Diurnal Mood Variation in Outpatients With Major Depressive Disorder: Implications for DSM-V From an Analysis of the Sequenced Treatment Alternatives to Relieve Depression Study Data

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Objective: Diurnal mood variation (DMV) with early morning worsening is considered a classic symptom of melancholic features in *The Diagnostic and Statistical Manual of Mental Disorders* (DSM) as well as *The International Classification of Diseases* (ICD) criteria for somatic major depressive disorder (MDD). Using the unique opportunity afforded by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study data, we examined whether DMV with afternoon or evening worsening, in addition to classic early morning worsening, was related to other symptom constructs to determine whether the exclusive reliance on morning worsening is justified in defining melancholic features.

Method: Baseline demographic and clinical characteristics, as well as depressive symptoms, including DMV, were evaluated in 3744 outpatients with nonpsychotic MDD enrolled in the STAR*D study.

Results: DMV in at least one of the time periods was reported by 22.4% (N = 837) of the sample. Only 3.3% (N = 28) of these 837 patients with DMV attributed it to environmental factors. Of the 809 participants (96.7%) with DMV unrelated to environmental events, only 31.9% (N = 258) reported morning worsening, while 19.5% (N = 158) and 48.6% (N = 393) reported afternoon and evening worsening, respectively. Minimal distinctions in demographic characteristics, clinical features, and depressive symptoms were found between participants with morning worsening and those with either afternoon or evening worsening. More importantly, other melancholic symptom features were associated with DMV regardless of time of worsening.

Conclusion: DMV was meaningfully related to other melancholia criteria regardless of when the DMV occurred. If replicated, these findings suggest that DMV as a component of melancholic features might be expanded to include any DMV, not simply early morning worsening.

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Approximately 19%[1,2] of outpatients with major depressive disorder (MDD) have symptom features defined as *melancholic* by *The Diagnostic and Statistical Manual of Mental Disorder*s, Fourth Edition, Text Revision (DSM-IV-TR).[3] These symptom features, with some variations, are defined as *somatic* by *The International Classification of Diseases,* 10th Revision (ICD-10),[4] and *endogenous* by the Research Diagnostic Criteria (RDC).[5] DSM-IV-TR melancholic symptoms include diurnal mood variation (DMV) with morning worsening, loss of pleasure in all, or almost all, activities that are normally enjoyable, lack of emotional reactivity to normally pleasurable stimuli, distinct quality of mood (depressed mood that is qualitatively distinct from sadness following death of a loved one), early morning awakening, psychomotor retardation or agitation, marked loss of appetite or significant weight loss, and excessive or inappropriate guilt. ICD-10 somatic symptoms are similar to those of the DSM-IV-TR, with 4 exceptions. Unlike the DSM-IV-TR, the ICD-10 includes lack of interest and

loss of libido but excludes excessive guilt and distinct mood quality.

Interestingly, though DMV with early morning worsening has been a traditional symptom of DSM melancholic and ICD somatic symptom features, neither diagnostic system includes DMV that is worse in either the afternoon or evening as a symptom. In addition, neither system comments on whether mood variation must be independent of (i.e., not attributed or related to) environmental events, such as difficult or unpleasant conditions at home or work,[6,7] although it is widely accepted that DMV due to environmental events is not a symptom of melancholic or somatic depression. Clinicians and researchers have traditionally adopted the classic DSM and ICD definitions of melancholic or somatic symptom features that accept only cases of DMV in which the worsening of mood occurs in the morning, systematically excluding DMV with afternoon or evening worsening as a symptom feature.

DMV is viewed by some as a dysregulation in the biologic system in general, which may involve abnormal circadian rhythms for body temperature,[8–11] and irregularities in adrenocorticotropic and somatotropic activities,[12,13] which normalize as depressive symptoms decrease in response to treatment. Phase-advanced circadian oscillation rhythms for cortisol, norepinephrine, and 3-methoxy-4-hydroxyphenylglycol have been reported in patients presenting with endogenous melancholic depression.[14–16] In assessing the cortisol fluctuation in depressed compared to nondepressed individuals, Stetler et al.[17] found that the depressed individuals showed abnormal diurnal patterns of cortisol compared to nondepressed. Peeters et al.[18] suggested that an erratic pattern of cortisol secretion may be a more characteristic feature of hypothalamic-pituitary-adrenal (HPA) axis dysregulation in MDD than a consistent circadian phase advance pattern of hypercortisolism. In sum, DMV may result from dysregulation in various biologic systems controlling circadian rhythms, such as body temperature or the HPA axis.

The large Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[19,20] study afforded a unique opportunity to evaluate the degree to which these definitions are valid based on over 4000 subjects enrolled in the "real-world" clinical trial of patients with MDD.

To this end, we addressed the following questions:

(1) How common is diurnal mood variation and how often is it attributable to environmental events? Traditionally, classic DMV (morning worsening of mood) has been associated with endogenous depression (i.e., melancholic and somatic features), as opposed to DMV with evening worsening, which has been thought of as a symptom of exogenous or neurotic depression (attributed to environmental factors).

(2) What baseline demographic and clinical features, including depressive symptoms and melancholic features, differentiate patients with classic DMV from those with no DMV? Being one of the hallmark features of melancholic depression, classic DMV should be associated with other symptoms of melancholia. Demographic and additional clinical features should not be confounding factors.

(3) What baseline demographic and clinical features, including depressive symptoms and melancholic features, differentiate patients with DMV at any time of day (morning, afternoon, or evening) from those with no DMV? If afternoon and evening DMV are not associated with melancholia, their inclusion in the definition of DMV should lessen the association found between classic DMV alone and the other symptom constructs used to define melancholia.

(4) What baseline demographic and clinical features, including depressive symptoms and melancholic features, distinguish patients with classic DMV (worse mood in the morning) from those with afternoon or evening DMV? The current diagnostic criteria for melancholic depression limit the definition of melancholia to DMV with morning worsening of mood, one of the inherent premises being that patients with classic DMV are clinically distinct from those with afternoon and evening DMV.

METHOD

This study was conducted using baseline pretreatment data gathered for the STAR*D study, a series of multicenter, randomized, controlled trials designed to evaluate the relative effectiveness of different subsequent antidepressant treatments for adults with nonpsychotic MDD who receive unsatisfactory benefit from an initial treatment, or subsequent treatments. The design and rationale of STAR*D are detailed elsewhere.[19–21] A brief summary is presented below.

Study Population

The STAR*D trial enrolled 4041 outpatients, 18 to 75 years of age, with nonpsychotic MDD, at 18 primary and 23 psychiatric care sites in the public and private sectors. Outpatients were identified by clinicians as having nonpsychotic MDD based on clinical judgment and a DSM-IV-TR diagnostic checklist. A baseline 17-item Hamilton Rating Scale for Depression (HAM-D-17)[22,23] score ≥ 14 was required for enrollment. Broad inclusion and minimal exclusion criteria were used to ensure recruitment of a sample representative of outpatients with nonpsychotic MDD seen in typical clinical practice. Patients with current substance abuse or dependence were included as long as inpatient detoxification was not clinically indicated. Participants could be taking concomitant medications, including anxiolytics or sedative hypnotics, if recommended by their physicians. Patients with schizophrenia, schizoaffective disorder, bipolar disorder, and anorexia nervosa were excluded, as were those with a

primary diagnosis of obsessive-compulsive disorder or bulimia nervosa. Patients with general medical conditions (GMCs) that contraindicated use of the protocol medications in the first 2 treatment steps were also excluded. Patients with a history of nonresponse or intolerance to protocol antidepressant medications in the first 2 treatment steps were also excluded, as were patients who were pregnant or intending to conceive.

This study was approved and overseen by institutional review boards (IRBs) at 14 regional centers that supervised protocol implementation of relevant clinical sites, as well as the National Institute of Mental Health Data Safety and Monitoring Board and IRBs at the National Coordinating Center (University of Texas Southwestern Medical Center) and the Data Coordinating Center (University of Pittsburgh). Participants provided written informed consent prior to study entry.

Assessment Procedures

After receiving written informed consent, clinical research coordinators (CRCs), trained and certified in protocol implementation and data collection procedures, reviewed inclusion/exclusion criteria, administered the HAM-D-17, and collected demographic (e.g., treatment setting, race, ethnicity, sex, marital status, employment status, insurance status, age, and education level) and clinical information (e.g., age at onset, number of prior episodes, length of current episode, length of current illness, Cumulative Illness Rating Scale [CIRS][24] scores, symptom severity, 12-Item Short-Form Health Survey [SF-12] scores, quality of life, family history of depression, current and past substance abuse, current and past suicidality, presence of depressive subtypes, and presence of comorbid Axis I disorders). In addition to DSM-IV major depressive episode (MDE) criteria symptom items, symptoms of melancholic, atypical, and anxious depressive subtypes were also evaluated.

At baseline, the CRCs completed the 13-item Cumulative Illness Rating Scale[24] (CIRS) to gauge the severity/morbidity of GMCs relevant to different organ systems. Each organ system was rated on a 5-point scale (0–4). The total CIRS score was obtained by a summation of the ratings from each of the categories on the CIRS. Participants also completed the 16-item Quick Inventory of Depressive Symptomatology–Self-Report[25–27] (QIDS-SR-16) and the Psychiatric Diagnostic Screening Questionnaire[28,29] (PDSQ). The PDSQ was scored at a threshold requiring 90% specificity to establish the presence of other current Axis I disorders.[30] Participants also completed the Quality of Life Enjoyment and Satisfaction Questionnaire[31] (Q-LES-Q), the Work and Social Adjustment Scale[32] (WSAS), and the 12-Item Short-Form Health Survey[33] (SF-12) by telephone within 72 hours of enrollment using the Interactive Voice Response system.[34,35] Research outcomes assessors (ROAs) conducted telephone interviews with participants within 72 hours of the baseline clinic visit to obtain the baseline HAM-D-17 and the 30-item Inventory of Depressive Symptomatology–Clinician-rated[26,36,37] (IDS-C-30), both of which rate depressive symptoms for the previous 7 days.

The IDS-C-30 assesses all criterion symptoms of a DSM-IV MDE, as well as all DSM-IV melancholic and atypical features, and all symptoms needed to diagnose a depressive episode with somatic symptoms as defined by the ICD-10. DMV was identified by the response to item 9 on the IDS-C-30. This item rates the presence of DMV, determines when the mood is lowest (e.g., in the morning, afternoon, or evening), and asks the respondent whether the DMV is attributed to environmental factors (i.e., difficulties at home or work that are consistently experienced at a specific time of day).

Definitions for melancholic[1] and atypical[38] depression (mood reactivity, increased appetite/weight, hypersomnia, leaden paralysis, and rejection sensitivity) were based on the DSM-IV criteria and were derived from the corresponding IDS-C-30 items. Anxious depression was defined using the HAM-D-17 anxiety/somatization factor (psychic anxiety, appetite, somatic energy, somatic anxiety, hypochondrias, and loss of insight).[39]

For the purpose of this report, classic morning DMV is defined as morning worsening of symptoms not attributed to the environment. Likewise, afternoon and evening DMV are defined as the worsening of symptoms in the afternoon or evening, respectively, not attributed to the environment.

Analyses

Participants were classified into the following 5 categories based on if and when they experienced DMVs: (1) classic morning, (2) afternoon, (3) evening, (4) "variations combined" (which grouped the first 3 categories), and (5) no DMV. Analyses were conducted to compare groups with regard to baseline demographic characteristics, clinical features, and depression symptoms. The 28 patients reporting DMV attributable to environmental factors were included in the no-DMV group for the purpose of analysis. The variations combined group (all DMV) was compared to the no-DMV group to determine whether DMV regardless of time of day is clinically significant and associated with other symptoms of melancholia. The classic morning group was compared to the no-DMV group to determine whether DMV with morning worsening is clinically significant. Classic morning DMV was compared to the afternoon and evening DMV groups to determine whether participants with classic morning DMV are clinically distinct from those with afternoon or evening DMV.

The IDS-C-30 rates DMV on a 0 to 3 scale (0 = "Notes no regular relationship between mood and time of day"; 1 = "Mood often relates to time of day due to environ-

mental circumstances"; 2 = "For most of week, mood appears more related to time of day than to events"; 3 = "Mood is clearly, predictably, better or worse at a fixed time each day"). To determine a patient's score, the rater first asked whether patients experienced DMV. If the answer was no, the patient received a score of 0. If the answer was yes, the rater asked, "Is mood typically worse in morning, afternoon, or night?" and the answer was noted. Finally, the patient was asked whether the DMV was due to environmental factors, such as work. If the rater determined that the DMV was clearly caused by environmental factors, the patient received a score of 1. A patient whose DMV was clearly unrelated to environmental factors received a score of 3. If the patient's DMV could be attributed both to endogenous and environmental sources, the patient received a score of 2 and was asked if the DMV were *primarily* due to environmental factors. Patients scoring a 2 who responded that their DMV was primarily the result of environmental factors were grouped with patients who scored 1 for the purposes of statistical analysis. Patients scoring a 2 who responded that their DMV was not primarily caused by environmental factors were grouped with patients who scored a 3 for the purposes of statistical analysis.

Statistical Methods

Data are presented as percentages for categorical variables and as means and standard deviations for continuous measures. Chi-square goodness-of-fit tests were used to compare the distribution of the categorical variables across DMV groups (classic morning vs. afternoon, classic morning vs. evening, classic morning vs. no DMV, and variations combined vs. no DMV). Continuous measures by DMV groups were compared by the appropriate parametric test (t test) or nonparametric test (Wilcoxon signed rank test).

For categorical variables such as employment status and insurance status, multiple logistic and cumulative logistic regression models were used to adjust the comparisons between DMV groups for the differences in baseline severity as measured by QIDS-SR-16 and for GMCs as measured by the total score for the CIRS. For continuous measures other than psychiatric history, age at onset of first MDE, number of episodes, length of current episodes, and length of illness, analysis of covariance methods were used to control for baseline QIDS-SR-16, and CIRS total score. For psychiatric variables, data were ranked and then analysis of covariance methods was used. For the IDS-C-30 items, the associations of symptom present or not with DMV groups was analyzed using a χ^2 test, and logistic regression analyses were used to adjust for baseline QIDS-SR-16 and CIRS total scores.

Statistical significance was defined as a 2-sided p value of less than .01. The analyses were exploratory in nature, with significance attached to both positive (differences between patients with DMV vs. those with no DMV) and negative (lack of differences between DMV patients with morning vs. afternoon vs. evening worsening) findings. Therefore, adjustments to p values were not made for the multiple comparisons. Consequently, the reader should bear in mind that, given the large number of comparisons, it is probable that the results of one or more analyses, while demonstrating a statistically significant difference, may be a function of random chance.

Table 1. Baseline Characteristics of the Evaluable Sample (N = 3744)

Characteristic	N	%
Setting		
Primary care	1440	38.5
Specialty care	2304	61.5
Race/ethnicity		
White	2838	75.8
Black or African American	649	17.3
Other	257	6.9
Hispanic ethnicity	465	12.4
Female sex	2357	63.0
Marital status[a]		
Never married	1121	30.0
Married	1559	41.7
Divorced	950	25.4
Widowed	110	2.9
Family history of depression[b]	2047	55.1
Employment status[c]		
Employed	2138	57.2
Unemployed	1383	37.0
Retired	218	5.8
	Mean (SD)	Median
Age, y	40.5 (13.2)	40
Education, y	13.5 (3.2)	13
Monthly family income, $	2419 (3144)	1600
Age at onset of 1st MDE, y	25.4 (14.4)	21
MDEs, no.	5.4 (9.4)	3
Length of current MDE, mo	24.5 (51.7)	8
Length of illness, y	15 (13.1)	12
HAM-D-17 score (ROA)	20 (6.5)	20
IDS-C-30 score (ROA)	35.6 (11.5)	36
QIDS-SR-16 score	15.4 (4.3)	16
SF-12 score		
Physical	49.4 (11.9)	52
Mental	26.6 (8.6)	26

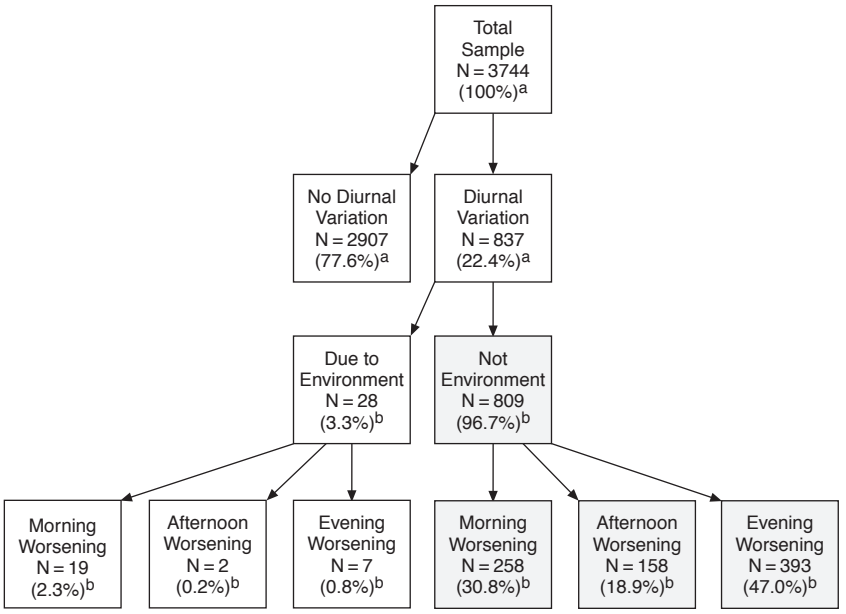
[a]Data missing for 4 patients (N = 3740).
[b]Data missing for 31 patients (N = 3713).
[c]Data missing for 5 patients (N = 3739).
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C-30 = 30-item Inventory of Depressive Symptomatology–Clinician-Rated, MDE = major depressive episode, QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology–Self-Report, ROA = research outcome assessor, SF-12 = 12-item Short Form Health Survey.

RESULTS

Description of Sample

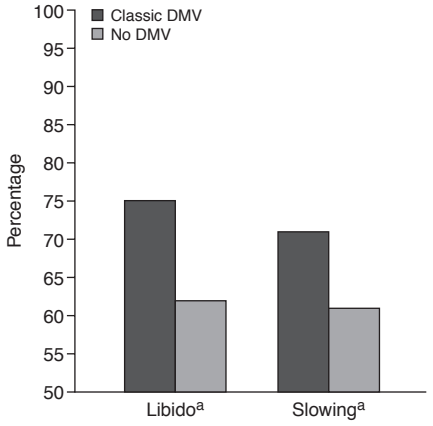
A total of 4041 outpatients were enrolled in the study. Of these, 3744 completed the baseline ROA assessment and contributed to the analyses in this report. Table 1

Figure 1. The Development of the Sample With and Without Diurnal Mood Variation



[a]Percentage of total patients.
[b]Percentage of patients with diurnal mood variation.

Figure 2. Significant* Differences in Frequency (%) Between Patients With Classic DMV and Those With No DMV



[a]Melancholic or somatic feature.
*p < .01.
Abbreviations: DMV = diurnal mood variation, Libido = decreased libido, Slowing = psychomotor slowing.

summarizes the clinical and demographic features of the sample.

Diurnal Mood Variation

Of the 3744 evaluated participants, 837 (22.4%) reported DMVs of any type (i.e., morning, afternoon, or evening worsening) (Figure 1). Only 28 of the 837 participants (3.3%) attributed their DMV to environmental events. Thus, 809 participants (21.6% of the total sample) reported DMV that was not attributable to environmental events. Of these 809 participants, 258 (31.9%) reported classic morning mood worsening, 158 (19.5%) reported afternoon mood worsening, and 393 (48.6%) reported evening mood worsening (Figure 1).

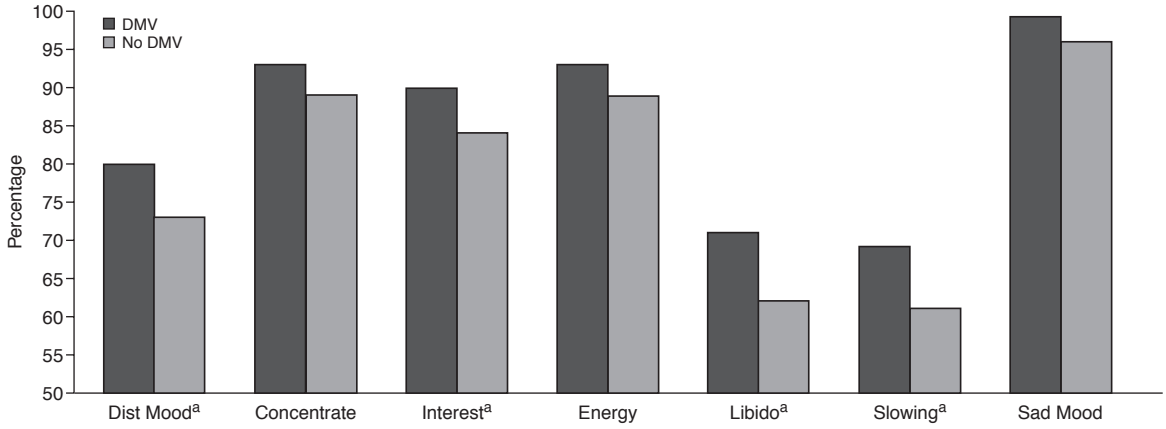
Classic Morning Worsening vs. No DMV

Participants with classic DMV (morning worsening) (N = 258) were slightly more educated (mean ± SD = 14.1 ± 3.1 years vs. 13.4 ± 3.3 years, $p < .010$) and had slightly higher levels of depression based on the IDS-C-30 score (mean ± SD = 39.4 ± 10.8 vs. 34.6 ± 11.5, $p < .001$) than those without any DMV. Participants with classic morning worsening were more likely to have melancholic features than those without any DMV (45.3% vs. 18.0%, $p < .001$), but they did not differ in the frequency of atypical or anxious features. In terms of baseline depressive symptoms, participants with classic morning worsening had higher rates of decreased mood reactivity (80.2% vs. 72.3%, $p < .007$), decreased libido (75.2% vs. 62.1%, $p < .001$), and psychomotor slowing (70.9% vs. 61.3%, $p < .003$) (see Figure 2). No other differences in demographic and clinical information were in evidence.

Presence and Absence of DMV of Any Form

A comparison of participants (N = 809) who reported any form of DMV (i.e., morning, afternoon, or evening worsening) not related to environmental factors with participants who reported no DMV revealed several statisti-

Figure 3. Significant* Differences in Frequency (%) Between Patients With Any Form of DMV and Those With No DMV



[a]Melancholic or somatic feature.
*p < .01.
Abbreviations: Concentrate = decreased concentration, Dist Mood = distinct quality of mood, DMV = diurnal mood variation, Energy = decreased energy, Interest = reduced involvement, Libido = decreased libido, Sad Mood = depressed mood, Slowing = psychomotor slowing.

cally significant differences. Those with any form of DMV had higher mean ± SD IDS-C-30 (39.3 ± 10.9 vs. 34.6 ± 11.5, p < .001) and HAM-D-17 (20.8 ± 6.1 vs. 19.7 ± 6.6, p < .001) total scores, had a higher rate for family history of drug abuse (27.2% vs. 22.5%, p < .007), and were more likely to meet criteria for melancholic features than those with no DMV (27.3% vs. 18.0%, p < .001). These groups did not differ in the frequency of atypical or anxious features, nor did they differ in terms of current comorbid DSM-IV Axis I disorders. No significant differences were found in demographic characteristics.

Regarding baseline depressive symptoms, participants with any form of DMV were more likely to report sad mood (99.3% vs. 96.7%, p < .001), distinct quality to the mood (80.0% vs. 73.4%, p < .001), concentration difficulties (93.2% vs. 89.4%, p < .007), reduced involvement (89.6% vs. 84.1%, p < .001), low energy (92.7% vs. 89.1%, p < .003), decreased libido (70.7% vs. 62.1%, p < .001), and psychomotor slowing (68.6% vs. 61.3%, p < .001) than participants with no DMV (see Figure 3).

Classic Morning Worsening vs. Afternoon and Evening Worsening

Participants with classic DMV (morning worsening) (N = 258) were compared to those with afternoon (N = 158) or evening worsening (N = 393). Significantly, more Hispanic participants reported afternoon than classic morning worsening (19.6% vs. 10.1%, p < .007). Participants with classic morning worsening had a higher mean ± SD education level than those with afternoon worsening (14.1 ± 3.1 years vs. 12.9 ± 3.3 years, p < .001), and those with classic DMV were significantly older than those with evening worsening (mean ± SD 41.0 ± 12.6 years of age vs. 37.8 ± 13.0 years of age, p < .001). No other significant differences in demographic information were present.

Regarding baseline clinical features, participants with evening worsening reported more social phobia than those with classic morning worsening (24.0% vs. 32.0%, p < .009). Only one significant difference was found in the frequency of baseline depressive symptoms. Participants with evening worsening reported more sleep-onset insomnia than those with classic morning worsening (64.7% vs. 74.8%, p < .003).

DISCUSSION

Our findings indicate that DMV (including classic morning, afternoon, and evening worsening) is fairly common in outpatients with nonpsychotic MDD, occurring in 22.4% of our sample. Only a small percentage (3.3%) of these participants attributed their DMV to environmental events. The occurrence of DMV caused by environmental factors is much lower than anticipated, suggesting that exogenous DMV may not be as clinically relevant as previously believed. Of those with any DMV not attributed to the environment, less than one third (31.9%) reported classic morning mood worsening, while 19.5% reported afternoon worsening, and nearly half (48.6%) reported evening mood worsening.

A comparison of participants with classic DMV (morning worsening) and those with no DMV yielded several significant differences. Participants with classic morning worsening more frequently reported other symptoms of melancholia (i.e., more psychomotor slowing, reduced sexual interest) and higher symptom severity scores on

the IDS-C-30 than other participants. While patients with classic DMV reported more symptoms of melancholia than participants with no DMV, the overall relationship between classic DMV and other symptoms of melancholia was only moderate.

The most pronounced differences were found when we compared participants with any form of DMV (morning, afternoon, or evening) and those with no DMV. Participants with any form of DMV consistently reported more symptoms of melancholia than those with no DMV, suggesting that the presence of DMV in any form may be clinically significant. If DMV patients with morning, afternoon, and evening worsening of mood are combined, the relationship between DMV and other symptoms of melancholia is much stronger than if morning worsening alone is used to define DMV.

Comparisons made between classic morning worsening and either afternoon or evening worsening revealed few significant differences in baseline demographic, clinical, and depressive features. The assumption that patients with classic morning worsening of mood are clinically distinct from those reporting a worsening of mood in the evening or afternoon was not supported.

While several unexpected findings were noted (e.g., patients with evening DMV had more social phobia than patients with morning DMV), the association between DMV and other symptoms of melancholia remained consistent. On no occasion was any melancholic symptom more frequently reported by patients with no DMV. Additionally, DMV was not associated with any other subtype of depression (e.g., atypical, anxious). Another interesting pattern in the data was that the association between DMV and other melancholic symptoms became much more pronounced by including patients with afternoon and evening DMV. Specifically, the comparison of patients with morning DMV and those with no DMV found an association between DMV and 3 additional symptoms of DSM melancholic depression and 4 additional symptoms of ICD somatic depression. Adding patients with afternoon and evening DMV increased the number of associated symptoms of melancholia to 6 and somatic depression to 7. Only 2 DSM-IV melancholic symptoms (early morning insomnia and excessive guilt) did not differentiate those with any form of DMV from those with no DMV. Overall, the results display a pronounced pattern of associations between DMV and other symptoms of melancholic depression, which is more clearly delineated by the inclusion of afternoon and evening worsening of mood in the definition of DMV. This pattern also demonstrated that DMV, regardless of time of day, was exclusively associated with melancholia, being positively related to melancholic symptoms and not related to atypical or anxious depression.

The degree to which DMV represents biologically distinct mechanisms in patients with depression is unknown. The extent to which patients with DMV will have distinct treatment response is also not well-defined. However, some treatments, such as sleep deprivation, have been shown to be effective in temporarily treating melancholic patients with DMV.[40–42] Additionally, melancholic or somatic symptom features have been found to be related to treatment selection or response.[39,43–45] From a clinical perspective, the recognition of DMV of any type may alert clinicians to consider the presence of melancholic or somatic depression, and may provide a baseline indicator that can be used to guide treatment decisions. However, the degree to which newer medications and more aggressive treatments, such as the use of maximal dosages, antidepressant medication combination treatments, and atypical antipsychotic augmenting agents, are successful in the treatment of melancholic patients is unknown.

There are several reasons to doubt that DMV with morning worsening represents a unique set of biologic mechanisms that differs significantly from those underlying DMV with mood worsening in the afternoon or evening. From a biologic perspective, DMV may be more than a simple phase shift or advance in biorhythms. Rather, it may represent a more complex systemic dysregulation, the manifestations of which may occur at anytime throughout the sleep/wake cycle. While patients report a general pattern of lowest mood in the morning, afternoon, or evening, DMV may not always follow a strict 24-hour circadian cycle, and it may not be present on all days. DMV may result from malfunctions in various biologic systems controlling other circadian rhythms, such as body temperature,[8,9,11] or dysregulation within the hypothalamic pituitary adrenal axis.[13,15,16,18] While the question of whether or not DMV is biologically based is not addressed in this study, the traditional notion that patients with morning worsening differ significantly from those with evening or afternoon worsening is challenged by the present study's findings.

The ramifications of properly defining DMV reach beyond clinical practice. An example from clinical genetics illustrates this point. DMV is one of a few putative psychopathologic endophenotypic markers of MDD and is thought of as representing an underlying polygenetic process involving several endogenous mechanisms, such as dysregulations in the production of glucocorticoids, monoamines, and/or melatonin. Other proposed endophenotypes found in patients with MDD include impaired executive cognitive function (response speed), attention deficits and impaired memory function, neurovegetative signs (appetite and weight change), and psychomotor disturbances.[46] Of these markers, DMV may be among the most salient; it is easily reported by patients, recognized by clinicians, and quantified by researchers. Researchers may need to focus not only on biomechanisms possibly responsible for classic morn-

ing worsening, but may need to expand the search to include biomechanisms underlying DMV with worsening of mood in the afternoon or evening as well.

One of the strengths of the study is the large representative sample. The participants did not initially present as volunteers for the study; they were recruited from a diverse cross-section of "real-world" outpatients presenting for treatment in both clinical and specialty care settings. However, the study is limited by the use of a single item based on clinician assessment to characterize the degree and type of DMV, rather than using a more extensive rating scale of DMV. Further, some patients were taking medication for general medical conditions, and the sample suffered substantial general medical and psychiatric comorbidity. Additionally, this report is based on a post hoc analysis; thus, results must be viewed as hypothesis-generating.

In summary, more than 1 in 5 participants in this large representative sample of outpatients with nonpsychotic MDD reported DMV. Only a small percentage of those attributed the variation to environmental events. DMV, regardless of time of day, was associated with melancholic symptoms, and participants with classic morning mood worsening were indistinguishable from participants with a clear pattern of afternoon or evening mood worsening.

CONCLUSION

The results of this study demonstrated that DMV was more meaningfully related to symptoms of melancholia if the definition was expanded to include afternoon and evening worsening of mood. DMV, regardless of time of day, was exclusively associated with melancholia, being positively related to melancholic symptoms and not related to other subtypes of depression. In addition, neither excessive guilt nor early morning insomnia distinguished those with any form of DMV and those without DMV. If these findings replicate, given the lack of distinguishing features between participants with classic morning, afternoon, or evening diurnal mood worsening and their shared association with other symptoms of melancholia, inclusion of any form of DMV and exclusion of excessive guilt and early morning insomnia in the definition of melancholic features may be a consideration.

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