3 assessments (enrollment, Year 1, Year 2) and at the following assessment a year later. The 4 groups comprised patients who – on any 2 consecutive assessments – were Depressed (D-D), Non-depressed (ND-ND), changed from Non-depressed to Depressed (ND-D), and those who changed from Depressed to Non-depressed (D-ND). Changes from beginning to ending values on each of the 32 functional outcomes were used to assess the course of functional outcomes over time as a function of change in depressive status.

2.3. Statistical Analysis

Comparisons between Depressed and Non-depressed cohorts on baseline characteristics were made using chi-square test for categorical variables and a *t* test for continuous variables. To compare the functional outcomes for the 2 cohorts over the 3-year period, we used mixed model with repeated measures analyses (MMRM) (Mallinckrodt et al., 2003) for continuous outcome measures. Generalized estimating equations (GEE) (Liang and Zeger, 1986) were used for binary variables.

Scores from the 4 assessments during the 3-year study (enrollment, end of Years 1, 2, and 3) were considered as the dependent variables. The models included socio-demographics (age, sex, and race) and depressed classification at enrollment (Depressed or Non-depressed) as independent variables. Due to planned multiple comparisons, results were first reported using a significance level of .05, and then were reported using Bonferroni correction for multiple comparisons (using an adjusted significance level cutoff of .0015).

Because functional outcomes may be associated with symptom and illness severity, extrapyramidal symptoms (EPS), tardive dyskinesia (TD), and diagnosis of schizoaffective disorder, we repeated the analyses with adjustments for these variables and other variables that significantly differed between the Depressed and Non-depressed cohorts at enrollment. The

expanded adjusted models included socio-demographics (age, sex, and race), total score on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), mean item score on the Simpson Angus Scale (Simpson and Angus, 1970), presence/absence of TD (Schooler and Kane, 1982), diagnosis of schizoaffective disorder, age at illness onset, less than high school education, single marital status, comorbid diagnosis of personality disorder, depressed classification (Depressed or Non-depressed) at enrollment by assessment.

To assess whether change in depressed status is associated with change in functional outcomes, we compared the beginning and ending values for patients in each of the 4 groups (D-D, ND-ND, D-ND, ND-D) on each of the 32 functional variables. Chi-square test was used to compare binary outcome variables, and a *t* test for continuous outcome variables. Due to potential correlation between outcome measures at different assessments of the same patient, we performed a sensitivity analysis, using only 1 observation per patient (the first episode).

In addition, to assess the stability of depression score over time, we calculated the Pearson product-moment correlations between MADRS total scores at different assessment times across the 3-year study (enrollment, Years 1, 2, and 3).

3. RESULTS

3.1. Subject Characteristics

Almost all US-SCAP enrollees (95.7% or 2228/2327) were assessed with the MADRS at enrollment and had at least 1 outcome measure following enrollment, and thus were included in this study. About one-third of those included (39.4%, *n*=877) were deemed to be depressed at enrollment ("Depressed"), whereas 61% were "Non-depressed" at enrollment (*n*=1351). Among all participants, depression rates were stable over the 3 years following enrollment, with 34.1% being depressed at the end of the first year, 30.3% at the end of the second year, and 33.00% at the end of the third year. The Depressed and the Non-depressed had comparable attrition rates throughout the 3-year study (74.3%, 64.7%, and 52.6% of the Depressed completed 1, 2, and 3 years of follow-up, respectively, compared to 76.0%, 65.8%, and 52.0% of the Non-depressed).

Compared to Non-depressed subjects at enrollment (Table 2), the Depressed were significantly more likely to be white, previously married, less educated, with earlier age at illness onset, schizoaffective disorder diagnosis, health insurance coverage by the Department of Veteran Affairs (but less likely to have private insurance), psychiatric hospitalization in the previous year, and a comorbid diagnosis of personality disorder (primarily personality disorder not otherwise specified). During the 6 months prior to enrollment, the Depressed were less likely to be treated with typical antipsychotics and were more likely to be treated with antidepressants, anti-anxiety agents, mood stabilizers, and hypnotics.

Although patients diagnosed with a schizoaffective disorder (33.6%) were more likely to be in the Depressed than the Non-depressed group at enrollment (40.1% vs. 29.3%, *p*<.001), about half of the schizoaffective group was Depressed (352/748, or 47.1%) and half was Non-depressed (396/7748 or 52.9%).

3.2. Functional Outcomes: Depressed Versus Non-Depressed

When compared across the 3-year study, with adjustments for age, sex, and race, the depressed cohort was significantly (*p*<.05) more likely than the Non-depressed to have poorer outcomes on most outcome variables (29 of 32 variables, Table 3).

Across the 3-year study, participants in the depressed cohort were significantly more likely to use relapse-related mental health services (emergency psychiatric services, contacts with

psychiatrists), to be of greater safety concern in the community (violent, arrested, victimized, suicidal thoughts, suicide attempts), to have more substance-related problems, to evidence poorer social and family relationships, and to have a poorer quality of life (overall quality of life measure, lower motivational level, poorer global level of functioning, poorer mental and physical health, lower level of medication adherence, and less general life satisfaction). Similar results were found at enrollment.

When using Bonferroni method to correct for multiple comparisons, 3 outcome measures lost their previous statistical significance (work days, daily activities, and independent housing). Furthermore, when adjusting for additional clinical and socio-demographic characteristics (detailed in the statistical analysis section), the groups significantly differed on 22/29 outcome measures.

3.3. Change in Depressed Status and Change in Functional Outcomes

As presented in Table 4, most patients (3071/4010 or 76.6%) maintained their Depressed/Non-depressed status over any 2 consecutive assessments, whereas 13.1% (524/4010) changed from Depressed to Non-depressed, and 10.3% (415/4010) from Non-depressed to Depressed. The relative stability in depressed status may reflect the moderately high correlations between MADRS scores over time, which ranged from .58 to .67 (all $p < .001$).

Patients who maintained their Depressed/Non-depressed status tended to not evidence significant changes on functional outcomes, whereas patients who changed their depressed status, tended to improve if changed from Depressed to Non-depressed, and worsen if changed from Non-depressed to Depressed. Specifically, the ND-ND group maintained functional outcomes on 26/32 or 81.3% of the measures, and the D-D group maintained 30/32 or 93.8% of the functional outcomes. In contrast, the D-ND group improved on 29/32 or 90.6% of the functional measures, with most of the improvements (62% or 18/29) being statistically significant. The ND-D group worsened on 93.8% (30/32) of the functional measures, with most of the worsening being statistically significant (53%, or 16/30). Interestingly, patients who maintained their Non-depressed status (ND-ND) evidenced significant improvements on several functional outcomes, such as reductions in hospitalizations, emergency psychiatric services, and arrests, in addition to significant increases in working days, in common activities, and in general life satisfaction. Sensitivity analyses using a 1-observation-per-patient approach produced consistent results.

4. DISCUSSION

This large, prospective, naturalistic, U.S., multi-site study found that about one-third (39.4%) of the participants with schizophrenia were concurrently depressed at enrollment, with marked stability in prevalence rates of depressive symptoms across the 3-year study. Findings are highly consistent with previous research (Elk et al., 1986; Harrow et al., 1994; Sands and Harrow, 1999; Summers et al., 1983), and appear to transcend differences in study populations, phases of the illness, and measures used to define depressed status, thus bolstering the validity of the current findings and enhancing the ability to generalize them to schizophrenia patients treated in various health care systems.

Across this 3-year study, depressive symptoms were found to be associated with considerable long-term burden in the treatment of schizophrenia. Compared to those without depressive symptoms at enrollment, participants with depressive symptoms had poorer long-term functional outcomes in multiple domains. The Depressed were more likely to use relapse-related mental health services (emergency psychiatric services, contacts with psychiatrists), to be of greater danger to self and others (violent, arrested, victimized, suicidal), to have more substance-related problems, to evidence poorer social and family relationships, and to have a

poorer quality of life, lower motivational level, poorer level of functioning, poorer mental and physical health, lower level of medication adherence, and less general life satisfaction.

Similar findings have been previously reported, especially the association between depressive symptoms in schizophrenia and a greater risk of psychiatric hospitalization (Birchwood et al., 1993; Mandel et al., 1982; Roy et al., 1983; Sands and Harrow, 1999); lower levels of activity (Birchwood et al., 1993; Sands and Harrow, 1999); greater suicidal ideations and attempts (Barnes et al., 1989; Harkavy-Friedman et al., 1999; Kelly et al., 2004; Sands and Harrow, 1999; Swartz and Cohen, 2001); greater substance use (Baker et al., 2005; Patkar et al., 1999); poorer quality of life (Huppert et al., 2001; Norholm and Bech, 2006; Pukrop, 2003; Sim et al., 2004; Tollefson et al., 1999); poorer social functioning (Glazer et al., 1981; Huppert et al., 2001; Jin et al., 2001; Sands and Harrow, 1999; Sim et al., 2004); poorer physical health (Sim et al., 2004); poorer medication adherence (Elbogen et al., 2005); and less satisfaction with life in general (Huppert et al., 2001; Sands and Harrow, 1999).

In addition to replicating previous findings, this study offers new and clinically valuable data on the dynamic and robust link between change in depression status and changes in functional outcomes in the long-term treatment of patients with schizophrenia in usual care settings. Study results have shown that maintenance of Depressed/Non-depressed status was associated with lack of significant changes in functional outcomes over a 1-year period, whereas subjects who changed their Depressed/Non-depressed status have evidenced substantial changes. Specifically, those who changed from Depressed to Non-depressed have improved on most (91%) of the 32 studied functional outcomes, and those who changed for Non-depressed to Depressed have evidenced worsening in most (94%) functional outcomes. Significant changes were noted on medication adherence, use of alcohol and illicit drugs, suicidal thinking and attempts, family relationships, social and occupational functioning, and general life satisfaction among others. For example, Depressed subjects who continued to be depressed, have maintained a high rate of suicidal thinking (34.6%–31.5%), and Non-depressed subjects who continued to be Non-depressed maintained a low rate of suicidal thoughts (3.3%–2.9%). In contrast, the rate of suicidal thinking has significantly decreased for Depressed subjects who became Non-depressed (from 22.8% to 9.0%), and almost doubled for Non-depressed who became Depressed (from 10.4% to 20.5%). Importantly, current findings also illustrate the growing benefits of maintaining Non-depressed status over time, as it was found to be associated with significant improvements that have personal and economic implications – significant decrease in rates of hospitalization and emergency psychiatric services, in the likelihood of being arrested, along with increase in working days, in community activities, and in general life satisfaction.

Current findings also extend prior research by demonstrating that the burden of depressive symptoms affects the criminal justice system in addition to the mental health system. People with schizophrenia and depressive symptoms were found to use more relapse-related mental health services and to have more frequent contacts with law enforcement agencies compared to those without concurrent depressive symptoms. These findings may be related to the poorer adherence to medications reported by patients with concurrent depressive symptoms, thereby increasing their risk of relapse, hospitalization, and symptom exacerbation that may lead to loss of control and greater display of impulsive and hostile behaviors. Findings suggest that this relatively large subgroup of people with schizophrenia is more volatile, vulnerable, crisis prone, and more likely to be arrested and jailed. These individuals may require, therefore, more specialized treatments and close coordination between the criminal justice and the mental health systems, as jails and prisons have become surrogate mental hospitals for large populations of severely mentally ill offenders (Munetz et al., 2001).

Another important contribution of this study is the finding that even after considering the relative influence of illness severity, and other clinical variables (including EPS, TD, and diagnosis of schizoaffective disorder), depressive symptoms were still found to be associated with many, but not all, studied outcomes.

This study has a number of limitations. First, most of the studied outcome measures were based on participants' self-reports, whereas the use of multiple sources of information, particularly for documenting violent behaviors, arrests, and substance use, might have provided more valid outcome parameters (Lafayette et al., 2003). Second, we defined participants as depressed or Non-depressed based on categorization of a depression measure at enrollment. This dichotomy is typically not made in clinical practice where depressive symptoms vary in magnitude, in symptom course, and in the subtype of the depressive symptomatology. Additional studies will be needed to further elucidate these details and clarify which specific subtype of depressive symptoms may drive what outcomes.

In conclusion, individuals with schizophrenia and concurrent depressive symptoms are common and require special treatment interventions to help increase their chances for effective recovery. Concurrent depressive symptoms are associated with significantly poorer long-term functional outcomes and substantial burden that is linked to greater use of emergency mental health services and the criminal justice system.

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Table 1

Definitions of Functional Outcome Variables

Outcome domain/Outcome variable		Measure
Mental Health Resource Utilization	Hospitalization	Any psychiatric hospitalization in the past 6 months per medical record (yes/no)
	Hospitalization duration	Number of days hospitalized for psychiatric purpose in the past 6 months per medical record (yes/no)
	Emergency psychiatric services	Use of any emergency psychiatric services with psychiatrist or therapist in past 4 weeks, per SCAP-HQ (yes/no)
	Emergency room visit	Any visit to emergency room in the past 6 months, per medical record (yes/no)
Safety to self or others	Contacts with psychiatrist	Number of outpatient contacts with psychiatrist in the past 6 months per medical record
	Violent behaviors	Strike/injure another, or threatened to strike/injure another in the past 4 weeks per SCAP-HQ (yes/no)
	Arrested/jailed	Arrested or spent a night in jail in the past 6 months per SCAP-HQ (yes/no)
	Victim of crime	A victim of any crime in the past 4 weeks per SCAP-HQ (yes/no)
Substance use	Suicidal thoughts	Participant's thoughts of killing oneself in the past 4 weeks per SCAP-HQ (yes/no)
	Suicidal attempts	Participant's report of actually attempting to hurt or kill oneself in the past 4 weeks per SCAP-HQ (yes/no)
	Alcohol-related problems	Total score on the 4-item alcohol CAGE, as reported by alcohol-drinking participants for the past 4 weeks on SCAP-HQ
	Drug-related problems	Total score on the 4-item illicit drug CAGE, as reported by drug-using participants for the past 4 weeks on SCAP-HQ
Productivity	Substance use	Use of alcohol or illicit drugs in the past 4 weeks per SCAP-HQ (yes/no)
	Work for pay	Paid employment in the past 4 weeks per SCAP-HQ (yes/no)
	Work days	Number of days worked for pay in the past 4 weeks per SCAP-HQ for working participants
	Work hours	Number of hours worked for pay per day in the past 4 weeks per SCAP-HQ for working participants
Activities and relationships	Occupational functioning	QLS score on the instrument role domain; clinician-rated
	Any productive activity	Engagement in a productive activity such as employment, schooling, volunteering, or childcare, in the past 4 weeks per SCAP-HQ (yes/no)
	Daily activity	Mean item score on a 5-item SCAP-HQ scale measuring frequency of performing daily activities in the past 4 weeks (e.g., own laundry, household chores) on a scale from all of the time (1) to none of the time (5)
	Leisure activity	Mean score on 4 SCAP-HQ items measuring engagement (yes/no) in leisure activities in the past 4 weeks (e.g., go shopping, do something fun); range 0–4
Quality of life	Common activities	QLS score on the Common Objects and activities domain; clinician-rated
	Social relationships	Mean item score on 3 SCAP-HQ items measuring frequency of social activities in the past 4 weeks (e.g., do things with friends, telephone someone) on a scale at least once a day (1) to not at all (5)
	Interpersonal functioning	QLS score on the interpersonal domain; clinician-rated
	Family relationships	Score on a SCAP-HQ item assessing patients' feelings about relationships with family members, scored from 1 (terrible) to 7 (delighted)
Quality of life	Quality of life, overall	Total score on the QLS; clinician-rated
	Motivation level	Score on the intrapsychic foundations domain; clinician-rated
	Global level of functioning	Score on the GAF; clinician-rated
	Mental functioning	Mental Component Score on the SF-12 (included in SCAP-HQ)
Quality of life	Physical functioning	Physical Component Score on the SF-12 (included in SCAP-HQ)
	Medication adherence	Patient-reported medication adherence in the past 4 weeks on a scale from 1 (never missed taking the medication) to 5 (stopped taking the medication altogether), per SCAP-HQ
	Independent housing	Housing arrangement not supervised by mental health professionals on the day of assessment (e.g., boarding homes, halfway houses, yes/no) per SCAP-HQ
	General life satisfaction	Patient's feelings about life in general the past 4 weeks on a scale from 1 (terrible) to 7 (delighted), per SCAP-HQ

Abbreviations: SCAP-HQ, Schizophrenia Care and Assessment Program Health Questionnaire; GAF, Global Assessment of Functioning; CAGE, Cut, Annoyed, Guilt, Early morning drinking - known as the CAGE questionnaire; SF-12, the 12-Item Short-Form Health Survey; QLS, Quality of Life Scale

Table 2

Characteristics of Depressed and Non-Depressed Patients at Enrollment

Characteristic	All n=2228	Non-Depressed n=1351	Depressed n=877	p- value*
Age, mean (SD), y	41.8 (11.2)	41.88 (11.6)	41.58 (10.5)	.530
Male gender, % (n)	61.5 (1371)	62.2 (840)	60.6 (531)	.440
Race, % (n)				.025
Caucasian	40.9 (1092)	47.1 (636)	52.0 (456)	
African American	36.7 (818)	38.9 (526)	33.3 (292)	
Other	14.3 (318)	14.0 (189)	14.7 (129)	
Single, never married, % (n)	61.4 (1364)	65.2 (878)	55.5 (486)	<.001
High school education or less, % (n)	67.9 (1506)	70.8 (953)	63.4 (553)	<.001
Age at illness onset, mean (SD), y	20.2 (8.9)	21.0 (8.9)	19.0 (8.6)	<.001
Schizophrenia diagnosis	57.2 (1274)	60.8 (822)	51.5 (452)	<.001
Schizoaffective disorder diagnosis	33.6 (748)	29.3 (396)	40.1 (352)	<.001
Other diagnosis of psychotic disorder	9.3 (206)	9.8 (133)	8.3 (73)	.226
Health insurance % (n)				.015
Medicaid/Medicare	81.8 (1806)	81.2 (1087)	82.8 (719)	
Department of Veteran Affairs	5.7 (126)	4.9 (66)	6.9 (60)	
Private insurance	4.1 (91)	5.1 (68)	2.7 (23)	
Other coverage	1.1 (24)	1.2 (16)	0.9 (8)	
No health insurance	7.3 (160)	7.6 (102)	6.7 (58)	
Hospitalized in past year, % (n)	39.3 (875)	34.5 (466)	46.6 (409)	<.001
Comorbid substance use disorder, % (n)	28.0 (623)	27.9 (377)	28.1 (246)	.941
Comorbid personality disorder, % (n)	14.5 (323)	11.5 (155)	19.2 (168)	<.001
Medications use during the 6 months prior to enrollment				
Antidepressants	38.8 (864)	29.5 (398)	53.1 (466)	<.001
Anti-anxiety agents	11.3 (252)	7.6 (103)	17.0 (149)	<.001
Mood stabilizers	31.2 (696)	28.7 (388)	35.1 (308)	.002
Hypnotics	1.7 (38)	1.2 (16)	2.5 (22)	.018
Antiparkinsonian agents	44.8 (998)	44.0 (595)	46.0 (403)	.376
Atypical antipsychotics	59.78 (1332)	58.62 (792)	61.57 (540)	.165
Typical antipsychotics	58.2 (1297)	60.3 (814)	55.1 (483)	.016
Any psychotropic	98.0 (2183)	98.1 (1325)	97.8 (858)	.692

* Chi-square test for categorical and *t* test for continuous variables

Abbreviations: SD, standard deviation

Functional Outcomes Variables for Non-Depressed and Depressed Cohorts at Enrollment and Across the Three-Year Study

Table 3

Outcome domain/variable	Assessed at enrollment		Three-Year Outcomes ^a	
	Non-Depressed n=1351	Depressed n=877	Non-Depressed	Depressed
Resource utilization				
Prior 6 months hospitalization, % (n)	21.7 (292) ***	29.7 (259)	14.9 (640) *** ^b	22.4 (514)
Hospitalized duration, mean (SD)	6.1 (23.2) ***	5.8 (18.5)	7.7 (37.5) *** ^b	6.4 (26.1)
Emergency psychiatric services, % (n)	5.4 (73) ***	15.3 (134)	4.1 (177) *** ^b	12.4 (289)
Emergency room visit, % (n)	15.5 (48) *	24.2 (37)	7.4 (197) ***	14.5 (171)
Contacts with psychiatrist, mean (SD)	3.8 (3.4) ***	4.9 (3.7)	3.3 (4.3) ***	4.0 (5.1)
Safety to self and others				
Violent behaviors, % (n)	3.3 (44) ***	12.4 (109)	3.5 (151) ***	10.3 (238)
Arrested/jailed, % (n)	5.6 (75) ***	8.6 (75)	3.8 (165) *** ^b	6.2 (145)
Victim of crime, % (n)	8.2 (110) ***	15.7 (137)	6.7 (290) ***	14.5 (337)
Suicidal thinking, % (n)	4.6 (62) ***	33.3 (291)	4.3 (187) ***	30.1 (698)
Suicidal attempts, % (n)	0.7 (10)	6.0 (52)	0.7 (31)	4.7 (108)
Substance use				
Alcohol-related problems, mean (SD)	0.2 (0.6) ***	0.4 (0.9)	0.2 (0.6) ***	0.3 (0.9)
Drug-related problems, mean (SD)	0.1 (0.6) **	0.2 (0.8)	0.1 (0.5) ***	0.2 (0.7)
Substance use, % (n)	25.2 (339)	32.2 (282)	21.4 (932)	28.8 (669)
Productivity				
Work for pay, % (n)	23.4 (316) *	18.8 (165)	25.4 (1107) ***	18.3 (426)
Work days/week, mean (SD)	11.5 (7.7)	10.5 (7.7)	12.1 (7.5) *** ^b	10.8 (7.4)
Work hours/day, mean (SD)	5.1 (2.7)	4.8 (2.4)	5.0 (2.6)	4.8 (2.6)
Occupational functioning (SD)	11.1 (7.0) ***	8.5 (6.1)	11.1 (7.) ***	8.7 (6.1)
Productivity, % (n)	67.2 (907)	63.9 (560)	70.7 (3079) *** ^b	63.9 (1486)
Activities/Relationships				
Daily activity, mean (SD)	3.4 (1.2) *	3.3 (1.2)	3.4 (1.2) *** ^b	3.3 (1.2)
Leisure activity, mean (SD)	2.7 (1.2)	2.7 (1.2)	2.8 (1.2) ***	2.6 (1.2)
Common activities, mean (SD)	6.4 (2.4)	6.5 (2.1)	6.5 (2.3)	6.4 (2.1)
Social relationships, mean (SD)	2.9 (1.2) **	2.8 (1.2)	2.9 (1.2) ***	2.7 (1.2)
Interpersonal functioning, mean (SD)	23.1 (10.6) ***	18.0 (9.2)	22.9 (10.2) ***	17.7 (8.9)
Family relationships, mean (SD)	4.9 (1.6) ***	4.1 (1.7)	5.0 (1.5) ***	4.2 (1.64)
Quality of life				
Quality of life, overall, mean (SD)	64.9 (22.5) ***	52.9 (18.9)	64.3 (22.0) ***	52.3 (18.9)
Motivation level, mean (SD)	24.0 (8.3) ***	19.2 (7.6)	23.6 (8.0) ***	19.3 (7.4)
Global level of functioning, mean (SD)	45.3 (13.0) ***	37.5 (12.0)	44.8 (12.3) ***	36.8 (10.9)
Mental functioning, mean (SD)	46.3 (11.7) ***	32.5 (12.1)	46.9 (11.6) ***	32.8 (11.6)
Physical functioning, mean (SD)	46.6 (9.6)	45.7 (11.7)	46.4 (9.8) ***	44.6 (11.7)
Medication adherence, mean (SD)	1.3 (0.7) ***	1.6 (0.9)	1.3 (0.6) ***	1.6 (0.9)
Independent housing, % (N)	67.5 (904)	68.5 (590)	68.0 (2948) *** ^b	71.1 (1634)
General life satisfaction, mean (SD)	5.1 (1.4) ***	3.9 (1.6)	5.2 (1.3) ***	3.9 (1.5)

^aTotal number of observations in the 4 assessments across the 3-year study for the Depressed (n=2326) and Non-depressed (n=4362) cohorts

^bGroup differences not significantly different after adjusting for age, sex, race, PANSS total score, mean item score on the Simpson Angus Scale, presence/absence of tardive dyskinesia, diagnosis of schizoaffective disorder, age at illness onset, less than high school education, single marital status, comorbid diagnosis of personality disorder, and depressed classification (Depressed or Non-depressed) at enrollment by assessment.

Significant differences between the Depressed and Non-depressed cohorts, adjusted for age, gender, and ethnicity

* p<0.05;

p ≤ .01;
**

p ≤ .001 (p ≤ .0015 is Bonferroni threshold)

Abbreviations: SD, standard deviation; QOL, quality of life; PANSS, Positive and Negative Syndrome Scale

Table 4
Changes in Depressed Status and Changes in Functional Outcomes Across the 3-Year Study

Outcome domain/variable	Beginning and ending depressed status ^d	Beginning value	Ending value	Difference
Resource utilization				
Prior 6 months hospitalization, % (n)	D-D	21.7 (186)	18.4 (158)	-3.3
	D-ND	21.9 (113)	14.0 (72)	-8.0 ***
	ND-D	17.4 (71)	15.2 (62)	-2.2
	ND-ND	13.9 (297)	10.6 (227)	-3.3 ***
Hospitalized duration, mean (SD)	D-D	6.1 (23.6)	6.0 (23.1)	-0.1 (25.6)
	D-ND	8.7 (32.7)	11.4 (47.3)	2.7 (40.0)
	ND-D	5.6 (26.6)	5.2 (24.9)	-0.4 (33.2)
	ND-ND	7.7 (37.0)	7.1 (38.8)	-0.6 (33.6)
Emergency psychiatric services, % (n)	D-D	12.4 (109)	11.4 (100)	-1.0
	D-ND	12.6 (66)	5.4 (28)	-7.3 ***
	ND-D	5.8 (24)	10.9 (45)	5.1 ***
	ND-ND	3.9 (84)	2.7 (59)	-1.2 *
Emergency room visit, % (n)	D-D	15.5 (51)	12.8 (42)	-2.7
	D-ND	10.5 (22)	7.6 (16)	-2.9
	ND-D	11.7 (21)	11.7 (21)	0.0
	ND-ND	6.2 (65)	4.8 (50)	-1.4
Contacts with psychiatrist	D-D	4.6 (6.8)	3.7 (3.5)	-0.9 (7.0) *
	D-ND	3.7 (3.2)	3.6 (5.4)	-0.1 (5.3)
	ND-D	3.8 (4.3)	3.7 (5.4)	-0.2 (6.0)
	ND-ND	3.5 (5.1)	3.1 (4.7)	-0.4 (6.3)
Safety to self and others				
Violent behaviors, % (n)				
	D-D	12.0 (105)	10.7 (94)	-1.3
	D-ND	7.7 (40)	5.2 (27)	-2.5
	ND-D	4.6 (19)	6.0 (25)	1.5
	ND-ND	3.0 (65)	3.1 (68)	0.1
Arrested/jailed, % (n)	D-D	5.8 (51)	4.8 (42)	-1.0
	D-ND	5.0 (26)	4.0 (21)	-1.0
	ND-D	4.6 (19)	4.4 (18)	-0.2
	ND-ND	3.5 (77)	2.4 (52)	-1.2 *
Victim of crime, % (n)	D-D	15.2 (134)	14.9 (131)	-0.3
	D-ND	14.0 (73)	9.0 (47)	-5.0 *
	ND-D	8.5 (35)	10.6 (44)	2.2
	ND-ND	5.8 (126)	5.5 (119)	-0.3
Suicidal thinking, % (n)	D-D	34.6 (304)	31.6 (277)	-3.1
	D-ND	22.8 (119)	9.0 (47)	-13.8 ***
	ND-D	10.4 (43)	20.5 (85)	10.1 ***
	ND-ND	3.3 (72)	2.9 (63)	-0.4
Suicidal attempts, % (n)	D-D	5.4 (47)	4.8 (42)	-0.6
	D-ND	4.0 (21)	1.0 (5)	-3.1 **
	ND-D	1.2 (5)	1.9 (8)	0.7
	ND-ND	0.6 (13)	0.6 (14)	0.0
Substance use				
Alcohol-related problems, mean (SD)	D-D	0.3 (0.9)	0.3 (0.8)	-0.0 (0.8)
	D-ND	0.3 (0.9)	0.2 (0.6)	-0.1 (0.8) ***
	ND-D	0.2 (0.6)	0.3 (0.8)	0.1 (0.8) ***
	ND-ND	0.1 (0.5)	0.1 (0.5)	-0.0 (0.6)
Drug-related problems, mean (SD)	D-D	0.2 (0.6)	0.2 (0.6)	0.0 (0.7)

Outcome domain/variable	Beginning and ending depressed status ^d	Beginning value	Ending value	Difference
	D-ND	0.2 (0.7)	0.1 (0.5)	-0.1 (0.7) **
	ND-D	0.1 (0.6)	0.2 (0.7)	0.1 (0.6) *
	ND-ND	0.1 (0.4)	0.1 (0.4)	-0.0 (0.4)
Substance use, % (n)	D-D	27.3 (240)	25.3 (223)	-1.9
	D-ND	27.0 (141)	21.7 (113)	-5.4 *
	ND-D	25.1 (104)	29.0 (120)	3.9
	ND-ND	20.4 (415)	19.4 (424)	-1.0
Productivity				
Work for pay, % (n)	D-D	18.1 (159)	16.1 (142)	-1.9
	D-ND	22.4 (117)	24.3 (127)	1.9
	ND-D	23.5 (97)	23.7 (98)	0.2
	ND-ND	25.5 (556)	26.9 (587)	1.4
Work days/week, mean (SD)	D-D	11.7 (7.9)	11.2 (7.2)	-0.4 (8.5)
	D-ND	12.0 (6.8)	12.5 (7.3)	0.4 (6.5)
	ND-D	12.5 (7.2)	11.5 (7.2)	-0.9 (7.5)
	ND-ND	12.7 (7.4)	13.6 (7.4)	0.9 (7.4) *
Work hours/day, mean (SD)	D-D	4.5 (2.4)	4.5 (2.3)	0.0 (1.8)
	D-ND	5.3 (3.4)	5.3 (3.1)	-0.0 (2.1)
	ND-D	5.3 (2.4)	5.3 (3.3)	-0.0 (3.3)
	ND-ND	5.2 (2.6)	5.2 (2.5)	0.0 (2.5)
Occupational functioning (SD)	D-D	8.4 (5.9)	8.4 (5.9)	0.0 (5.4)
	D-ND	8.8 (6.5)	10.6 (7.0)	1.8 (6.3) ***
	ND-D	10.9 (7.1)	9.7 (6.6)	-1.2 (6.5) ***
	ND-ND	11.1 (7.0)	11.3 (7.0)	0.2 (6.5)
Productivity, % (n)	D-D	64.3 (566)	63.0 (554)	-1.4
	D-ND	68.1 (356)	73.0 (382)	5.0
	ND-D	74.6 (309)	70.3 (291)	-4.4
	ND-ND	69.9 (1528)	72.5 (1584)	2.6
Activities/Relationships				
Daily activity, mean (SD)	D-D	3.3 (1.2)	3.3 (1.2)	-0.1 (1.0)
	D-ND	3.3 (1.2)	3.3 (1.2)	-0.0 (1.0)
	ND-D	3.5 (1.2)	3.4 (1.2)	-0.1 (1.0)
	ND-ND	3.4 (1.2)	3.4 (1.3)	0.0 (0.9)
Leisure activity, mean (SD)	D-D	2.6 (1.2)	2.6 (1.2)	-0.1 (1.2)
	D-ND	2.7 (1.2)	2.8 (1.1)	0.1 (1.2)
	ND-D	2.9 (1.1)	2.8 (1.1)	-0.1 (1.2)
	ND-ND	2.7 (1.2)	2.8 (1.2)	0.0 (1.2)
Common activities, mean (SD)	D-D	6.6 (2.1)	6.5 (2.1)	-0.1 (1.7)
	D-ND	6.5 (2.1)	6.7 (2.3)	0.2 (1.8) *
	ND-D	6.8 (2.2)	6.5 (2.2)	-0.3 (1.8) ***
	ND-ND	6.4 (2.3)	6.5 (2.3)	0.1 (1.8) *
Social relationships, mean (SD)	D-D	2.7 (1.2)	2.6 (1.2)	-0.1 (1.2)
	D-ND	2.8 (1.2)	2.9 (1.2)	0.1 (1.3)
	ND-D	2.9 (1.2)	2.7 (1.2)	-0.3 (1.3) ***
	ND-ND	3.0 (1.2)	2.9 (1.2)	-0.0 (1.2)
Interpersonal functioning, mean (SD)	D-D	17.2 (8.6)	17.1 (8.4)	-0.1 (7.8)
	D-ND	19.8 (9.1)	22.3 (9.8)	2.6 (9.3) ***
	ND-D	22.7 (9.9)	19.3 (9.2)	-3.3 (9.0) ***
	ND-ND	23.1 (10.3)	23.1 (9.9)	0.0 (8.7)
Family relationships, mean (SD)	D-D	4.1 (1.6)	4.1 (1.6)	0.0 (1.7)
	D-ND	4.4 (1.6)	4.8 (1.4)	0.4 (1.8) ***

Outcome domain/variable	Beginning and ending depressed status ^d	Beginning value	Ending value	Difference
	ND-D	4.7 (1.5)	4.4 (1.6)	*** -0.3 (1.6)
	ND-ND	5.2 (1.4)	5.2 (1.4)	0.0 (1.6)
Quality of life				
Quality of life, overall, mean (SD)	D-D	51.7 (17.9)	51.2 (17.8)	-0.4 (14.8)
	D-ND	55.1 (19.6)	63.2 (20.4)	*** 8.1 (18.5)
	ND-D	64.9 (22.0)	56.3 (20.0)	*** -8.6 (17.7)
	ND-ND	65.0 (21.9)	65.3 (21.3)	0.3 (17.1)
	D-D	19.0 (7.1)	19.0 (7.1)	-0.1 (6.1)
	D-ND	20.4 (8.0)	23.2 (7.7)	*** 2.8 (7.3)
	ND-D	23.9 (8.1)	20.5 (7.7)	*** -3.3 (7.3)
	ND-ND	24.1 (8.0)	23.8 (7.8)	-0.3 (6.7)
Global level of functioning, mean (SD)	D-D	36.4 (10.9)	35.6 (10.2)	* -0.8 (10.4)
	D-ND	39.2 (11.7)	42.5 (11.4)	*** 3.3 (12.1)
	ND-D	43.9 (12.3)	38.3 (10.4)	*** -5.7 (12.5)
	ND-ND	45.4 (12.5)	45.2 (12.2)	-0.2 (11.6)
	D-D	30.8 (11.0)	31.3 (10.9)	0.5 (12.0)
	D-ND	36.1 (11.7)	41.8 (11.4)	*** 5.7 (13.5)
	ND-D	41.2 (11.5)	36.7 (11.2)	*** -4.5 (13.7)
	ND-ND	48.0 (11.1)	48.4 (11.1)	0.4 (12.0)
Physical functioning, mean (SD)	D-D	44.2 (11.9)	43.5 (11.7)	-0.8 (11.0)
	D-ND	46.2 (11.0)	46.3 (10.7)	0.1 (11.4)
	ND-D	46.7 (10.9)	44.8 (11.5)	*** -1.9 (11.7)
	ND-ND	46.5 (9.5)	46.4 (9.5)	-0.1 (10.0)
	D-D	1.6 (0.8)	1.6 (0.9)	0.0 (1.0)
	D-ND	1.5 (0.9)	1.4 (0.6)	*** -0.2 (1.0)
	ND-D	1.4 (0.6)	1.5 (0.8)	** 0.1 (0.9)
	ND-ND	1.3 (0.6)	1.3 (0.6)	-0.0 (0.8)
Independent housing, % (N)	D-D	73.0 (631)	73.6 (637)	0.7
	D-ND	68.0 (351)	71.1 (367)	3.1
	ND-D	72.4 (296)	73.6 (301)	1.2
	ND-ND	67.3 (1460)	68.3 (1483)	1.1
General life satisfaction, mean (SD)	D-D	3.7 (1.5)	3.7 (1.5)	0.0 (1.6)
	D-ND	4.2 (1.5)	4.8 (1.4)	*** 0.5 (1.7)
	ND-D	4.7 (1.4)	4.3 (1.6)	*** -0.4 (1.7)
	ND-ND	5.2 (1.3)	5.3 (1.2)	** 0.1 (1.4)

^a Subjects who changed or maintained their depressed status during any 2 consecutive depression assessments across the 3-year study. Group sizes: D-D N=881, D-ND N=524, ND-D N=415, ND-ND N=2190. Group sizes differ across outcome variables due to missing values.

Significant group differences

* p<.05;

** p ≤ .01;

*** p ≤ .001

Abbreviations: D-D, Depressed to Depressed; D-ND, Depressed to Non-Depressed; ND-D, Non-depressed to Depressed; ND-ND, Non-depressed to Non-depressed.