

Brief report

Predicting recovery from episodes of major depression

David A. Solomon^{a,*}, Andrew C. Leon^b, William Coryell^c, Timothy I. Mueller^d,
Michael Posternak^e, Jean Endicott^f, Martin B. Keller^a

^a Department of Psychiatry and Human Behavior, The Warren Alpert Medical School of Brown University, Providence, RI, United States

^b Department of Psychiatry, Weill Medical College of Cornell University, NY, NY, United States

^c Department of Psychiatry, University of Iowa College of Medicine, Iowa City, IA, United States

^d Southern Arizona VA Health Care System, Department of Psychiatry, University of Arizona Health Sciences Center, Tucson, AZ, United States

^e Department of Psychiatry, Harvard Medical School, Boston, MA, United States

^f Department of Research Assessment and Training, New York State Psychiatric Institute, NY, NY, United States

Received 5 March 2007; received in revised form 29 August 2007; accepted 5 September 2007

Available online 17 October 2007

Abstract

Background: This study examined psychosocial functioning as a predictor of recovery from episodes of unipolar major depression. **Methods:** 231 subjects diagnosed with major depressive disorder according to Research Diagnostic Criteria were prospectively followed for up to 20 years as part of the NIMH Collaborative Depression Study. The association between psychosocial functioning and recovery from episodes of unipolar major depression was analyzed with a mixed-effects logistic regression model which controlled for cumulative morbidity, defined as the amount of time ill with major depression during prospective follow-up. Recovery was defined as at least eight consecutive weeks with either no symptoms of major depression, or only one or two symptoms at a mild level of severity.

Results: In the mixed-effects model, a one standard deviation increase in psychosocial impairment was significantly associated with a 22% decrease in the likelihood of subsequent recovery from an episode of major depression (OR=0.78, 95% CI: 0.74–0.82, $Z=-3.17$, $p<0.002$). Also, a one standard deviation increase in cumulative morbidity was significantly associated with a 61% decrease in the probability of recovery (OR=0.3899, 95% CI: 0.3894–0.3903, $Z=-7.21$, $p<0.001$).

Limitations: The generalizability of the study is limited in so far as subjects were recruited as they sought treatment at academic medical centers. The analyses examined the relationship between psychosocial functioning and recovery from major depression, and did not include episodes of minor depression. Furthermore, this was an observational study and the investigators did not control treatment.

Conclusions: Assessment of psychosocial impairment may help identify patients less likely to recover from an episode of major depression.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Major depression; Recovery; Psychosocial functioning; Psychosocial impairment; Risk factors; Predictors

1. Introduction

Patients suffering from an episode of major depressive disorder often want to know when they will recover. Clinicians and researchers are also interested in prognosis,

* Corresponding author. Mood Disorders Program, Department of Psychiatry, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island, 02903-4970, United States. Tel.: +1 401 444 5448; fax: +1 401 444 6180.

E-mail address: DASolomon@Lifespan.org (D.A. Solomon).

as it has implications for treatment, is part of psychoeducation, and may help delineate different subtypes of depression. Information about prognosis assumes even more importance, given that unipolar major depression is the single most common psychiatric disorder in the U.S. adult population, with a lifetime prevalence of 16.6% (Kessler et al., 2005).

There currently are no markers or diagnostic tests to help clinicians determine when a patient will recover from an episode of major depression. Although it is known that the median length of major depressive episodes is approximately 20 weeks, duration of illness is highly variable from one patient to another, and for any individual patient, duration of illness varies considerably from one recurrent episode to the next (Solomon et al., 1997). This lack of certainty limits clinical decision-making, and leaves patients and family members wondering what will happen and what they should do.

In response to the need for more information about prognosis, investigators have examined a multitude of variables for their association with faster or slower rates of recovery from episodes of major depression. Unfortunately, no sociodemographic, clinical, biological, or psychosocial functioning variable has been established as a consistent predictor of recovery across the numerous studies that have been conducted. The most that can be said is that sociodemographic variables do not predict the likelihood of recovery, including age at study intake, sex, marital status, and socioeconomic status (Solomon et al., 1997).

For many variables that have been examined, the inconsistent results between different studies are at least partly due to methodological differences. One common methodological problem is that studies of predictors examine recovery from only one episode of major depression. It is clear, however, that major depressive disorder is usually a recurring illness (Solomon et al., 1997) and studying subjects for only a single episode may yield incomplete results.

The present paper investigates the issue of prognosis by building upon previous work that evaluated overall psychosocial functioning as a predictor of recovery. Previously, the authors found a significant relationship between psychosocial impairment and longer episodes of major depression, over a two-year follow-up period (Leon et al., 1999). The present paper extends that work by 1) increasing the length of follow-up for up to 20 years, 2) accounting for cumulative morbidity over time, defined as the amount of time ill with major depression during prospective follow-up (the reason being that psychosocial impairment may simply be a correlate of cumulative morbidity), and 3) conducting

two separate analyses, one using a standard definition of recovery and the other a more rigorous definition.

The data for the present study come from the National Institute of Mental Health- Collaborative Program on the Psychobiology of Depression (Collaborative Depression Study). The Collaborative Depression Study is a prospective, observational, longitudinal program that has investigated course of illness in the mood disorders since 1978, and is well suited to study prognosis. The sample of subjects with major depressive disorder is large, diagnostically homogeneous, and well characterized by standardized diagnostic criteria and standardized assessments for follow-up. Subjects in the Collaborative Depression Study have been prospectively followed for up to 20 years, and assessed repeatedly throughout the follow-up period. Many subjects have suffered multiple episodes of major depression during that time. Based upon our previous finding, we hypothesized that increased psychosocial impairment was significantly related to a decreased probability of recovery from episodes of major depression.

2. Methods

2.1. Overview

Subjects with unipolar major depression were regularly assessed during follow-up. Level of psychopathology was rated for each week of the study, and level of psychosocial functioning was rated for the particular month in which the rater interviewed the subject. The investigators examined psychosocial functioning in each subject who was actively ill with an episode of major depression at the time of an assessment (time 1). The investigators then examined whether or not those subjects had recovered by the time the next assessment occurred (time 2). The relationship between psychosocial functioning at time 1 and recovery status (recovered vs. not recovered) at time 2 was then analyzed.

2.2. Subjects

From 1978 to 1981, individuals receiving inpatient or outpatient treatment for a mood disorder were recruited and enrolled into the Collaborative Depression Study at academic medical centers in Boston, MA; Chicago, IL; Iowa City, IA; New York, NY; and St. Louis, MO. Inclusion criteria included age of at least 17 years, intelligence quotient greater than 70, ability to speak English, white race (genetic hypotheses were tested), no signs of a mood or psychotic disorder secondary to a general medical condition, and written informed consent.

The sample for the present analyses consisted of 231 subjects with 1) an episode of major depression at study intake, and no underlying minor depression or chronic intermittent depressive disorder of at least two years duration; 2) no history of bipolar disorder or schizoaffective disorder prior to intake; and 3) no episodes of mania, hypomania, schizoaffective mania, or schizoaffective depression during the 20-year follow-up period.

2.3. Assessments

Diagnoses were made at study intake according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), based upon assessment with the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) and a review of medical records. Following intake, raters interviewed subjects every 6 months for the first five years of the study and annually thereafter, using variations of the Longitudinal Interval Follow-up Evaluation (Keller et al., 1987), to obtain weekly symptom severity ratings. Each subject was assessed up to 25 times during the 20-year follow-up period. A total of 1284 assessments were completed for the 231 subjects.

Severity of psychopathology was rated on a 6-point scale called the “psychiatric status rating” (PSR). A PSR of 1 corresponded to no symptoms. A PSR of 2 corresponded to 1 or 2 symptoms of a mild degree, with no impairment of functioning. A PSR of 3 corresponded to moderate psychopathology considerably less than that meeting the full criteria for the RDC disorder, with no more than moderate impairment in functioning. A PSR of 4 denoted marked symptoms not meeting the full criteria for the RDC disorder, with major impairment in functioning. A PSR of 5 corresponded to symptoms meeting the full criteria for the RDC disorder, and a PSR of 6 indicated full criteria for the RDC disorder along with psychosis or extreme impairment in functioning. At each interview, the rater assigned a psychiatric status rating for each week of the assessment interval, starting from the time of the last interview. To accomplish this, the rater first identified chronological anchor points such as birthdays and holidays, to assist the subject in remembering those times when significant clinical improvement or deterioration occurred. Whenever possible, corroborative data were obtained from medical records and other informants. During prospective follow-up, the investigators have revised diagnoses of subjects as warranted by their clinical course.

Consistent with Research Diagnostic Criteria, the outcome of *recovery* was defined as at least eight consecutive weeks with either no symptoms of major depression, or only one or two symptoms at a mild level

of severity. In a second set of analyses, recovery was defined as at least eight consecutive weeks with no symptoms of major depression. This more rigorous definition of recovery precluded the presence of any subsyndromal symptoms.

Raters also used the Longitudinal Interval Follow-up Evaluation to assess psychosocial functioning during the particular month in which the rater interviewed the subject. Several domains of functioning were assessed, including work, interpersonal relationships, recreation, and satisfaction. These four items were used to construct a brief summary scale of functional impairment, called the Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool (Leon et al., 1999). For each of the four items, the interviewer rated the level of functioning on a 5-point scale (1=no impairment, 5=severe impairment), guided by behavioral anchors for each point of the scale. The Longitudinal Interval Follow-up Evaluation–Range of Impaired Functioning Tool yielded a single score ranging from 4 (no impairment) to 20 (severe impairment), and is summarized in Table 1.

To study the relationship between psychosocial functioning and recovery from an episode of unipolar

Table 1
Summary of the Longitudinal Interval Follow-up Evaluation—Range of Impaired Functioning Tool (Leon et al., 1999)

Domain of functioning*	Rating
Work	Employment, household duties, and school work are each rated for the past week where applicable, and the score for the item with the greatest impairment is used to provide a rating for work
Interpersonal relations	Relationship with spouse, children, other important relatives, and friends are each rated for the past month where applicable, and the score for the item with the greatest impairment is used to provide a rating for interpersonal relations
Satisfaction	The overall level of satisfaction, contentment, degree of fulfillment, and gratification derived from various activities and areas of functioning during the past week
Recreation	The overall level of involvement in and enjoyment of recreational activities and hobbies during the past week

*Each domain of functioning is rated on a 5-point scale that includes behavioral anchors for each point:

1 = no impairment, very good functioning.

2 = no impairment, good functioning.

3 = mild impairment, fair functioning.

4 = moderate impairment, poor functioning.

5 = severe impairment, very poor functioning.

The score for the four domains are summed to generate a single score, ranging from 4 (no impairment, very good functioning) to 20 (severe impairment, very poor functioning).

major depression, the investigators examined psychosocial functioning in each subject who was actively ill with major depression at the time of an assessment (time 1). We then examined whether or not those subjects had subsequently recovered by the time the next assessment occurred (time 2). The relationship between psychosocial functioning at time 1 and recovery status (whether the subject had recovered from the episode) at time 2 was then analyzed. This procedure was carried out at each assessment, regardless of how long any single episode of major depression persisted, and regardless of how many episodes the subject suffered.

The data analytic models included the variable “cumulative morbidity.” Cumulative morbidity was defined as the number of weeks ill with major depression during prospective follow-up, beginning at intake into the study and ending at the time of the most recent assessment of the psychiatric status rating with the Longitudinal Interval Follow-up Evaluation. The analyses thus controlled for the effect of cumulative morbidity on recovery, with the reasoning that psychosocial impairment may simply be a correlate of cumulative morbidity.

2.4. Treatment

The Collaborative Depression Study is an observational study in that treatment is not randomly assigned by design and not controlled by anyone connected with the study. In an observational study, the causal relationship between intensity of treatment and level of psychopathology is not known. For example, some subjects are asymptomatic because they receive robust amounts of treatment, while other subjects receive robust amounts of treatment because their symptoms are unremitting.

Each specific psychotropic medication and dose was recorded for each week of the study. Throughout the follow-up period, the intensity of treatment varied within subjects as well as between subjects. Previous analyses have shown that for subjects who are in episode with major depression, the average level of somatic treatment is at the low end of the therapeutic dose range (Solomon et al., 1997).

2.5. Data analytic procedures

Mixed-effects logistic regression models were used to examine the association of the independent variables psychosocial impairment and cumulative morbidity, with the binary dependent variable, recovery from an episode of major depression. The mixed-models incor-

porated multiple observations per subject, based on the number of assessments that occurred while the subject was in an episode of major depression. The models included a random effect for the subject-specific intercept. The MIXOR program was used for analyses (Hedeker and Gibbons, 1996). A two-tailed alpha level of 0.05 was used for each statistical test.

3. Results

Table 2 displays the sociodemographic and clinical characteristics of the 231 study subjects. Subjects were followed for an average of approximately 14 years (mean = 719 weeks, SD = 300 weeks; median = 860 weeks, range: 74 to 1040 weeks).

For each subject, the mean (SD) number of recoveries from episodes of major depression was 3.1 (SD = 2.6), (median = 2.0, range: 0 to 18). The mean (SD) rating of psychosocial impairment on the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool during an episode of major depression was 13.9 (3.0) (the possible range was 4 [no impairment] to 20 [severe impairment]).

The first mixed-effects logistic regression model examined the association of both psychosocial impairment and cumulative morbidity with recovery from an episode of major depression. Recovery from each episode of depression was defined according to Research Diagnostic Criteria, as eight consecutive weeks with either no symptoms of major depression, or only one or two symptoms at a mild level of severity. For subjects ill with major depression, decreased psychosocial functioning at the time of assessment was significantly associated with a decreased probability of recovery by the time the next follow-up assessment was completed (assessments were performed every six months for the first five years of the study and annually thereafter). Specifically, a one standard deviation increase in impairment (3.0 points on the Longitudinal Interval Follow-up Evaluation-Range of Impaired Functioning Tool) was associated with a 22% decrease in likelihood of recovery from major depression (odds ratio = 0.78, 95% CI: 0.74–0.82, $Z = -3.17$, $p < 0.002$). Furthermore, a one standard deviation unit (216 weeks) increase in cumulative morbidity was significantly associated with a 61% decrease in the probability of recovery by the time of the next follow-up assessment (odds ratio = 0.3899, 95% CI: 0.3894–0.3903, $Z = -7.21$, $p < 0.001$).

A second mixed-effects logistic regression model examined the association of psychosocial impairment and cumulative morbidity with recovery from an episode of

Table 2
Sociodemographic and clinical characteristics at intake of 231 probands with major depressive disorder^a

Sex	No. (%)
Male	84 (36)
Female	147 (64)
Status at intake	
Inpatient	173 (75)
Outpatient	58 (25)
No. of previous episodes of MDD	
0	77 (33)
1	57 (25)
2	37 (16)
3+	60 (26)
RDC subtypes of MDD	
Endogenous	
probable or definite	207 (90)
Definite	138 (60)
Psychotic (current)	
probable or definite	17 (7)
Definite	13 (6)
Primary (current)	135 (58)
Current marital status	
Never married	68 (29)
Married/living together	118 (51)
Divorced/separated/widowed	45 (19)
Socioeconomic status (Hollingshead–Redlich scale) ^b	
I	11 (5)
II	40 (17)
III	61 (26)
IV	76 (33)
V	43 (19)
Intake medical center location	
New York, NY	21 (9)
St. Louis, MO	81 (35)
Boston, Mass	39 (17)
Iowa City, Iowa	56 (24)
Chicago, Ill	34 (15)
Global assessment scale score ^{c,d}	44/41/11/8/75
Severity of major depressive episode extracted Hamilton score ^{c,e}	26/26/7/10/45
Age at entry, years ^c	39/36/15/17/79

^a Percentages do not always add to 100 because of rounding.

^b Hollingshead–Redlich scale: I = highest, V = lowest.

^c Mean/median/SD/minimum/maximum.

^d The range for the Global Assessment Scale is 1 to 100, and higher numbers indicate less psychopathology and better functioning (Endicott et al., 1976).

^e 17-item Hamilton Rating Scale for Depression score (Endicott et al., 1981).

major depression to an asymptomatic state. In this model, recovery from each episode of major depression was defined more rigorously as at least eight consecutive weeks with no symptoms of major depression. The results showed that a one standard deviation increase in impairment was associated with a 19% decrease in likelihood of recovery from major depression (odds ratio=0.81, 95% CI: 0.78–0.85, $Z=-2.83$, $p=0.005$). In

addition, a one standard deviation unit increase in cumulative morbidity was significantly associated with a 53% decrease in the probability of recovery (odds ratio=0.4657, 95% CI: 0.4653–0.4660, $Z=-7.97$, $p<0.001$). Thus, in both mixed-effects models, psychosocial impairment and cumulative morbidity were each significantly associated with a reduced probability of recovery.

4. Discussion

The present results indicate that psychosocial impairment is associated with a decreased probability of recovery from an episode of major depression, above and beyond the decreased probability accounted for by cumulative morbidity. Even when a more rigorous definition of recovery was used – at least eight consecutive weeks with no symptoms of major depressive disorder – the association between psychosocial impairment and a reduced probability of recovery was large and statistically significant. It is worth noting that the association between cumulative morbidity and a reduced probability of recovery was also large and statistically significant.

The findings are limited by several factors. The analyses examined the relationship between psychosocial functioning and recovery from major depression, and did not include episodes of minor depression and chronic intermittent depression. Furthermore, this was an observational study and the investigators did not control treatment. As such, treatment varied both within and between subjects, and this may have influenced the findings. Another limitation is that recovery was examined 6 or 12 months after functioning was assessed; thus, it's not known if functioning was associated with recovery at some later time, e.g., 24 months after functioning was assessed.

The generalizability of the study is also limited in so far as subjects were recruited as they sought treatment at academic medical centers, and 75% of the subjects were recruited as inpatients. The findings may therefore be less relevant for outpatients. However, it should be noted that subjects were recruited during the late 1970s and early 1980s, when the threshold for inpatient hospitalization was lower than it is today.

The value of psychosocial functioning as a prognostic factor ultimately depends upon the results of future studies, and whether they replicate the present findings. The authors believe the present results warrant further investigation, as they come from the only known study to evaluate prognostic variables over a follow-up period lasting up to 20 years. In addition, the analyses used mixed-effects models, which are highly advantageous

for analyzing longitudinal data, because mixed models can incorporate multiple observations per subject and a varying number of observations between subjects.

In evaluating different variables as predictors, it's worth noting that a variable that is strongly associated with a particular outcome, such as recovery or recurrence, is of little use if that variable is rarely present within the population of interest. Conversely, a variable that is more prevalent in a population is potentially more useful for prognosis. In patients with major depressive disorder, psychosocial impairment appears to be very common. One epidemiological survey found that 96.9% of subjects with an episode of major depression had impairment of family life/home responsibilities, work, and/or social life at some point during the episode, ranging from mild to very severe (Kessler et al., 2003).

The results reported here may be clinically relevant beyond prognosis. The analyses were conducted in such a manner as to simulate the situation in which a clinician evaluates a patient who is suffering from an episode of major depression. In this circumstance, the clinician cannot intervene to alter any aspect of the patient's past clinical history, such as cumulative morbidity. However, the presence of psychosocial impairment may suggest the need for more intense treatment, perhaps including an intervention to address the impairment.

Role of funding source

Funding for this study was provided by NIMH grant MH25478-29A2. The NIMH had no further role in the design of the study; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

Dr. Solomon has served as an investigator for research funded by the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, Janssen Pharmaceutica, Wyeth-Ayerst Laboratories, and Merck; as a consultant to Solvay Pharmaceuticals, Shire, and Novartis; and on the lecture bureaus of AstraZeneca, Pfizer, GlaxoSmithKline, and Shire.

Dr. Leon has served as an investigator for research funded by the National Institute of Mental Health, the National Institute of Drug Abuse. He is on two Data Safety Monitoring Boards for Pfizer and has served as a consultant to Eli Lilly and Cyberonics.

Dr. Coryell has no conflicts of interest.

Dr. Mueller is currently an employee of the federal government and receives no outside funding. During his involvement with the research reported in this manuscript he received grant funding from National Institute of Mental Health, Pfizer, Alkermes, and Lipha.

Dr. Posternak has no conflicts of interest.

Dr. Endicott has been an investigator for research funded by four of the National Institutes of Health and the New York State Department of Mental Health. She has received research support from Abbott, Bristol-Meyers, Cyberonics, Interneuron, Merck, Parke-Davis, Pfizer, UpJohn,

and Wyeth-Ayerst and has served as a consultant or advisory board member for Abbott, AstraZeneca, Berlex, Bristol-Meyers Squibb, Cyberonics, Eli Lilly, GlaxoSmithKline, Novartis, Otsuka, Janssen, Ovation, Pfizer, Sanofi-Synthelabo Research, and Wyeth-Ayerst.

Dr. Keller has served as a consultant or received honoraria from Collegium, Cypress Bioscience, Cyberonics, Eli Lilly, Forest Laboratories, Janssen, Organon, Otsuka, Pfizer, Pharmastar, Sepracor, Vela Pharmaceuticals, and Wyeth Pharmaceuticals. He has received research support from Eli Lilly, Pfizer, and Wyeth Pharmaceuticals. He has served on advisory boards for Abbott Laboratories, Bristol-Meyers Squibb, Cyberonics, Cypress Bioscience, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen, Novartis, Organon, Pfizer, Sepracor, and Wyeth Pharmaceuticals.

Acknowledgements

This study was conducted with the current participation of the following investigators: M.B. Keller, M.D. (Chairperson, Providence, RI); W. Coryell, M.D. (Co-Chairperson, Iowa City, IA); D.A. Solomon, M.D. (Providence, RI); W. Scheftner, M.D. (Chicago, IL); J. Endicott, Ph.D., A.C. Leon, Ph.D., and J. Loth, M.S.W. (New York, NY); and J. Rice, Ph.D., (St. Louis, MO). Other current contributors include H.S. Akiskal, M.D., J. Fawcett, M.D., L.L. Judd, M.D., P.W. Lavori, Ph.D., J.D. Maser, Ph.D., and T. I. Mueller, M.D. This manuscript has been reviewed by the Publication Committee of the Collaborative Depression Study and has its endorsement.

The data for this manuscript came from the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression-Clinical Studies. The Collaborative Program was initiated in 1975 to investigate nosologic, genetic, family, prognostic, and psychosocial issues of mood disorders, and is an ongoing, long-term multidisciplinary investigation of the course of mood and related affective disorders. The original principal and co-principal investigators were from five academic centers and included Gerald Klerman, M.D.* (Co-Chairperson), Martin Keller, M.D., Robert Shapiro, M.D.* (Massachusetts General Hospital, Harvard Medical School), Eli Robbins, M.D.*, Paula Clayton, M.D., Theodore Reich, M.D.*, Amos Wellner, M.D.* (Washington University Medical School), Jean Endicott, Ph.D., Robert Spitzer, M.D., (Columbia University), Nancy Andreasen, M.D., Ph.D., William Coryell, M.D., George Winokur, M.D.* (University of Iowa), Jan Fawcett, M.D., William Scheftner, M.D., (Rush-Presbyterian-St. Luke's Medical Center). The NIMH Clinical Research Branch was an active collaborator in the origin and development of the Collaborative Program with Martin M. Katz, Ph.D., Branch Chief as the Co-Chairperson and Robert Hirschfeld, M.D. as the Program Coordinator. Other

past collaborators include J. Croughan, M.D., M.T. Shea, Ph.D., R. Gibbons, Ph.D., M.A. Young, Ph.D., D. C. Clark, Ph.D.

*deceased.

References

- Endicott, J., Spitzer, R.L., 1978. A diagnostic interview. *Arch. Gen. Psychiatry* 35, 837–844.
- Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch. Gen. Psychiatry* 33, 766–771.
- Endicott, J., Cohen, J., Nee, J., Fleiss, J., Sarantakos, S., 1981. Hamilton Depression Rating Scale: extracted from regular and change versions of the Schedule for Affective Disorders and Schizophrenia. *Arch. Gen. Psychiatry* 38, 98–103.
- Hedeker, D., Gibbons, R.D., 1996. MIXOR: a computer program for mixed-effects ordinal regression analysis. *Comput. Methods Programs Biomed.* 49, 157–176.
- Keller, M.B., Lavori, P.W., Friedman, B., Nielsen, E., Endicott, J., McDonald-Scott, P., Andreasen, N.C., 1987. The longitudinal interval follow-up evaluation. *Arch. Gen. Psychiatry* 44, 540–548.
- Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62, 593–602.
- Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289, 3095–3105.
- Leon, A.C., Solomon, D.A., Mueller, T.I., Turvey, C.L., Endicott, J., Keller, M.B., 1999. The range of impaired functioning tool (LIFE-RIFT). *Psychol. Med.* 29, 869–878.
- Solomon, D.A., Keller, M.B., Leon, A.C., Mueller, T.I., Shea, M.T., Warshaw, M., Maser, J.D., Coryell, W., Endicott, J., 1997. Recovery from major depression. *Arch. Gen. Psychiatry* 54, 1001–1006.
- Spitzer, R.L., Endicott, J., Robins, E., 1978. Research diagnostic criteria. *Arch. Gen. Psychiatry* 35, 773–782.