ORIGINAL ARTICLE

Psychosocial Disability During the Long-term Course of Unipolar Major Depressive Disorder

Lewis L. Judd, MD; Hagop S. Akiskal, MD; Pamela J. Zeller, PhD; Martin Paulus, MD; Andrew C. Leon, PhD; Jack D. Maser, PhD; Jean Endicott, PhD; William Coryell, MD; Jelena L. Kunovac, MD; Timothy I. Mueller, MD; John P. Rice, PhD; Martin B. Keller, MD

Background: The goal of this study was to investigate psychosocial disability in relation to depressive symptom severity during the long-term course of unipolar major depressive disorder (MDD).

Methods: Monthly ratings of impairment in major life functions and social relationships were obtained during an average of 10 years' systematic follow-up of 371 patients with unipolar MDD in the National Institute of Mental Health Collaborative Depression Study. Random regression models were used to examine variations in psychosocial functioning associated with 3 levels of depressive symptom severity and the asymptomatic status.

Results: A progressive gradient of psychosocial impairment was associated with a parallel gradient in the level of depressive symptom severity, which ranges from asymptomatic to subthreshold depressive symptoms to symptoms at the minor depression/dysthymia level to symptoms at the MDD level. Significant increases in disability occurred with each stepwise increment in depressive symptom severity.

Conclusions: During the long-term course, disability is pervasive and chronic but disappears when patients become asymptomatic. Depressive symptoms at levels of subthreshold depressive symptoms, minor depression/dysthymia, and MDD represent a continuum of depressive symptom severity in unipolar MDD, each level of which is associated with a significant stepwise increment in psychosocial disability.

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From the National Institute of Mental Health Collaborative Program on the Psychobiology of Depression, Rockville, Md (Drs Judd, Akiskal, Leon, Maser, Endicott, Coryell, Mueller, Rice, and Keller); Department of Psychiatry, University of California–San Diego (Drs Judd, Akiskal, Zeller, Paulus, and Kunovac); and the Psychiatry Service, San Diego Veterans Affairs Medical Center (Drs Akiskal, Paulus, and Kunovac).

RECENT STUDIES indicate that unipolar major depressive disorder (MDD) is associated with significant psychosocial disability, often exceeding that noted in common medical illnesses.[1-9] A definitive monograph in 1996 by the World Health Organization identified unipolar MDD as the fourth-ranked cause of disability-adjusted life-years and premature death worldwide.[10]

Part of the reason unipolar MDD is responsible for so much global disability is that it is a very common disorder, with nearly 1 in 5 people in the general population suffering a lifetime major depressive episode (MDE).[11] In addition, the clinical course typically is very chronic in that MDEs relapse and recur very frequently[12-18] and depressive symptoms are present approximately 60% of the time during long-term follow-up.[19,20] Thus, a large number of individuals in the general population are likely to experience significant chronic disability from unipolar MDD.

Most of what is established about psychosocial disability in unipolar MDD has been derived from between-groups comparisons based on cross-sectional epidemiological or short-term treatment studies. We know of no investigation to date that has characterized disability in the same patients with unipolar MDD during the long-term course of their illness. The National Institute of Mental Health Collaborative Depression Study (CDS)[21,22] provides a unique resource for investigating impairment over time, since patients were studied prospectively, longitudinally, and naturalistically for many years after entering the study during an MDE.

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The design of the CDS allows psychosocial disability to be investigated in the same patient while at different levels of depressive symptom severity and provides the basis to test 3 important hypotheses about psychosocial impairment during the long-term course of unipolar MDD: (1) disability associated with unipolar MDD is pervasive, affecting most areas of everyday function; (2) disability associated with unipolar MDD varies directly as a function of depressive symptom severity; (3) disability associated with unipo-

SUBJECTS AND METHODS

SUBJECTS

The analysis sample consisted of 371 patients with unipolar MDD who entered the CDS[21,22] during an MDE at 1 of 5 tertiary care centers from 1978 to 1981 and were followed up longitudinally for more than 2 years. Patients were diagnosed using Research Diagnostic Criteria (RDC)[23] based on the Schedule for Affective Disorders and Schizophrenia (SADS)[24] interviews. Only patients with no evidence of bipolar disorder (mania, hypomania, cyclothymic personality), schizoaffective disorder, or schizophrenia as of intake or at any time during follow-up were included in this investigation. Subjects were white, spoke English, had an IQ score of at least 70, and had no evidence of organic mental disorder or terminal medical illness. Informed consent was obtained. Intake demographic and clinical characteristics of the 371 patients with unipolar MDD are presented in **Table 1**.

WEEKLY DEPRESSIVE SYMPTOM RATINGS

Trained professional raters interviewed patients every 6 months for the first 5 years and yearly thereafter, using variations of the Longitudinal Interval Follow-up Evaluation (LIFE).[25] Patient interviews were the primary information source of the LIFE, with chronological memory prompts used to obtain information on changes in weekly symptom severity for MDD and other psychiatric disorders. Level of depressive symptomatology was rated weekly using a 6-point Psychiatric Status Rating Scale (PSR-MDD) for MDEs and a 3-point scale (PSR-MinD) for episodes of minor depression or dysthymia, as described in detail elsewhere.[19,25] The CDS raters undergo rigorous training, resulting in high interrater reliability for the weekly psychiatric status (intraclass correlation coefficients ≥0.90).[25] Of the 5776 available LIFE forms, 2% were omitted because interviewers judged the information obtained to be of "poor" or "very poor" accuracy. Remaining follow-up data for the analysis sample of 371 CDS patients with unipolar MDD covered an average of 518.5 weeks or 10 years per subject (SD = 156.2 weeks), with a median of 624.0 weeks or 12.0 years.

DEPRESSIVE SYMPTOM SEVERITY LEVELS

Weekly depressive symptom severity levels were derived by combining all depression-related Psychiatric Status Rating Scale scores as described in a previous publication.[18] Each week was assigned to 1 of 4 mutually exclusive depressive symptom severity levels anchored to the diagnostic threshold for commonly observed levels of depression or the asymptomatic status. These constitute a continuum of severity: level 4 (most severe), at the threshold for MDD; level 3 (moderately severe), at the threshold for minor depressive or dysthymic disorders (MinD); level 2 (mildly severe), below the diagnostic threshold for MinD or MDD and thus representing subthreshold depressive symptoms; and level 1 (least severe), representing complete absence of depressive symptoms and return to the asymptomatic, usual self.

PSYCHOSOCIAL IMPAIRMENT RATINGS

Using the LIFE forms,[25] the patient's "worst level of psychosocial functioning per month," reflecting impairment due only to the patient's depressive symptomatology, was rated by trained interviewers in 9 specific functional domains. The key dependent measures examined in this article are global rating of overall psychosocial functioning and 2 individual domains of major life functions: work/employment and relationship with spouse/partner. These

lar MDD is state dependent—when any level of depressive symptomatology is present disability is present, and when the same patients are asymptomatic, disability decreases and psychosocial function becomes good.

RESULTS

The measures of psychosocial functioning investigated in this study showed increasing impairment as patients' levels of depressive symptomatology increased during long-term follow-up (see means and SDs in Table 3 and the Figure, derived from mixed regression analyses adjusting for within-subject variation across multiple ratings). Progressive increments in depressive symptom severity (asymptomatic to subthreshold, subthreshold to MinD, and MinD to MDD), were associated with significant parallel increases ($P<.001$ level) in psychosocial disability.

Average ratings for work/employment functions showed "no impairment, satisfactory to high performance" during months when patients with unipolar MDD were asymptomatic. When the same patients experienced subthreshold symptoms, mean employment impairment ratings rose 1 full-scale value to a point midway between "satisfactory" and "mild impairment." From the subthreshold to MinD level there was an 0.9 increment in work impairment (to a mean of 3.5), so that work ratings on average approached the "severe impairment" range (mean = 4.7) when the subjects were experiencing MDD-level symptoms.

Relationships with spouse/partner were also significantly associated with changes in depressive symptom severity. Mean ratings were "good" when patients were asymptomatic, then worsened to somewhat less than "good" when patients had subthreshold symptoms, "fair" during months when they were at the MinD level, and between "fair" and "poor" during months when the same patients had MDD-level symptoms.

Global ratings of overall psychosocial functioning showed a linear pattern of 0.7 or 0.8 increases in impairment with each increment in depressive symptom severity (Figure). Average global functioning ratings were "good" when these patients were asymptomatic, were close to "fair" at the subthreshold level, approached "poor" at the MinD level, and were between "poor" and "very poor" at the MDD level.

Another way to express the relationship between depressive symptom severity level and psychosocial functioning is to examine the distribution of global overall functioning at the 4 different symptom levels. During the 4887 person-months when these patients were asymp-

were selected because of their modest correlation with each other (0.34) and their strong correlation with the global functioning rating (0.69 and 0.52, respectively). These 2 measures represent everyday life functioning within the home (relationship with spouse/partner) and outside the home (work/employment) in domains of function that can be expected to be central to patients' overall well-being.

Ratings of psychosocial function were made on 1 of 2 ordinal Likert scales. Scoring on scale A ranges from 1 (no impairment, high-level function) to 6 (did not do this activity at all owing to depressive psychopathology). On scale B scores range from 1 (very good) to 5 (very poor). Psychosocial ratings during the first 2 years were based on entire 6-month evaluation periods; because it was seldom possible to associate these with one and only one depressive symptom level, these data were not analyzed. Monthly ratings of psychosocial impairment used for these analyses were obtained for each month during follow-up years 3 to 5 and the last month only of follow-up years 6 to 12.

For simplicity and accuracy in examining the relationship to depressive symptom severity levels, psychosocial ratings were included in the analyses only for those months when a patient was at 1 of the 3 depressive symptom levels or the asymptomatic status during all weeks of the month in question. **Table 2** shows the distribution of subjects with each combination of symptom severity levels. These contribute varying numbers of subjects and person-months to the random regression statistics for the 3 psychosocial function measures, as indicated in **Table 3** and the **Figure**.

STATISTICAL ANALYSES

The SAS software[26] was used to create monthly levels of severity and functioning and to describe the overall patient sample. Random (mixed) regression analysis was then used to model the relationship between each impairment rating (dependent variable) and the 4 levels of depressive symptom severity (independent variable) using the MIXREG software of Hedeker and Gibbons.[27] Mean impairment ratings were obtained per depressive symptom level, adjusting for within-subject variation. Because multiple ratings of impairment for each subject are assumed to be correlated, an intraclass correlation coefficient was used in calculating SDs. The random regression models included a random intercept term to account for correlated observations within subjects over time, and dummy variables to represent levels of symptom severity.[28,29]

Because impairment ratings are not normally distributed, the significance of contrasts between levels (2 tailed) was tested by means of random-effects ordinal regression analyses using the MIXOR program,[30] parameterized to test the significance of the contrast between subthreshold depression and each of the other symptom severity levels.

From more than 3000 relatives and controls interviewed within the CDS, 1817 were selected who had no current diagnosis of any RDC psychiatric or substance abuse disorder as of their 6-year follow-up, at which time they were evaluated for psychosocial functioning in the prior month. These ratings provide an opportunity to see whether patients with unipolar MDD return to "normal" levels of functioning when they are asymptomatic. The Wilcoxon rank sum test was used to compare the single-month impairment rating for each subject in the "currently well" (control) group with the patients with unipolar MDD when asymptomatic, using 1 randomly selected month for patients with multiple evaluations at the asymptomatic level, or the single asymptomatic rating for patients with only 1 month at that level.

An α level of .05 (2 tailed) was used to assess the significance of all statistical tests.

tomatic, the great majority of global ratings (79.3%) fell in the very good or good range; during 1699 person-months when the patients were at the subthreshold level, 85.0% of ratings were good or fair; during 2404 person-months at the MinD level, 86.0% were fair or poor; and during 964 person-months at the MDD level, 87.1% of global functioning ratings were poor or very poor.

Patients with unipolar MDD were slightly more impaired during months when they were asymptomatic than the control group with no current RDC diagnosis (Table 3). In the large samples used for this study, even mean differences of 0.1 or 0.2 points on the 5- or 6-point rating scales were significant at the $P<.001$ level. Monthly global functioning ratings for currently well controls fell more in the very good and good range (93.6%) than those from the patients with unipolar MDD during months when they were asymptomatic (79.3%). The mean global rating for nondepressed controls was 1.8 (SD = 0.6) (good), compared with 2.0 (SD = 0.8) (good) for patients with unipolar MDD when asymptomatic (Wilcoxon rank sum test, $P<.001$).

COMMENT

To our knowledge, this is the first study to examine the degree of psychosocial disability in the same patients while they were experiencing 3 different levels of depressive symptom severity (subthreshold, MinD, and MDD) and the asymptomatic status during the long-term course of unipolar MDD. Using structured interview data, we have examined functional disability related to work/employment, relationship with spouse/partner, and global overall psychosocial function during an average of 10 years of systematic follow-up. The results confirmed the following hypotheses: (1) psychosocial disability associated with unipolar MDD is pervasive and chronic, affecting most areas of everyday function; (2) disability varies directly with the level of depressive symptom severity during the course of illness; and (3) disability is state dependent—when depressive symptoms are present, disability is present; when the same patients are asymptomatic, disability decreases significantly and psychosocial function is good or very good. We also confirmed findings we reported previously[6,8,9] that even a few depressive symptoms (subthreshold), below the diagnostic threshold for MinD, dysthymia, or MDD, are associated with a small but significant increase in psychosocial disability compared with months when the same patients are asymptomatic.

Major domains of life functioning show differences in their overall association with levels of depressive symptom severity and in the depressive symptom severity level

at which significant increases in impairment appear. For example, depressive symptoms at even the lowest level (subthreshold) seem to have an effect on work/employment function, whereas the subthreshold effect on relationship with spouse/partner, although significant, is much smaller.

While specific domains of function differ in their patterns of associations with depressive symptom severity, the global rating of overall psychosocial functioning shows a remarkable linear relationship to changes in depres-

Table 1. Demographic and Clinical Characteristics of 371 Patients With Unipolar Major Depressive Disorder*

Sex	
M	138 (37.2)
F	233 (62.8)
Mean (SD) [range] age at intake, y	39.8 (14.7) [17-79]
Marital status†	
Married/living together	193 (52.3)
Separated/divorced/widowed	71 (19.2)
Never married	105 (28.5)
Education completed†	
High school or less	177 (48.0)
College or more	192 (52.0)
Mean (SD) [range] age at onset of first lifetime depressive episode, y	28.9 (14.0) [5-72]
Inpatient status at intake	274 (73.9)
Median (range) No. of lifetime depressive episodes	2 (1-107)
Mean (SD) [range] global assessment of severity at intake	38.6 (10.7) [5-65]

*Data are presented as number (percentage) unless otherwise indicated.
†Two subjects had missing data.

Table 2. Monthly Psychosocial Impairment Ratings by Levels of Depressive Symptom Severity in 371 Patients With Unipolar Major Depressive Disorder*

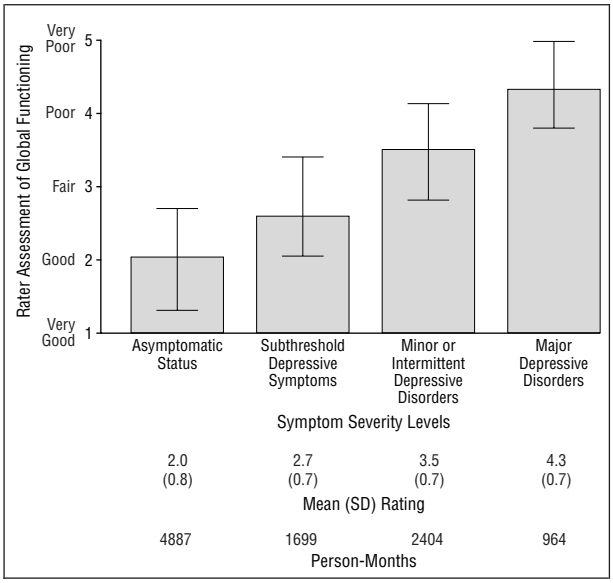
Depressive Symptom Severity Levels	No. (%)
All 4 levels	
Asymptomatic, subthreshold, MinD, MDD	64 (17.3)
3 Levels	123 (33.2)
Asymptomatic, subthreshold, MinD	54 (14.6)
Asymptomatic, subthreshold, MDD	5 (1.3)
Asymptomatic, MinD, MDD	29 (7.8)
Subthreshold, MinD, MDD	35 (9.4)
2 Levels	107 (28.8)
Asymptomatic, subthreshold	22 (5.9)
Asymptomatic, MinD	25 (6.7)
Asymptomatic, MDD	9 (2.4)
Subthreshold, MinD	20 (5.4)
Subthreshold, MDD	2 (0.5)
MinD, MDD	29 (7.8)
1 Level	77 (20.8)
Asymptomatic	65 (17.5)
Subthreshold	4 (1.1)
MinD	4 (1.1)
MDD	4 (1.1)
Incremental levels†	
Asymptomatic and subthreshold	145 (39.1)
Subthreshold and MinD	173 (46.6)
MinD and MDD	157 (42.3)

*MinD indicates the threshold for minor depressive or dysthymic disorders; MDD, major depressive disorder. Psychosocial ratings were obtained using the Longitudinal Interval Follow-up Evaluation II (LIFE-II) or Catch-Up Form (CUF) variants of that instrument for all months in years 3 to 5 follow-up, and using the Streamlined Longitudinal Interval Continuation Evaluation (SLICE) for the last month (only) of years 6 to 12. Ratings are analyzed only for months when patients with unipolar MDD were entirely at 1 of 4 depressive symptom severity levels, defined by weekly Psychiatric Status Rating.
†These subjects may have ratings at 2, 3, or 4 symptom severity levels.

Table 3. Worst Level of Psychosocial Functioning During Follow-up Months Spent at 3 Different Levels of Depressive Symptom Severity and the Asymptomatic Status by Patients With Unipolar Major Depressive Disorder and Currently Well Controls*

	Levels of Depressive Symptom Severity During Entire 1-Month Periods: Patient Level of Depressive Symptom Severity				Currently Well Controls
Domains†	1 (Asymptomatic)	2 (Subthreshold)	3 (Minor)	4 (Major)	Past Month Ratings
Work/employment (N = 322 patients, 1314 controls)	1.7 (1.0)‡ 4450	2.6 (1.7) 1564	3.5 (1.7) 2303	4.7 (1.5) 1046	1.5 (0.6)‡ 1314
Relationship with spouse/partner (N = 241 patients, 1247 controls)	2.0 (0.9)§ 3278	2.2 (1.1) 1108	2.9 (1.1) 1254	3.3 (1.1) 635	1.6 (0.8)§ 1247

*Data are presented as mean (SD) number of person-months. Impairment ratings are derived from the LIFE-II, CUF, and SLICE variants of the Longitudinal Interval Follow-up Evaluation interviews, conducted in follow-up years 3 through 12. Ratings are analyzed only for months spent entirely at 1 symptom severity level based on weekly Psychiatric Symptom Ratings (person-months). Means in table are from random (mixed) regression analysis and control for within-subject variation across multiple ratings. Control subjects are relatives, spouses, and community controls with no current Research Diagnostic Criteria mental or substance abuse disorder. Impairment ratings show level of functioning during the month prior to 6-year follow-up interviews, based on Life Base Psychosocial instruments, yielding 1 person-month per control subject. Means and SDs are derived from random (mixed) repression analysis controlling for within-subject variations across multiple ratings. Each of 3 stepwise increments in depressive symptom severity is associated with a significant increase in functional impairment ($P<.001$, 2 tailed), as determined by random-effects ordinal regression analysis, using the MIXOR software of Hedeker and Gibbons.[30] Odds ratios (ORs) and 95% confidence intervals (CIs) for stepwise increments in depressive symptom severity are as follows: Work/employment: subthreshold vs asymptomatic OR = 4.0 (95% CI = 3.7-4.4); MinD vs subthreshold OR = 5.9 (95% CI = 5.5-6.4); and MDD vs MinD OR = 2.8 (95% CI = 2.6-3.1). Relationship with spouse/partner: subthreshold vs asymptomatic OR = 1.4 (95% CI = 1.2-1.5); MinD vs subthreshold OR = 7.6 (95% CI = 6.8-8.3); MDD vs MinD OR = 2.4 (95% CI = 2.2-2.7). For explanations of symptom severity levels, see footnote to Table 2. Since only 1 month's psychosocial rating is available for currently well controls, one rating was randomly selected for patients with unipolar MDD in the asymptomatic status; these were contrasted with a Wilcoxon rank sum test on ordinal impairment ratings.
†Scale key: work/employment: 1 = no impairment, high level; 2 = no impairment, satisfactory level; 3 = mild impairment; 4 = moderate impairment; 5 = severe impairment; 6 = did not do this all during the period because of depressive psychopathology. Relationship with spouse/partner: 1 = very good; 2 = good; 3 = fair; 4 = poor; and 5 = very poor.
‡$P<.01$.
§$P<.001$.



Rater assessment of global psychosocial functioning by levels of depressive symptom severity during follow-up of 371 patients with unipolar major depressive disorder, based on months entirely at 1 depressive symptom severity level. Ratings are based on a 5-point scale with 1 = very good and 5 = very poor. Means and SDs are derived from random (mixed) regression analysis, controlling for within-subject variation across multiple ratings. Each stepwise increment in depressive symptom severity is associated with a significant increase in functional impairment ($P<.001$, 2 tailed), determined by random-effects ordinal regression analysis, using the MIXOR software of Hedeker and Gibbons.[30] Odds ratios (ORs) and 95% confidence intervals (CIs) for stepwise increments in depressive symptom severity are as follows: subthreshold vs asymptomatic OR = 7.7 (95% CI = 7.1-8.3); minor or intermittent depressive disorder vs subthreshold OR = 13.3 (95% CI = 12.2-14.6); and major depressive disorder vs minor or intermittent depressive disorder OR = 23.3 (95% CI = 20.7-26.2).

sive symptom level, strongly supporting one of our hypotheses. On average, each increment in depressive severity (asymptomatic to subthreshold, subthreshold to MinD, or MinD to MDD) is associated with large and nearly equal increments in overall impairment ratings.

Questions may be raised about the reliability and validity of data used for these analyses. The LIFE interviews have been shown to yield psychiatric symptom status and psychosocial functioning ratings with good interrater reliability.[25,31] In the CDS it was not feasible to validate ratings against other sources of information such as from employers or family members. However, we believe that the structured interviews, the systematic long-term follow-up, and the sample size of the CDS provide a uniquely valuable resource for examining psychosocial functioning over time within the same patients with unipolar MDD.

To the degree that raters incorporate functional impairment into their rating of depressive symptom severity, one would expect a high correlation between functional ratings and symptom status. The correlations between global functioning and depressive symptom severity were found to be strong (0.72), suggesting considerable overlap between these 2 constructs. However, the other 2 specific areas of functioning (work/employment and relationship with spouse/partner) did show variation in the magnitude of correlation with each other, the global functioning rating, and level of depressive symptoms, which suggests these measures also contain a substantial amount of unique information.

Psychosocial function ratings of patients with unipolar MDD return to unimpaired or good levels during months when they are asymptomatic, but still show very subtle although significant levels of impairment compared with control subjects with no current RDC diagnosis. In this study we did not examine the ultimate level of functioning reached by patients with unipolar MDD during intermorbid periods, which may be better than the levels we identified. Mintz et al[32] have described a "trajectory" of recovery of work functioning that parallels, but lags considerably behind, the curve of depressive symptom recovery.[32] The course and ultimate level of recovery of psychosocial function in relation to levels of depressive symptomatology will be examined in greater detail in a subsequent article.

Our data are consistent with the findings of Coryell et al[33,34] that very small degrees of residual interepisode impairment in certain areas may persist in patients between episodes. This may be the case particularly when unipolar MDD has reached a certain threshold of number and/or length of episodes over the lifetime course of illness. This will also be examined in a separate article.

Prior research has focused primarily on disability associated with MDEs. Our results converge with other recent evidence that symptoms at levels below the threshold for MDE also have clinical and psychosocial significance in the lives of patients with unipolar MDD.[1-9] Results from this study support the conclusion that subthreshold depressive symptoms, symptoms at the MinD level, and those at the MDD level represent a continuum of depressive symptom severity in unipolar MDD, each step of which is associated with significant and substantial increments in psychosocial disability through the course of illness. These results suggest that as long as any level of depressive symptoms and disability are present the unipolar disease remains active and continued treatment is highly recommended.

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Reprints: Lewis L. Judd, MD, Department of Psychiatry, University of California–San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0603.

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