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Diurnal Rhythms and Symptom Severity in Panic Disorder
A Preliminary Study of 24-Hour Changes in Panic Attacks, Generalised Anxiety, and Avoidance Behaviour

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Diurnal changes in the frequency of panic attacks and symptoms of generalised anxiety, phobic anxiety and phobic avoidance in 34 panic-disorder patients and 40 normal controls were evaluated. The panic-disorder patients had significant diurnal changes in generalised and phobic anxiety, but not phobic avoidance. Increased severity of symptoms and prominent diurnal changes were most evident in the panic-disorder patients with a history of depression. Although panic attacks were distributed throughout the 24-hour period, patients with a current episode or history of depression tended to have more frequent panic attacks in the morning or early afternoon. These observations challenge the traditional belief that 'anxious neurotic' patients are relatively asymptomatic upon awakening in the morning and then develop more severe symptoms of anxiety later in the day.

Several lines of evidence suggest a partial overlap in the phenomenology, neurobiology and treatment of panic and major depressive disorders (Roth, 1960; Stein & Uhde, 1988; Uhde & Nemiah, 1989). Despite these areas of overlap, several authors have noted important differences between panic disorder and major depression (Roth *et al*, 1972; Stein & Uhde, 1988).

Panic disorder and its diagnostic forerunners, e.g. neurocirculatory asthenia, anxiety neurosis, and nervous exhaustion, have been thought to be characterised by daytime worsening of symptoms. In contrast, early awakening and maximum symptoms of depression in the morning represent classic features of so-called biological or endogenous depression (Wehr & Goodwin, 1981; Davidson & Turnbull, 1986). In fact, diurnal variation with early morning worsening is so widely accepted as a vegetative symptom of depression that it is among the symptoms included in the DSM–III–R (American Psychiatric Association, 1987) criteria for melancholic depression.

We investigated the diurnal changes in symptoms of generalised anxiety, phobic anxiety and phobic avoidance and the 24-hour distribution of panic attacks in panic-disorder patients compared with normal control subjects. We chose to study panic-disorder patients because of the putative linkage between this neuropsychiatric syndrome and major depression.

Method

All subjects gave voluntary oral and/or written consent for participation. Panic-disorder patients were self-referred in response to articles in newspapers or television, or referred by local clinicians to participate in one or more of our ongoing National Institute of Mental Health (NIMH) research projects.

After an initial screening interview by telephone, potential candidates for our programme were routinely invited to NIMH for a more detailed evaluation using a semi-structured interview adapted from the Schedule for Affective Disorders and Schizophrenia (SADS-L) (Fyer *et al*, 1985; Mannuzza *et al*, 1986). All patients included in the current study were selected on the basis of a long-standing history of panic attacks. Questions regarding diurnal or seasonal variation in mood were not explicitly solicited, nor used in the selection process. All patients met DSM–III–R criteria for panic disorder, with or without agoraphobia.

A total of 40 panic-disorder patients participated in this study (2 in-patients, 38 out-patients). Six (15%) patients also met criteria for major depression at the time of the study. These six patients participated in the study but it was decided, *a priori*, that their data would be excluded from the statistical analyses to avoid any contribution of overt depressive symptoms to the specific measure (i.e. diurnality) under investigation. In retrospect, this exclusion criterion seemed justified as these six patients did, in fact, demonstrate morning worsening of generalised and phobic anxiety symptoms.

The remaining 34 panic-disorder patients made up the formal study group. Of these, 20 (59%) had past episodes of major depression. In all cases their panic attacks occurred independently of all or most episodes of major depression. Thus, the final group of panic-disorder patients contained 20 non-depressed panic patients with a history of depression and 14 non-depressed panic patients without a history of depression. This combined patient group consisted of 25 women (mean age 35.4 (s.d. 9.0) years) and 9 men (mean age 32.3 (s.d. 5.2) years).

There were no gender or age differences between the panic patients with a positive versus negative history of depression, nor were there significant differences in the proportion of patients in each subgroup who were judged to have even

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'mild' symptoms of dysthymia or depression (ratings >3) on the Bunney-Hamburg (1963) scale (range 1–15) ($\chi^2 = 4.0$, d.f. = 2, NS). The panic-disorder patients in this study, therefore, could be characterised as having moderate to very high levels of 'anxiety' but normal to mild (subclinical) degrees of depression.

Following admission to the programme, all patients were started on medication trials, including at least a four-week placebo washout period. During this time, patients were seen for weekly evaluations by a non-blind psychiatrist to assess the stability of clinical status. An experienced rater (MFG), blind to the patients' treatment status, also completed ratings of anxiety during this washout period. Ratings for the patient group during this baseline evaluation documented that the panic-disorder patients did experience pathological degrees of anxiety as reflected by their scores on the Spielberger State (44.9 (s.d. 14.6), range 20–73) and Zung Anxiety (42.4 (s.d. 7.4), range 31–55) scales (Spielberger *et al*, 1970; Zung, 1971). The patients also reported a mean of 2.1 (s.d. 4.5) (range 0–25) panic attacks during the baseline evaluation period.

The use of caffeine and alcohol was strongly discouraged but not prohibited during the study period. Patients typically self-limited their consumption of caffeine due to individual experiences of increased anxiety associated with its use (Uhde, 1990).

Healthy subjects were employees at the National Institutes of Health Clinical Center and their friends or relatives. All healthy subjects gave voluntary consent to participate in this research study. A semi-structured interview documented that none of the 25 female (mean age 36.7 (s.d. 8.5) years) or 15 male (mean age 32.0 (s.d. 4.2) years) controls had a history of neuropsychiatric diseases, including agoraphobia or panic disorder. There were no significant differences in age or gender distribution between patient and control groups. None of the healthy subjects were taking any psychoactive medications during the two weeks of their participation in this study. They were not asked to change their normal habits and were permitted to continue moderate use of caffeine and alcohol.

All subjects reported no serious current or past medical illnesses. All patients had normal physical examinations, electrocardiograms, electroencephalograms, and laboratory tests for hepatic, haematopoietic, and thyroid functioning.

Patients were asked to complete an anxiety rating scale four times daily and were asked to record the time of all panic attacks. The anxiety scale included a visual analogue rating for each of the following symptoms: generalised anxiety, phobic anxiety, and phobic avoidance. These measures were rated each day at 11.00 a.m., 3.00 p.m., 7.00 p.m. and bedtime. The patients were instructed to rate the degree to which they had experienced a particular symptom during the preceding time interval. Thus, a rating at 11.00 a.m. reflected a self-rated score of anxiety for the time period from bedtime, after falling asleep the previous evening, until 11.00 a.m. the following morning. (Only one patient had a sleep panic attack. In this case, the patient took this experience into account when making the first morning rating. In the remaining 33 cases, the 11.00 a.m. rating represents the four-hour interval between awakening at approximately 7.00 a.m. and the 11.00 a.m. rating.) Similarly, 3.00 p.m. scores represented self-ratings of anxiety from 11.01 a.m. through to 3.00 p.m. The four time intervals of four hours each were, therefore, the following: awake or 7.00 a.m.–11.00 a.m. (morning), 11.01 a.m.–3.00 p.m. (early afternoon), 3.01 p.m.–7.00 p.m. (late afternoon), and 7.01 p.m.–11.00 p.m. or bedtime (evening).

Ratings were made on a 100 mm line, rating symptoms from 0 'none at all' to 100 'extreme'. Previous assessment in these subjects had indicated significant positive correlations between measures on the analogue scale of generalised anxiety and the STAI (Spielberger, 1970) ($r = 0.61$, $P < 0.0001$) and Zung (1971) ($r = 0.46$, $P < 0.003$) anxiety scales. We decided to use 100 mm analogue rating scales, rather than the more time-consuming standardised rating scales (i.e. Spielberger and Zung), in order to maximise compliance of the participating subjects. Over the 14-day period of the study, each subject was asked to complete 168 analogue ratings. There was a high rate of compliance with this task as reflected by a mean (s.d.) completion rate of 99.4 (3.7)% in the normal control subjects and 95.2 (9.7)% in the patients. Thirteen subjects (12 patients, 1 normal control) did not complete all scales, failing to complete ratings on an average of only 2 (1.7) days (range 1–7) out of the 14. In these individuals the means of the relevant time-points of the remaining days were substituted in the data analyses.

Analysis

A preliminary analysis of the 14 days demonstrated no significant differences by repeated-measures analysis of variance (ANOVA) across days in either group. Therefore, self-ratings for each of the four time intervals were separately averaged across the 14 days and then analysed for possible differences between groups by two-way ANOVA.

In a series of secondary analyses (presented in the Results), the patients were stratified according to a history of depression and evaluated in terms of severity and diurnality of generalised anxiety, phobic anxiety, and phobic avoidance. In these analyses, both one- and two-way repeated-measures ANOVA were employed as indicated in the text. The repeated measure was the four time periods (i.e. awake–11.00 a.m., 11.01 a.m.–3.00 p.m., 3.01 p.m.–7.00 p.m., 7.01 p.m.–bedtime). Within-group comparisons utilised Huynhfeldt probabilities with adjusted degrees of freedom. Post-hoc analysis was performed by the Bonferroni method.

Comparisons between diagnostic groups (i.e. patients v. normal controls or patients 'with' v. 'without' a history of depression) used the Student's *t*-test or Mann-Whitney *U* test, where appropriate, for two-group analyses of non-repeated measures. The distribution of panic attacks and other dichotomous data were assessed by the χ^2 or Fisher's exact test.

Results

Of the 34 patients, 14 (41%), but none of the 40 normal controls, experienced panic attacks during the study (Fisher's

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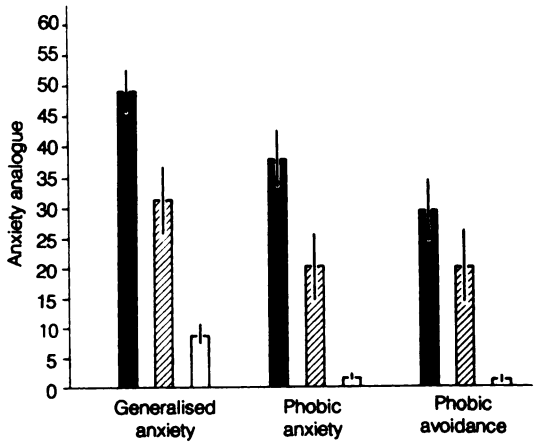


Fig. 1 Ratings of generalised anxiety, phobic anxiety, and phobic avoidance in patients with panic disorder with a history of depression (■), panic disorder without a history of depression (▨), and normal controls (□).

exact test, $P<0.0001$). The panic-disorder patients also had scores indicative of more severe generalised anxiety ($F=83.24$, d.f. = 1, 72, $P<0.0001$), phobic anxiety ($F=72.68$, d.f. = 1, 72, $P<0.0001$), and avoidance behaviour ($F=45.52$, d.f. = 1, 72, $P<0.0001$) than normal controls.

A history of depression did not influence the overall frequency of panic attacks ($\chi^2=1.40$, d.f. = 1, NS) or degree of avoidance behaviour, respectively. However, as illustrated in Fig. 1, patients with a history of depression did report more severe ratings of generalised anxiety ($P<0.007$) and phobic anxiety ($P<0.01$) compared to panic-disorder patients without a history of depression.

Diurnal rhythm and morning worsening of anxiety symptoms

The normal controls reported significant fluctuations ($F=3.97$, d.f. = 2.3, 90.7, $P<0.02$) in symptoms of generalised anxiety throughout the day. However, as presented in Table 1, these fluctuations represent increased ratings in the early and late afternoon rather than the morning. In fact, there was no difference between the ratings in the earliest morning period (i.e. awake–11.00 a.m.) and the period associated with the lowest overall ratings for the entire day (i.e. 7.01 p.m.–bedtime) (NS). Thus, while symptoms of generalised anxiety were not fixed throughout the 24-hour period, there was no evidence of early morning worsening in the normal control subjects. The only significant differences found were between early/late afternoon and evening ($P<0.05$).

Table 1
Diurnal changes of anxiety in normal control subjects (mean (s.d.) no. of symptoms)

Symptom	Time period			
	awake–11.00 a.m.	11.00 a.m.–3.00 p.m.	3.00 p.m.–7.00 p.m.	7.00 p.m.–bedtime
Generalised anxiety	8.7 (10.8)	9.5 (11.7)	9.5 (11.2)	7.8 (10.1)
Phobic anxiety	1.4 (2.7)	1.5 (3.1)	1.5 (3.1)	1.7 (3.1)
Phobic avoidance	1.4 (3.0)	1.5 (3.8)	1.5 (3.5)	1.4 (3.0)

The healthy subjects demonstrated no significant 24-hour rhythm changes in phobic anxiety ($F=0.54$, d.f. = 2.1, 82.8, NS) or avoidance ($F=0.24$, d.f. = 2.2, 85.5, NS).

The panic-disorder patients had significant 24-hour fluctuations in both generalised ($F=4.51$, d.f. = 1.7, 56.8, $P<0.02$) and phobic anxiety ($F=5.75$, d.f. = 1.8, 58.8, $P<0.007$). Figures 2 and 3 indicate that these diurnal changes were due to higher measures of generalised anxiety (GA) and phobic anxiety (PhA) in the morning (i.e. awake–11.00 a.m.) (GA: Bonferroni $t=2.73$, $P<0.05$, PhA: Bonferroni $t=3.4$, $P<0.01$) and early afternoon (11.01 a.m.–3.00 p.m.) (GA: Bonferroni $t=3.4$, $P<0.01$; PhA: Bonferroni $t=3.7$, $P<0.01$) periods compared to the evening (i.e. 7.01 p.m.–bedtime) period, respectively.

It was the panic-disorder patients with a history of depression who largely accounted for the diurnal changes in symptoms of generalised and phobic anxiety. That is, patients with a history of depression demonstrated significant changes in symptoms of both generalised ($F=7.38$, d.f. = 2.2, 41.0, $P<0.001$) and phobic anxiety ($F=6.28$, d.f. = 2.0, 37.4, $P<0.005$) whereas the panic-disorder patients without a history of depression had no significant 24-hour fluctuations in either generalised ($F=0.41$, d.f. = 1.5,

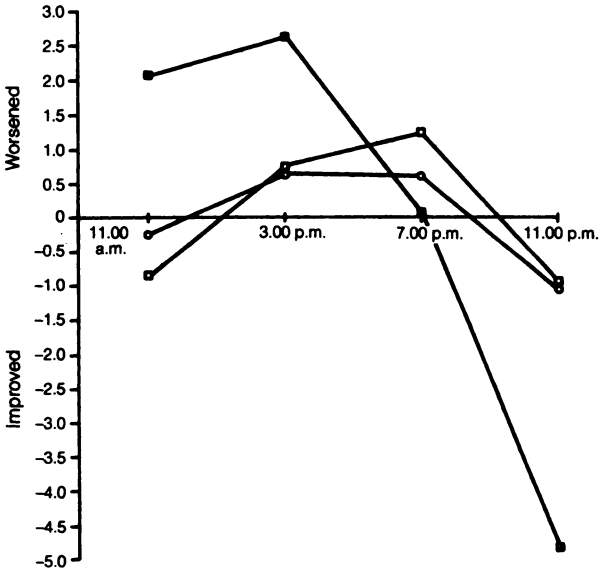


Fig. 2 Diurnal changes in generalised anxiety relative to mean daily score on the 100 mm analogue rating scale, for normal controls (○), panic patients without a history of depression (□), and panic patients with a history of depression (■).

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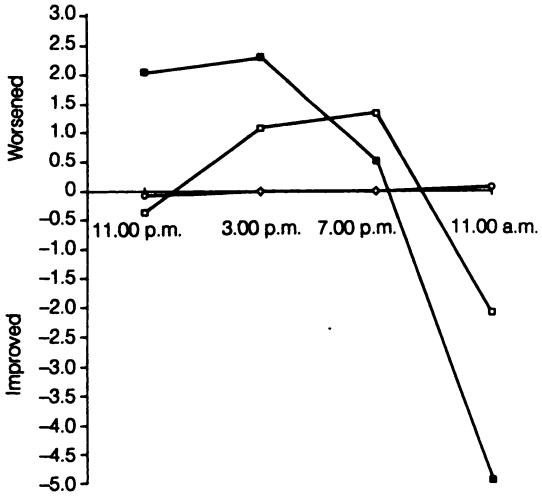


Fig. 3 Diurnal changes in phobic anxiety relative to each group's mean daily score, for normal controls (○), panic patients without a history of depression (□) and panic patients with a history of depression (■).

19.8, NS) or phobic ($F=0.89$, d.f. = 1.8, 23.2, NS) anxiety over time.

Neither the panic-disorder patients as a whole ($F=0.46$, d.f. = 2.2, 74.0, NS) nor those with ($F=1.06$, d.f. = 2.2, 41.5, NS) or without ($F=0.77$, d.f. = 2.1, 26.7, NS) a history of depression had significant 24-hour changes in avoidance behaviour.

A total of 39 panic attacks were experienced by 14 patients during the study. Of patients with and without a history of depression, 71% and 45%, respectively, experienced more of their panic attacks in the first half of the day. Although this failed to achieve statistical significance (Fisher's exact test), there was a trend for patients with a history of depression to experience most of their panic attacks in the morning. In fact, of the total number of panic attacks within each group, 50% of the attacks in the patients with a positive, compared with 13% in those with a negative, history of depression took place in the earliest four-hour period (7.00–11.00 a.m.) of the day.

There were no main significant gender effects or gender × diagnosis or gender × time interactions.

Discussion

A tenet of phenomenological psychiatry is that major depression, particularly melancholia, is associated with diurnal variation in mood, with early morning worsening. This assumption carries significant weight among clinicians in the differential diagnosis of mood v. anxiety disorders. That is, it has long been taught that patients with 'neurotic' conditions have worsening of symptoms later in the day. In fact, anxious 'neurotic' conditions were thought to be aggravated by the patients' incremental exposure during the day to routine stressors (e.g. work environment) of living. Our findings appear to challenge the wisdom of the historical linkage between panic disorder, as an expression of so-called 'neurosis', and worsening of symptoms later in the day.

Our data further suggest that particular symptoms (i.e. generalised anxiety and phobic anxiety) in selective subgroups of panic patients (i.e. those with a history of depression) may have a marked diurnal change characterised by the highest levels of anxiety in the morning and early afternoon with gradual tapering in intensity as the day progresses. This same trend was noted in the distribution of panic attacks, although this did not achieve statistical significance due to the low power of our sample.

In an uncontrolled study, we initially reported (Uhde *et al*, 1985) that panic attacks appeared to be randomly distributed throughout the day. Cameron *et al* (1986) also investigated the diurnality of anxious symptoms in a group of patients with mixed anxiety disorders. They found anxious patients to have more severe symptoms during later segments of the day. The dissimilar results between this latter study and our current investigation, however, can be explained on the basis of different methodological approaches. Moreover, Cameron *et al* (1986) actually found rather unimpressive afternoon increases in anxiety when patients with panic disorder were analysed as a separate group, suggesting, as we found in our study, that only selective subgroups of anxious patients may have diurnal variations. We found also that patients without a history of depression had a relatively flat level, and in many cases actual worsening, of symptoms of generalised or phobic anxiety as the day progressed. Both research teams excluded patients with current major depression; however, when patients with a history of depression were independently analysed in our current study, we found a morning or early afternoon worsening in symptoms of generalised and phobic anxiety. The combined observations of these studies underscore the likelihood that it is panic-disorder patients with a history of depression who are most apt to demonstrate morning–early-afternoon worsening of symptoms.

Our positive findings of diurnality underscore the need in future studies for more frequent rating intervals to assess possible ultradian rhythms. It will also be desirable to evaluate different subtypes of anxious symptoms since we found that some, but not all, qualitative forms of anxious mood or fear behaviour exhibited diurnal variations. This applies to the evaluation of normal control subjects as well since they were found in our study to have some, although relatively minor in degree, diurnal changes.

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Abe & Suzuki (1985) also found that 'normal people' often feel 'worse' in the morning than the evening. Although our findings suggest a linkage between affective vulnerability (as reflected by a positive history of depression) and diurnal changes in generalised anxiety, phobic anxiety, and (most likely) panic attacks in panic-disorder patients, it is noteworthy that even within this group there was significant variability. It is unlikely, therefore, that an affective history alone endows the panic-disorder patient with an increased likelihood of diurnal changes or peak levels of anxiety in the morning or early afternoon. Other, unknown factors, in addition to a history of depression, would appear to be operative in this regard.

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