The role and clinical significance of subsyndromal depressive symptoms (SSD) in unipolar major depressive disorder

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Abstract

Analyses conducted in 10,526 community respondents investigated by the NIMH Epidemiological Catchment Area (ECA) Program, revealed the 1-month point prevalence of depressive symptoms and disorders in the general population, at the first ECA interview (Wave 1) to be 10%, as follows: 2.3% major depressive disorder (MDD); 2.3% dysthymic disorder (DD); 1.5% minor depressive disorder (MinD); and 3.9% subsyndromal depressive symptoms (SSD), defined as two or more depressive symptoms beneath the diagnostic threshold of MinD, DD or MDD. There appears to be two classes of SSD in this community sample: first, SSD, which occurred as an integral component of the course of unipolar major depressive disorder (MDD); and, second, SSD occurring spontaneously in non-unipolar depressed community subjects. In the first instance, SSD was frequently prodromal to episodes of MinD or MDD or residual to resolving episodes. Analyses also support the conclusion that SSD is a clinically significant, interepisode, depressive subtype of unipolar MDD, since SSD is associated with harmful dysfunction in five of six measures of adverse outcome, has a significantly increased prevalence of past histories of major depressive episodes, and an elevated lifetime prevalence of suicide attempts. Comparison of subsyndromal depressive symptomatology or depressive disorder diagnoses at Wave 1 with diagnoses obtained, 1 year later, at the Wave 2 interview, confirm the persistent and chronic nature of depression in this large representative sample of community respondents, in which 71% of subjects with depressive symptoms or disorders at Wave 1 continued to be symptomatic at Wave 2. In addition, subjects experienced a surprising degree of change in depressive symptom and disorder diagnoses during the 1-year observational window between Wave 1 and Wave 2, in which a remarkable percentage of individuals, who began the year in a depressive symptom or disorder diagnostic category, ended the year in another. This has led us to hypothesize that the typical clinical picture of unipolar MDD is dynamic and pleomorphic in nature, characterized by substantial symptomatic fluidity, in which patients frequently change diagnoses from one depressive subtype to another during their course of illness. © 1997 Elsevier Science B.V.

1. Introduction

It has been established that people with subthreshold depressive symptoms, compared to persons without symptoms, experience significantly more impairment and social dysfunction. Respondents with subthreshold depression in community and outpatient populations report significantly more
health service use (Johnson et al., 1992), need for public assistance (Judd et al., 1994), more limitations in role (work) function (Wells et al., 1989; Broadhead et al., 1990; Judd et al., 1996), increased physical limitations (Wells et al., 1989; Judd et al., 1996), increased job absenteeism (Broadhead et al., 1990; Johnson et al., 1992), increased bed days (Wells et al., 1989; Judd et al., 1996) and increased social irritability and household strain (Judd et al., 1996). In addition, it has been reported that the lifetime (Johnson et al., 1992), 1-year (Judd et al., 1994) and 6-month (Broadhead et al., 1990) prevalence of depressive symptoms, below the diagnostic threshold for dysthymic disorder or major depression, is elevated over that observed for the syndromal depressive disorders. For example, we reported the 11.8% 1-year prevalence of subthreshold depressive symptoms in Epidemiological Catchment Area (ECA) community residents (n = 9160) was twice that of major depression at approximately 5.5% (Judd et al., 1994). One-third of persons with subthreshold symptoms also met criteria for minor depressive disorder (DSM-IV); the remaining two-thirds endorsed from two to eight depressive symptoms, while not meeting criteria for minor depressive, dysthymic or major depressive disorders.

Some clarity of the role and clinical significance of subthreshold depressive symptoms has begun to be reported recently, for example, Broadhead et al. (1990) found that 10% of minor depressed individuals with mood disturbance at one ECA site (Durham, NC) developed major depression 1 year later. In addition, Howarth et al. (1992) have reported that ECA respondents with lifetime subthreshold depressive symptoms (two or more lifetime) were 5.5 times more likely to develop first onset major depression during the next year. These studies suggest that subthreshold depressive symptoms may be a significant risk factor for future major depressive episodes.

To investigate the clinical relevance of subsyndromal depression, Sherbourne et al. (1994) compared the clinical and demographic characteristics of 775 depressive disorder patients to 1420 subsyndromal depressives from the Medical Outcomes Study. The two patient cohorts were qualitatively similar in demographic and clinical characteristics as follows: 41% of patients with subsyndromal depression had family histories of depression, which was comparable to the 59% observed in patients with depressive disorder; both cohorts had a significantly higher preponderance of women and shared similar patterns of medical and psychiatric comorbidity. It was concluded that patients with subsyndromal depression more closely resembled depressive disorder patients than they did non-depressed medical patients, indicating that subsyndromal depressive symptoms are a variant of unipolar major depression.

To further our understanding of the clinical significance of subthreshold depression, we have proposed a more restrictive clinical condition, subsyndromal depressive symptoms (SSD), defined by at least two or more current depressive symptoms, present every day for most or all of the time, at least 2 weeks in duration, in persons not meeting criteria for minor depressive disorder, dysthymic disorder or major depression (Judd, 1994; Judd et al., 1994). Using this definition of SSD, we conducted a series of analyses in a subset of the ECA database to determine the following: 1-month point prevalence of depressive symptoms and depressive disorders in the community; the psychosocial impairment associated with both depressive symptoms and disorders; and the role and clinical significance of subsyndromal depressive symptoms in community respondents.

2. Methods

2.1. Subjects

The analysis sample is derived from three of the five data collection sites (Baltimore, MD; Durham, NC; and Los Angeles, CA) of the NIMH Epidemiological Catchment Area Program. Sampling methodology, human subject consent procedures, study design, survey methods, demographic characteristics and prevalence of mental disorders of the sample have been fully described in other reports (Eaton et al., 1984; Regier et al., 1984, 1994; Eaton and Kessler, 1985). Respondents’ DSM-III diagnoses are obtained from recorded responses to at least one structured interview conducted by trained lay interviewers using the Diagnostic Interview Schedule
(DIS) (Robins et al., 1981a,b). From these data, computer-assisted algorithms assigned DSM-III diagnoses (Diagnostic Statistical Manual of Mental Disorders, 1980, Third Edition) and record the timeframe in which the diagnoses have occurred in relationship to the DIS interview (1 month, 6 months, 1 year or lifetime). At only three of the ECA sites (referenced previously) data were also collected for each individual mental symptom probed by the DIS and the timeframe when the symptom occurred (i.e., 1 month, 6 month, 1 year or lifetime). The DIS specifies a standardized threshold to determine if a depressive symptom is clinically significant and should be recorded. A depressive symptom must be present for at least 2 weeks and significant enough that respondents had either talked to a health professional or had taken medications because of it or felt the symptoms had interfered substantially in their everyday activities. Thus, depressive symptoms identified by the DIS are clinically substantial in severity and duration, extending well beyond the vicissitudes of mood that are integral to the human condition. Most importantly, the DIS specifies that depressive or other mental symptoms should not be associated with current medical illnesses, nor as the side effects of drug or alcohol consumption or problems.

2.2. Diagnostic categories of depressive symptoms and depressive disorders

All respondents from the ECA three-site community sample \( n = 10,526 \) were classified into seven mutually exclusive categories based on the presence or absence of depressive symptoms or disorders. These groups are derived from the 1-month prevalence data from the first ECA interview (Wave 1), defined as follows:

2.2.1. Group 1: no depressive symptoms or depressive disorders (nsd)

Persons included in this group are those who did not report any depressive symptoms nor met criteria for any depressive disorder in the 1 month prior to the first ECA interview (Wave 1). It should be noted that persons with other mental and/or substance use disorders are included in this comparison group.

2.2.2. Group 2: one depressive symptom

Persons in this group endorsed only one depressive symptom during the month prior to the first ECA interview but did not qualify for diagnosis of SSD minor depressive disorder (DSM-IV), DSM-III dysthymic disorder or DSM-III major depressive episode.

2.2.3. Group 3: subsyndromal depressive symptoms (SSD)

Persons in this group endorsed two or more depressive symptoms in the month prior to the Wave 1 interview, but did not qualify for diagnoses of minor depressive disorder (DSM-IV), DSM-III dysthymic disorder or DSM-III major depressive episode.

2.2.4. Group 4: minor depressive disorder

These individuals met DSM-IV criteria for minor depressive disorder, which specifies the presence of two to four depressive symptoms, one of which must be the 'A' criterion symptom of 14 days of depressed blue or dysphoric mood or loss of interest or pleasure in most things (Diagnostic Statistical Manual of Mental Disorders, 1994, Fourth Edition).

2.2.5. Group 5: dysthymic disorder

Individuals in this group met DSM-III criteria for a diagnosis of dysthymic disorder, which requires at least a 2-year duration of illness.

2.2.6. Group 6: major depression

Persons in this group met criteria for DSM-III major depression, in addition, persons with 'double depression' in which a major depressive episode is superimposed on dysthymic disorder are included here.

2.2.7. Group 7: depressive symptoms occurring in the presence of another mental or substance use disorder

Individuals in this group endorsed one or more subthreshold depressive symptoms occurring in the context of another mental or substance use disorder.
2.2.8. **Control for comorbid mental and or substance abuse disorders in the two depressive symptom groups (see Groups 2 and 3)**

To isolate subthreshold depressive symptoms from the influence of comorbid mental and substance use disorders, individuals with the following current (1-month prevalence) disorders were removed from the one depressive symptom and the subsyndromal depressive symptom groups: manic episode, schizophrenia, schizophreniform disorder, obsessive-compulsive disorder, phobia, somatization disorder, panic disorder and antisocial personality disorder, alcohol abuse or dependence, drug use or dependence, cannabis use or dependence.

3. **Statistical analyses**

The weighting procedures utilized in the ECA program adjust for differences in respondent’s demographic characteristics, based upon the likelihood of the respondents being selected for interview from the mental health catchment areas used in the study. The weighting procedure also adjusts with the individual respondent’s representativeness in the 1980 US population on the basis of age, gender, race ethnicity, education and socio-economic status. The ECA study utilizes an efficient, multi-stage sampling design. SUDAAN software is used to estimate variances for prevalence, means, cross-tabulations and logistic regressions. SUDAAN uses a tailored series linearization to estimate standard errors and the statistical significance of regression coefficients. The analyses applied CROSSTAB, DESCRIPT and RTI LOGIT routines. Cross-tabulation and descriptive statistics are used to investigate differences across study groups. Odds ratio estimates are used to measure association between disease status and studied outcomes. Odds ratios approximate the relative risk of the presence of an attribute or outcome that is attributable to membership in a particular depressive symptom or depressive disorder group in comparison to a study group that is ‘held out’.

All dependent variables in the logistic regressions could take on only two possible values that signify either the presence or absence of the attribute or outcome. The logistic regression controlled for group differences or age, gender, race ethnicity and study site as follows: (1) three-category age-variable, partition groups, 18–34, 34–64, 65+; (2) an indicator signifying female gender; (3) an indicator signifying white or non-white race ethnicities; (4) indicators signifying ECA study site; and (5) several indicators signifying study group.

Odds ratio estimates are obtained by exponentiation of logistic regression coefficients. Asymmetrical 95% confidence intervals for the odds ratio estimates are computed from the exponentiated LOGITs and estimated standard errors of regression coefficients. Only the adjusted odds ratios significant at the $P < 0.5$ level are reported.

4. **Results**

4.1. **One-month point prevalence of depressive symptoms and disorders in the community sample**

The initial analysis determined the 1-month point prevalence of depressive symptoms and depressive disorders in the ECA three-site community sample as derived from the first DIS interview (Wave 1). The data in Table 1 include the weighted percentages (prevalences) and unweighted numbers of individuals in each of the seven groups. The 1-month point prevalence for depressive symptoms and DSM-III depressive disorders totals 22.6% in this representative adult community sample. Excluding the depressive symptoms comorbid with other disorders (3.9%), approximately 12.6% of this sample of adults report one or more non-comorbid depressive symptoms, under the diagnostic threshold for any depressive disorder; a prevalence rate twice that of minor depressive, dysthymic, and major depressive disorder combined. The 3.9% 1-month point prevalence of subsyndromal depressive symptoms (SSD), combined with the 6.1% for the other syndromal depressive disorders, totals 10% of the adult population studied.

4.2. **Demographic characteristics of the depressive symptom and depressive disorder diagnostic groups**

Comparison of selected demographic characteristics in six of the seven depressive symptom and depressive disorder groups are shown in Table 2.
Table 1
One-month point prevalence of depressive symptoms and depressive disorders in the three-site ECA (Baltimore, Durham and Los Angeles) community sample (n = 10,526)

<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>No depressive symptoms or disorders</td>
<td>77.4</td>
<td>8005</td>
</tr>
<tr>
<td>One depressive symptom</td>
<td>8.7</td>
<td>905</td>
</tr>
<tr>
<td>Subsyndromal depressive symptoms</td>
<td>3.9</td>
<td>449</td>
</tr>
<tr>
<td>Minor depressive disorder</td>
<td>1.5</td>
<td>164</td>
</tr>
<tr>
<td>Dysthmic disorder</td>
<td>2.3</td>
<td>262</td>
</tr>
<tr>
<td>Major depression</td>
<td>2.3</td>
<td>253</td>
</tr>
<tr>
<td>Subsyndromal depressive symptoms comorbid with other mental and/or substance use disorders</td>
<td>3.9</td>
<td>443</td>
</tr>
</tbody>
</table>

*Prevalences are weighted to adjust for sampling bias.
Numbers are unweighted.

Table 2
Demographic characteristics of groups divided on the basis of depressive symptoms or disorders

<table>
<thead>
<tr>
<th></th>
<th>No symptoms or disorders (n = 8005)</th>
<th>Depressive symptom (n = 950)</th>
<th>One depressive symptom (SSD) (n = 449)</th>
<th>Two or more depressive disorders (n = 164)</th>
<th>Minor dysthmic disorder (n = 262)</th>
<th>Major depression (n = 253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (S.E.) (years)</td>
<td>42.45 (0.25)</td>
<td>44.32 (0.73)</td>
<td>43.62 (1.01)</td>
<td>41.64 (1.54)</td>
<td>41.88 (1.13)</td>
<td>40.32 (1.07)</td>
</tr>
<tr>
<td>Percent (%) (S.E.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51 (0.8)</td>
<td>59 (1.9)</td>
<td>65 (3.1)</td>
<td>59 (5.1)</td>
<td>70 (3.5)</td>
<td>70 (3.3)</td>
</tr>
<tr>
<td>Male</td>
<td>49 (0.8)</td>
<td>41 (1.9)</td>
<td>35 (3.1)</td>
<td>41 (5.1)</td>
<td>30 (3.5)</td>
<td>30 (3.3)</td>
</tr>
<tr>
<td>Mean years education completed (S.E.)</td>
<td>12.44 (0.06)</td>
<td>11.94 (0.15)</td>
<td>11.67 (0.20)</td>
<td>11.71 (0.34)</td>
<td>12.26 (0.30)</td>
<td>12.12 (0.26)</td>
</tr>
<tr>
<td>Mean annual household income ($) (S.E.)</td>
<td>22,283 (268)</td>
<td>20,133 (683)</td>
<td>18,992 (890)</td>
<td>17,481 (1555)</td>
<td>19,195 (1109)</td>
<td>16,179 (1160)</td>
</tr>
</tbody>
</table>

*Numbers unweighted.
All other attributes are weighted to correct for sampling bias.

Since one of our primary interests is in evaluating clinical significance of subthreshold depressive symptoms without the confounding influence of other comorbid disorders, respondents in the depressive symptoms comorbid with mental and/or substance use disorders group have been eliminated from these analyses. The major depression group has the lowest mean age, on average they are younger by approximately 2 years than the other groups. The five groups with depressive symptoms or disorders have lower mean household incomes, this is especially true in the major depression group, where it is the most marked (approximately 27% lower). There is a distinct over-representation of women in the depressive symptom and depressive disorder groups, progressively increasing at each increment in depressive symptom severity with the dysthmic and major depressive groups having 70% women. Apart from these variables, the demographic characteristics are essentially similar among the groups.

4.3. Comparison of psychosocial function in the depressive symptom and depressive disorder diagnostic groups

Lifetime prevalences of selected domains of functional outcome and well-being, probed in the ECA interview, are compared in Table 3. Compared to the no depressive symptom or disorder group, significant differences in adjusted odds ratios are present for seven of nine outcome variables for the one depressive symptom, for eight of nine variables for the subsyndromal depressive symptoms (SSD) groups and for nine of nine variables in the minor depressive disorder, dysthmic disorder and major depression groups. Reciprocally, the odds ratios are significantly higher for the lifetime prevalence rates for the major depression group for all nine outcome variables when compared to the one depressive symptom group, for eight of nine compared to SSD (exception disability benefits) for seven of nine compared to...
Table 3
Adjusted odds ratios comparing prevalence of lifetime health service use, public assistance and suicidal ideations and attempts in the one depressive symptom (n = 950)*, subsyndromal symptomatic depression (n = 449), minor depressive disorder (n = 169), dysthymic disorder (n = 262) and major depression groups (n = 253) with the no depressive symptoms or depressive disorders group (n = 8005)*

<table>
<thead>
<tr>
<th>Health service use for:</th>
<th>One depressive symptom vs. no symptoms/disorders</th>
<th>Subsyndromal depressive symptoms (SSD) vs. no symptoms/disorders</th>
<th>Minor depressive vs. no symptoms/disorders</th>
<th>Dysthymic disorder vs. no symptoms/disorders</th>
<th>Major depression vs. no symptoms/disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental health problem</td>
<td>OR* (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Any OPD</td>
<td>1.6 (1.4–1.9)***</td>
<td>2.9 (2.3–3.7)***</td>
<td>4.5 (3.2–6.4)***</td>
<td>5.8 (4.4–7.6)***</td>
<td>9.5 (7.3–12.5)***</td>
</tr>
<tr>
<td>Medical OPD</td>
<td>1.8 (1.5–2.2)***</td>
<td>2.1 (1.6–2.8)***</td>
<td>3.9 (2.7–5.5)***</td>
<td>5.7 (4.4–7.6)***</td>
<td>13.3 (10.0–17.6)***</td>
</tr>
<tr>
<td>Psychiatric OPD</td>
<td>1.6 (1.3–1.9)***</td>
<td>3.0 (1.8–4.9)***</td>
<td>3.3 (1.6–6.9)***</td>
<td>7.7 (4.8–12.2)***</td>
<td>12.3 (8.3–18.4)***</td>
</tr>
<tr>
<td>ER use</td>
<td>2.1 (1.4–3.2)***</td>
<td>2.0 (1.2–3.4)***</td>
<td>3.8 (2.0–7.2)***</td>
<td>7.5 (4.9–11.5)***</td>
<td>15.4 (10.8–21.9)***</td>
</tr>
<tr>
<td>Psychiatric INPT</td>
<td>1.1 (0.8–1.6)***</td>
<td>1.2 (0.8–1.9)***</td>
<td>3.3 (2.0–5.7)***</td>
<td>2.2 (1.3–3.7)***</td>
<td>2.6 (1.7–4.2)***</td>
</tr>
<tr>
<td>Public assistance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Welfare benefits</td>
<td>1.1 (0.8–1.6)***</td>
<td>2.2 (1.5–3.1)***</td>
<td>3.4 (2.0–5.6)***</td>
<td>2.4 (1.5–3.8)***</td>
<td>3.1 (2.0–4.8)***</td>
</tr>
<tr>
<td>Disability benefits</td>
<td>1.4 (1.1–6.9)***</td>
<td>4.1 (3.1–5.4)***</td>
<td>5.8 (3.9–8.6)***</td>
<td>13.8 (10.3–18.3)***</td>
<td>27.3 (20.4–36.6)***</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>2.0 (1.6–2.5)***</td>
<td>3.4 (2.0–5.8)***</td>
<td>2.8 (1.2–6.4)***</td>
<td>12.1 (8.1–17.9)***</td>
<td>21.8 (15.3–31.2)***</td>
</tr>
</tbody>
</table>

*Numbers unweighted.
*Odds ratios adjusted for gender, age, race/ethnicity.
*95% confidence interval.
*P < 0.05; **P < 0.01; ***P < 0.001.

minor depressive disorder (exceptions welfare benefits and disability benefits), and in six of nine compared to dysthymic disorder groups (exceptions emergency room treatment, welfare benefits and disability benefits).

4.4. History of prior episodes of major depression in the depressive symptom and disorder diagnostic groups

Since the diagnostic groupings were derived from 1-month prevalence data at Wave 1, it provided the opportunity to compare the prevalence of previous episodes (lifetime) of major depression in the six diagnostic groups. Adjusted odds ratios for these prevalence comparisons are included in Table 4. The one depressive symptom group does not have a significantly elevated prevalence of prior major depressive episodes (3% lifetime prevalence) compared to the no depressive symptom or disorder group (2% lifetime prevalence). However, the subsyndromal depressive symptoms (5%), the minor depressive disorder (6%), the dysthymic disorder (30%) and the major depressive disorder (83%) groups all have significantly increased lifetime prevalences of prior major depressive episodes over that of the no depressive symptom or disorder respondents. When comparing the one depressive symptom group with the others, the SSD (P < 0.05), minor depressive disorder (P < 0.05), dysthymic disorder (P < 0.001) and the major depression (P < 0.001) groups have significantly higher prevalence of past major depressive episodes. In addition, the dysthymic disorder and the major depression groups have significantly higher lifetime prevalences of prior episodes compared to the SSD and minor depression groups. However, the major depression group has significantly higher prevalence of prior episodes over that of all the groups including the dysthymic disorder group (P < 0.01).

4.5. Changes in the depressive symptom and disorder diagnostic groups during a 1-year period of time

One of the unique features of the ECA experimental design is that identical DIS interviews were conducted 1 year apart (Waves 1 and 2). Approxi-
Table 4
Adjusted odds ratios comparing the prevalence of prior lifetime major depressive episodes in the one depressive symptom (n = 950)\(^a\), subsyndromal symptomatic depression (n = 440), minor depressive disorder (n = 164), dysthymic disorder (n = 262) and major depression groups (n = 253) with the group with no depressive symptoms or disorders (n = 8005)

<table>
<thead>
<tr>
<th></th>
<th>One depressive symptom vs. no symptoms/disorders</th>
<th>Subsyndromal depressive symptoms (SSD) vs. no symptoms/disorders</th>
<th>Minor depressive vs. no symptoms/disorders</th>
<th>Dysthymic disorder vs. no symptoms/disorders</th>
<th>Major depression vs. no symptoms/disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior lifetime episode of major depression</td>
<td>OR(^b) (95% CI)(^c)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>1.3 (0.8–1.9)</td>
<td>2.8 (1.7–4.5)***</td>
<td>2.9 (1.4–5.9)**</td>
<td>18.4 (13.3–25.5)***</td>
<td>274 (185–405)***</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Numbers weighted.  
\(^b\) Odds ratios adjusted for gender, age, race/ethnicity.  
\(^c\)95% confidence interval.  
\(*P < 0.05; **P < 0.01; ***P < 0.001.

Twenty-two percent of the respondents who began the year with no depressive symptoms or disorders during the year between Wave 1 and Wave 2 had developed depressive symptoms or disorders. Forty-four percent of the one depressive symptom respondents had either continued with one symptom (24%) or qualified for inclusion in the other depressive categories.

Of the 350 respondents in the SSD group at Wave 1, 48% became asymptomatic during the next year, but 16% (n = 56) now met criteria for minor depression (10%), dysthymia (2%) or major depression (4%). However, 17% continued with SSD and 19%

Table 5
Prevalence (%) of depressive symptoms and disorders based upon 1-month prevalence data from the Wave 1 DIS interview compared with the 1-year incidence\(^e\) of depressive symptoms and disorders in the same respondents obtained 1 year later at the Wave 2 DIS interview: from 7863 of the 10,526 respondents originally interviewed at Wave 1

<table>
<thead>
<tr>
<th>Wave 2 diagnostic groups (1-year incidence)(^*)</th>
<th>Wave 1 diagnostic groups (1-month prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No depressive symptom or disorder (n = 6238)(^f, % \quad \text{(S.E.)})</td>
<td>One depressive symptom (n = 763), % (S.E.)</td>
</tr>
<tr>
<td>One depressive symptom</td>
<td>12 (0.5)</td>
</tr>
<tr>
<td>Subsyndromal symptomatic depression</td>
<td>5 (0.4)</td>
</tr>
<tr>
<td>Minor depressive disorder</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Major depression</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
</tr>
</tbody>
</table>

\(^*\)Incidence is defined as onset or continuation of depressive symptoms and depressive disorders during the one year period (Wave 1 and Wave 2 DIS interview).  
\(^\text{f}\)Numbers are unweighted.  
\(^\text{e}\)Percentages are adjusted to correct for sampling bias.
dropped sufficient symptoms to move into the one depressive symptom category (Table 5).

In Table 5, of those who started the year with minor depression only 28% no longer had depressive symptoms or disorders at the end of 1 year, 22% decreased symptoms to subsyndromal depressive symptoms (SSD) and 17% remained in the minor depression category. Five percent of the minor depressives increased symptoms and now met criteria at Wave 2 for either major depression or dysthymia, respectively. Consistent with the severe chronicity that is characteristic of dysthymic disorder, all 198 respondents who began the year (Wave 1) in the dysthymia category, either continued dysthymic or had developed a major depressive episode at Wave 2.

Eighty-six percent of the respondents with major depression at Wave 1 continued to be symptomatic 1 year later. However, only 28% continued to meet criteria for major depression, whereas, at the Wave 2 interview 23% had moved into the dysthymic disorder category, 15% were diagnosed as minor depression, and 13% decreased symptoms to SSD or to one depressive symptom (7%).

5. Discussion

The methodological strengths and weaknesses of the ECA database to answer clinical questions have been discussed elsewhere (Judd et al., 1994). The diagnoses reported here are based upon DSM-III categories and symptom criteria and, even though some of the diagnostic categories in DSM-III have undergone substantial revision over the years, the definitions of depressive symptoms and the depressive disorder diagnoses described here are largely unchanged. The one exception is minor depressive disorder which has recently been included in Appendix B of the DSM-IV. However, the manner in which depressive symptom data are recorded at the three ECA sites used in these analyses, allowed us to develop diagnoses for minor depressive disorder (DSM-IV).

Another caveat is that two of the five depression categories were based upon the presence of a single or two or more depressive symptoms; beneath the diagnostic threshold of minor depressive, dysthymic or major depressive disorders. The validity of creating ‘diagnostic’ groupings based upon a single or a few depressive symptoms will raise some questions. We agree; however, we were interested in determining if a few current depressive symptoms were clinically significant and related to adverse outcome. Further, the threshold specified by the DIS to determine whether a depressive symptom qualifies as a symptom to be used in developing a DSM-III diagnoses is standardized, rigorous and substantial. Specifically, in order for a depressive symptom to be recorded, it has to be 2 weeks in duration, present every day for most or all of the time, and of sufficient magnitude that the respondent had sought help or taken a medication because of it or the symptom has interfered significantly in their daily activities. With depressive symptoms defined in this way, it is not unreasonable to anticipate that the presence of even one current depressive symptom may be clinically ‘significant’ and associated with some psychosocial dysfunction or risk.

Another issue of concern is the ubiquitous nature of depressive symptoms, which can be observed to co-occur frequently with many medical illnesses, mental and substance use disorders. Several procedures were used to eliminate the possible influence of comorbid conditions. First, the DIS interview requires the elimination of any depressive symptoms associated with a current medical illness or with alcohol or drug use or problems. Second, respondents endorsing depressive symptoms (n = 443) with any current (1-month) comorbid mental disorder or substance use disorder were removed from the analyses.

5.1. Point prevalence (1-month) of depressive symptoms and depressive disorders in the community

The 1-month point prevalence at Wave 1 of depressive symptoms and depressive disorders in 10,526 representative adult community respondents is 22.6%. One-third (6.1%) is accounted for by recognized formal diagnostic categories of minor depressive disorder (1.9%), dysthymic disorder (2.3%) and major depression (2.3%). Two-thirds, or 12.6%, are made up of community respondents endorsing one (8.7%) or two or more non-comorbid
subsyndromal depressive symptoms (SSD; 3.9%). Total community respondents in the two subthreshold depressive symptom categories are twice the prevalence of the syndromal diagnoses of depression.

5.2. Health service use and adverse outcome associated with depressive symptoms and depressive disorders

These analyses confirm previous reports identifying significant increases in health service use and psychosocial impairment associated with subsyndromal depressive symptoms and syndromal depressive disorders (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992; Judd et al., 1994, 1996). We also found, as have others, that the associated impairment increases incrementally with increasing severity of the depressive symptoms and disorders. In comparison to no depressive symptoms, respondents in the one depressive symptom category reported the lowest, but still significantly increased, prevalence of lifetime service use, need for public assistance and suicidal ideation and attempts. It was surprising and sobering that the even one current non-comorbid symptom of depression, compared to no depressive symptoms, was associated with significantly more adverse outcome in seven of nine variables.

The SSD group, compared to the one symptom group, had a significantly increased lifetime prevalence of outpatient treatment and need for disability benefits. In other words, even though respondents with one symptom reported significant increases in impairment over those with no depressive symptoms, there is a significant incremental increase in impairment associated with SSD. This indicates that subsyndromal depressive symptoms (SSD), as we define it (Judd, 1994; Judd et al., 1994), more broadly meet criteria for 'harmful dysfunction' (Wakefield, 1992), criteria which have been proposed to determine when a clinical condition qualifies for 'disorder' status. These data, together with the other reports in the literature (Wells et al., 1989; Broadhead et al., 1990; Johnson et al., 1992; Judd et al., 1994, 1996; Spitzer et al., 1995) provide consistent strong support for the conclusion that a 'disorder' level impairment and service use is associated with SSD. It appears that SSD may be the lowest depressive symptom threshold which should be considered to be clinically significant during the course of unipolar depression.

Consistent with other reports, respondents with major depression are the most severely and pervasively impaired, having significantly higher prevalences of lifetime service use, need for public assistance, suicide ideation and suicide attempts in eight of nine outcome measures compared to SSD, for seven of nine compared to minor depression subjects, and six of nine compared to dysthymic disorder respondents.

5.3. The relationship of current depressive symptoms and depressive disorders to previous major depressive episodes

The SSD, minor depressive, dysthymic and major depression groups each had significantly higher prevalence of prior (lifetime) major depressive episodes when compared to the no symptom or disorder or the one depressive symptom groups. The significant relationship between SSD and past episodes of major depression confirm the observations reported by Sherbourne et al. (1994) in Medical Outcome Study patients, in which 17% of the subsyndromal depressives and 55% of the depressive disorder patients reported at least two depressive episodes in the preceding year. This also supports the conclusion there is a relationship between subsyndromal depressive symptoms (SSD) and both past and future major depressive episodes, the latter as reported by Broadhead et al. (1990) and Howarth et al. (1992). We interpret this to mean SSD is a relatively common inter-episode manifestation of unipolar major depression. In addition, 30% of dysthymic disorder respondents had past major depressive episodes supporting the observations of Keller et al. (1983) and Regier et al. (1994) that a very close and clinically significant relationship exists between dysthymia and episodes of major depression. It is also very revealing that 83% of the 253 respondents with major depression at Wave 1 also had histories of at least one prior major depressive episode. Indirectly, this confirms the very high episode recurrence rates reported by Keller et al. (1982), (1984) and Angst (1986) in prospective longitudinal follow-up studies of unipolar major depression patients.
5.4. Change in depressive symptoms and depressive disorders during 1-year follow-up

Even though we were aware that depressive symptom severity levels and depressive disorder diagnoses clinically change over time, we were not prepared for the enormous amount of flux and change observed in these respondents during only 1 year of follow-up (Table 5). These analyses indicate a very dynamic, constantly changing clinical course for individuals with unipolar depression. Obviously, some of this change, such as the reduction in symptom severity, has been related to treatment, but, at best, only about one-half of the ECA respondents with major depression were receiving some type of treatment according to Regier et al. (1994). Therefore, we believe that this dynamic pattern of change in the levels of depressive symptoms in disorder diagnoses across time, largely reflects the true natural course of individuals with unipolar depression.

It is interesting to note 22% of the respondents who began the year with no depressive symptoms or disorders, during the next year at Wave 2, had developed depressive symptoms and disorders, a prevalence rate similar to that originally observed in the full sample at Wave 1. This indicates there may be a relatively stable dynamic equilibrium in the community in the point prevalence of depressive symptoms and disorders. We believe that this is created by individuals continually moving in and out of the symptomatic or asymptomatic status, with relatively the same numbers in the population, at any one point in time, manifesting depressive symptoms and disorders. For example, 56% of the one depressive symptom, 43% of the SSD group, 28% of the minor depressive disorder and 14% of the major depression groups were no longer symptomatic at Wave 2. Reciprocally, 22% of the no symptom and disorder group manifested new symptoms and disorders, 44% of the one symptom, 53% of the SSD, 72% of the minor depression and 100% of the dysthymic disorder, and 83% of the major depression groups continued with depressive symptoms or disorders 1 year later. This is also an indirect, but powerful confirmation of the intensely chronic and tenacious nature of depressive disorders and symptoms.

A remarkable percentage in each of the depressive symptom and disorder groups, who began the year in one of the five possible diagnostic categories, ended the year in another category. For example, of the 201 (Wave 2) people beginning the year with a diagnosis of major depression, who were interviewed at Wave 2, only 28% continued with a major depression diagnoses and 23% moved into the dysthymic disorder category, these latter respondents, we believe, are persons with double depression who have resolved their major depressive episodes and returned to their chronic dysthmic disorder. Approximately 15% of major depressives dropped symptoms, now meeting criteria for minor depressive disorder at Wave 2, and the symptom severity level of 20% of the original major depressives at Wave 1 decreased to that of one or more subsyndromal depressive symptoms ‘residual’ to their episodes. The same type of pattern was present with all of the other diagnostic groups, in which subjects with one diagnosis at Wave 1 moved during the next year (Wave 2) into other diagnostic groupings. It is very clear from these data, even though the follow-up time is relatively brief (1 year), that persons with subsyndromal or syndromal unipolar mood disorders frequently change diagnoses across time. Although it must be empirically tested in unipolar patient populations, we believe that this pattern reflects the true typical clinical course of patients with unipolar disorders. We hypothesize the course of unipolar depression is more pleomorphic than previously thought, and is characterized by the continual upward and downward fluctuation of depressive symptom severity levels in which patients move in a constant fashion between the various depressive disorder diagnoses or subtypes which have been identified in unipolar depression.

5.5. Subsyndromal depressive symptoms (SSD) prodromal or residual to episodes of minor or major depressive disorder

Their appears to be a qualitative difference between SSD observed in community respondents during the course of illness in unipolar major depression and SSD which spontaneously occurs in non-unipolar depressed, which seems to disappear over time (see Table 5). In some respondents, SSD appears to be an inter-episode condition of unipolar depression, in which subsyndromal symptoms are
either prodromal or residual to episodes of major or minor depression. This means that a substantial portion, but not all, of SSD identified in community respondents is a symptomatic component of unipolar depressive disorders. The question remains is SSD a condition that is merely correlated with major or minor depressive episodes, or is it an actual continuous subthreshold extension of major or minor depressive episodes? We strongly favor the latter hypothesis for several reasons. First, the findings of Sherbourne et al. (1994) that patients with subsyndromal or major depression share common demographic and clinical attributes. Second, Kendler et al. (1992), in genetic epidemiological studies, has reported that a broader definition of the depressive phenotype, which include milder or minor forms of depression, as compared to narrow definitions (e.g., melancholia) provided significantly better support for the genetic models applied. Third, Akiskal et al. (1980) has reported that neurophysiological sleep EEG markers (short REM latency, etc.) are shared in common, by acute major depressive, dysthymic and subsyndromal depression patients. Fourth, based on these analyses, it is clear that SSD qualifies for a ‘disorder’ status by meeting the harmful dysfunction criteria used to determine when a condition becomes a disorder. In the aggregate, all this supports the conclusion that subsyndromal depressive symptoms (SSD) and syndromal unipolar depressive episodes share the same underlying biological and clinical substrates and are different facets or manifestations of the same unipolar disease process.

Finally, based upon the high prevalence of SSD reported in epidemiological and clinical samples, we contend that SSD, is a common, inter-episode condition in unipolar major depression, which may prove to be a risk factor for future major and minor depressive episodes, as well as potentially important, but largely ignored, targets for treatment. However, this proposition must be tested in controlled investigations in clinical samples of patients with unipolar major depressive disorders.

6. Summary

1. The 1-month point prevalence of depressive symptoms or disorders is 22.6% in this large sample of adult community respondents (n = 10 526). This prevalence level was stable between the Wave 1 and Wave 2 (1 year later) DIS interviews, possibly due to the fact that there appears to be a dynamic equilibrium in the general population, in which, across time, substantial numbers of persons develop depressive symptoms or disorders, while others drop symptoms and become asymptomatic.

2. Subsyndromal depressive symptoms (SSD) are a prevalent clinically significant depressive condition in community residents with a 1-month point prevalence of 3.9% compared to major depression at 2.3%, dysthymia at 2.3% and minor depression at 1.9%.

3. Compared to no depressive symptoms, SSD are not benign, and meet criteria for harmful dysfunction by being associated with significant increases in lifetime service use for mental health problems, lifetime welfare and disability benefits and lifetime suicidal ideation and suicide attempts.

4. A notable percentage of SSD respondents in the general population experience depressive symptoms as an aspect of the clinical course of unipolar major depression, in which some respondents experience SSD prodromal to the onset of a major or minor depressive episode, and in others the symptoms are residual to resolving episodes. This is consistent with the observation that SSD is associated with increased prevalence of past major depressive episodes and is a risk factor for future ones as well.

5. Not all subsyndromal depressive symptoms in the community exist as a component of unipolar depression, since one-half of SSD respondents became asymptomatic during the next year, indicating there may be qualitative differences between SSD observed in the course of unipolar disorders and SSD occurring spontaneously in community respondents.

6. Evidence from this and other studies (Akiskal et al., 1980; Kendler et al., 1992; Sherbourne et al., 1994) suggests that SSD observed during the course of unipolar disorder is a clinically significant inter-episode condition of unipolar major depression. Based on its prevalence in the community, we hypothesize SSD will be observed frequently during the inter-episode course of
unipolar major depression—a hypothesis which must be tested in unipolar major depression patients.

7. Comparison of the depressive symptom and disorder diagnoses at Wave 1 with diagnoses 1 year later at Wave 2, revealed a substantial amount of change and flux in diagnostic categories during the brief follow-up window (1 year) between the two interview waves. As a result, we hypothesize that the typical course of unipolar major depression is very dynamic and characterized by substantial fluidity and change of depressive symptom levels, subtypes and depressive disorder diagnoses over time. This hypothesis will also require confirmation in systematic investigations of patients with unipolar major depressive disorders.

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References


Discussion of “The role and clinical significance of subsyndromal depression symptoms”: Discussion led by Jean Endicott, Ph.D., from Columbia University

When approaching diagnosis, the world is divided into splitters vs. lumpers. By nature, I am more of a ‘splitter’ than a ‘lumper’. However, I question whether subsyndromal depressive symptoms (without depressed mood) is the same illness as unipolar MDD, even though it was associated with psychosocial impairment and risk for relapse. I question who among those with subsyndromal symptoms (two symptoms) will develop major depressive disorder (i.e., are these legitimate risk factors?) Are those individuals at risk those with a past history of depression? Perhaps those patients who are partially remitted are at increased risk for future episodes, and, therefore, our efforts should be directed towards rendering them symptom free. In patients who never become symptom free, does this outcome affect the recurrence and the progress of their illness? Are those patients who have residual symptoms different from those without such symptoms (e.g., biologically or genetically)?

The research issues needing to be addressed include the following: (1) If symptoms are decreased, does this interrupt the current course of the illness or does the course occur anyway? (2) What interventions render a patient symptom free most effectively? Is it psychopharmacology interventions or psychotherapeutic interventions or the combination of both? (3) Do residual symptoms differentiate different subtypes of the illness as manifested in long-term follow-up? (4) What implications are there for treating the first episode? Does this necessitate continued prophylactic treatment? (5) Among subjects who have never met criteria for MDD, who is at risk for the occurrence of MDD? (6) Will early intervention avoid the onset of MDD?

I feel that it is going to be a ‘hard sell’ to convince the field that aggressively treating residual subsyndromal symptoms at the first episode is an optimal or valid treatment approach. This approach would be problematic to patients, third-party payers, researchers, and drug companies who focus on the placebo response rate. For bipolar illness, prophylactic treatment initiated at the first episode seems reasonable, but can we argue the same for unipolar illness and interepisode subsyndromal depression?

General discussion

Dr. Clayton discussed the problem of distinguishing patient from control data. Thirty-five percent of a normal volunteer population reports insomnia. Is this a subsyndromal symptom or is this actually part of the normal variation? Dr. Hirschfield likewise pointed to questions of purity of the sample. Dr. Fawcett pointed to anxiety and worry symptoms (the same, not different symptoms, in his view) as risk factors for suicide prediction that should be part of the diagnosis but are not. Dr. Frances pointed to the importance of longitudinal studies looking at the course of the episode over time and the effects of treatment. Dr. Paykel questioned whether aches and pains were not a part of every day life and of normality and asked ‘what is a case’ and ‘what is a symptom?’ Dr. Rush pointed out that in their studies if they removed comorbidity of patients with depression not otherwise specified (DNOS), 40% of patients still remained with diagnoses of DNOS. Dr. Paykel re-emphasized that fatigue was the most common symptom in the general medical office, and that in the Manhattan study many individuals were just unhappy. The other point raised by Dr. Frances was that we need to focus on who to treat, and what is a medical necessity, not just on symptoms, in the managed care worked and to differentiate diagnosis in terms of false positives and negatives.

Dr. Quitkin showed data illustrating that in patients who do not respond to placebo in chronic vs. non-chronic depressive conditions, 22 patients who had chronic depression did not respond to placebo, whereas there were only two placebo responders (Hamilton ≤ 10); in non-chronic depressions, only
one patient was a non-responder to placebo and four were responders to placebo. He concluded that the chronic conditions are worth treatment. He felt the distinction between double depression vs. dysthymia was artificial, and that we need to be concerned about the implications for unipolar depression. Many people may be unhappy, and this phenomenon may exacerbate the course of unipolar depression. Alternatively, subsyndromal depression may have its own course and exist independently.

Dr. Winokur made the point that, in his collaborative study of depression amongst probands and normal controls, there was a subset of 30–35% with major depressive disorder signifying a large number of depressive. At 5–10 years follow-up, their relatives were sicker than the comparison group. Dr. Fawcett re-emphasized that the severity of symptoms needs to be documented vs. the number of symptoms. Dr. Judd emphasized that fatigue and insomnia were the most common depressive symptoms in the general population. Dr. Gillin pointed out that the interpretation of sleep difficulties was difficult in the ECA studies with regard to insomnia and hypersomnia with the problem of partialing out the differential effects of anxiety, other medical disorders and substance abuse. Dr. Frances emphasized that relapse in major depressive disorders may mean incomplete remission of an MDE or an interviewing a minor depression. Dr. Blazer warned of the danger of going from community studies to clinical populations, and Dr. Glassman questioned whether we were under-treating patients by ignoring subsyndromal depression. Dr. Clayton discussed chronic depression in light of bereavement which will be addressed in a separate discussion section. Dr. Rush pointed out that DNOS may be distinct from subsyndromal depressive symptoms or residual symptoms after a major depressive episode (MDE), in terms of risk factors for recurrence, since individuals with residual subsyndromal symptoms were at high risk for recurrence. Dr. Angst pointed out that neuroticism was a poor predictor of future course and Dr. Bunney pointed out that non-specific subsyndromal symptoms of insomnia and fatigue at Wave 1 in the ECA database predicted onset of an MDE 1 year later (Wave 2), which may indicate that specific depressive symptoms are qualitatively different as risk factors for future episodes.