Simultaneous Panic and Depressive Disorders: Clinical and Sleep EEG Correlates

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Abstract. Panic and depressive symptoms occur simultaneously in many depressed patients. To study the frequency of this association and to determine whether patients with simultaneous panic and major depression differed from those with only major depressive disorder (MDD) in clinical features and in sleep electroencephalographic (EEG) variables, we evaluated a total sample of 336 patients with MDD. Fifty-eight (17%) had both panic and MDD; 50 had complete data and were matched for age and severity of illness with other patients having only MDD. Patients with simultaneous panic and depression had significantly higher ratings for psychic and somatic anxiety, and rapid eye movement (REM) latencies approximating normal values. Patients with only MDD (without panic disorder) rated significantly higher in guilt feelings and had shorter REM latencies. Our results suggest that the simultaneous occurrence of panic and depression is relatively frequent, is accompanied by differences in sleep EEG variables, and may have implications for treatment.

Key Words. Major depressive disorder, panic disorder, sleep electroencephalogram.

Anxious and depressive symptoms occur simultaneously in many psychiatric patients. This combination of symptoms may create problems in the differential diagnosis and formulation of treatment of the primary condition. Considerable nosological research has been done in this area without consensus. Some authors (Mapother, 1926; Lewis, 1934, 1966) support the unitarian view and categorize the anxiety symptoms as part of the affective illness. Others advocate a dualistic approach (Gurney et al., 1972; Roth et al., 1972; Schapira et al., 1972; Kerr et al., 1974; Mountjoy and Roth, 1982a) in which two syndromes can be identified on the basis of clinical features and treatment outcome. Finally, an intermediate position is promoted in the Research and Diagnostic Criteria (RDC) (Spitzer et al., 1978) and the DSM-III (American Psychiatric Association, 1980). These nosologies indicate that anxiety and depressive
conditions can exist separately, but when they occur jointly, the predominant diathesis is the affective illness.

The acceptance of two separate anxiety syndromes in *DSM-III* and RDC, i.e., panic disorder and generalized anxiety disorder, seems to have promoted progress in this area. It appears that when panic disorder accompanies major depressive disorder (MDD), the resulting clinical syndrome may differ in a variety of parameters from either condition alone. For example, the prognosis of patients with panic disorder is poorer if they also manifest depressive features (Noyes and Clancy, 1976; Clancy et al., 1978). The response to antidepressant medication is less favorable in patients who have joint panic disorder and MDD (Van Valkenburg et al., 1982; Grunhaus et al., in press). In patients with anxiety disorders, MDD is associated more frequently with panic disorder than with generalized anxiety disorder (Dealy et al., 1981) and the incidence of psychopathology in the relatives of patients with MDD is higher when the proband also meets the diagnosis of panic disorder (Leckman et al., 1983a, 1983b; Weissman et al., 1984). These preliminary reports suggest that the joint occurrence of panic symptomatology with MDD leads to a clinical syndrome with a more ominous prognosis.

It is unknown whether the syndrome of MDD with simultaneous panic disorder is characterized by biological variables that differ from those found when either syndrome occurs in isolation. In this communication, we address this question by extending our previous preliminary report (Grunhaus et al. 1984) on the sleep polysomnographic (sleep electroencephalographic) recordings in patients with simultaneous panic disorder and MDD compared to control patients with MDD alone. Our findings continue to indicate that patients with the joint syndrome have sleep electroencephalographic (EEG) tracings that are different from those of patients with MDD alone. We also report the frequency of this condition in our clinical setting.

**Methods**

The Clinical Studies Unit (CSU) of the University of Michigan is a 12-bed inpatient unit with an accompanying outpatient program that specializes in the research and treatment of affective disorders. Patients studied include both inpatients and outpatients. Our CSU diagnostic evaluation, described in greater detail elsewhere (Carroll et al., 1981), consists of a 14-day drug-free period (patients are completely free of psychotropic medications during this period); several clinical interviews; a structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia (SADS and SADS-Lifetime Version) (Spitzer and Endicott, 1975); a thorough medical evaluation; and a diagnostic family interview whenever feasible. Comprehensive diagnoses are formulated based on RDC and clinical criteria (Carroll et al., 1980).

The study was designed to compare two groups of patients: those with simultaneous panic disorder and MDD (simultaneous subgroup) and those with only MDD (depressed subgroup).

Information concerning panic disorder was extracted from the ratings of the current episode of illness in the SADS interview. For inclusion of patients into the simultaneous panic and MDD group, our first step was to determine whether they met RDC/*DSM-III* criteria for MDD. For this we reviewed SADS interviews of those meeting MDD who also had a Hamilton Rating Scale for Depression score \( \geq 12 \). Our next step was to determine whether subjects met RDC/*DSM-III* criteria for panic disorder; if so, we diagnosed both conditions regardless of whether subjects had MDD (this is a modification of written RDC/*DSM-III* criteria). None of the patients with only MDD (depressed group) met diagnostic criteria for panic disorder, either
for the current episode or in their life history (as reported by the SADS-L).

Other inclusion criteria for both groups were: (1) Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) score ≥ 12; (2) no research exclusion criteria known to invalidate biological correlates (Carroll et al., 1981; Privitera et al., 1982); (3) no other illness that could account for the panic attacks; (4) absence of pregnancy; and (5) informed consent. Investigators and clinical raters were blind to research variables.

Our initial sample consisted of 336 patients who met MDD criteria. Within this total sample, subjects meeting the joint diagnosis of MDD and panic disorder were matched for age (within a range of 5 years) and severity of illness (within a range of 5). To determine the “adjusted HRSD,” anxiety items — somatic and psychic anxiety — were extracted to give an adjusted score.

Sleep recordings were performed following 2 weeks of drug-free status. Inpatients were recorded on 2 consecutive nights and while sleeping in their own hospital beds. Most outpatients came to the sleep laboratory 3 consecutive nights, with data for the first night being discarded to avoid the “first night” effect. The sleep variables were averaged for the “good” nights. Some outpatients had only 2 nights of recordings, in these, we include only the second night. These patients were studied during the initial stages of our sleep laboratory, hence, these methodological differences.

The following definitions were applied when studying the sleep recordings: awake: time (minutes) awake between sleep onset and end of sleep; delta sleep: stages III and IV; early morning awakenings (EMA): time (minutes) awake between end of sleep and arising (end of recording); REM activity (RA): the sum of the eye movement scores during REM sleep for the entire night, based on a score of 0-8 for each minute of REM sleep; REM density: REM activity/REM time (RA/RT); REM latency: time (minutes) from sleep onset to onset of stage REM; REM latency minus awake (RLMA): REM latency minus any time awake between sleep onset and REM onset (minutes); REM percent (REM%): RT/(TS-A) x 100%; REM time (RT): time (minutes) spent in stage REM; sleep efficiency: (TS-A)/TRP x 100%; sleep latency: time (minutes) from beginning of recording to sleep onset; time sleeping (TS-A): time (minutes) from sleep onset to end of sleep minus awake; total recording period (TRP): time (minutes) from beginning of recording (“lights out”) to end of recording; REM period: a period containing at least three 1-minute epochs of REM sleep, with not more than 30 minutes of non-REM sleep between any two epochs of REM (Feinberg et al., 1982); sleep onset: ≥ 3 minutes of continuous REM sleep, or 10 consecutive minutes of sleep with the first minute being stage 2, 3, 4, or REM sleep and at most 1 minute of time awake during this 10-minute period; sleep offset: last minute of stage 1, 2, 3, 4, or REM preceded by 9 consecutive minutes of sleep with 1 minute awake allowed.

Ordinal data were analyzed with the χ² or the Fisher’s exact test. Matched clinical ratings were studied with paired Student’s t test, while the sleep variables and nonpaired measurements required the two-sample t test. Whenever variances were significantly different between the two groups, we used t tests adapted for unequal variances.

Results

Frequency of Simultaneous Panic and Depressive Disorder. Fifty-eight of the original 336 patients (17%) met the diagnostic criteria for MDD with simultaneous panic disorder. Another 23 patients (7%) had reported clinical complaints consistent with panic attacks, but the severity and frequency of the attacks failed to reach DSM-III/RDC criteria; these patients were excluded from later data analyses.

Clinical Features. To evaluate clinical features and sleep EEG variables in more detail, we then focused on those 58 subjects who had simultaneous MDD and panic features. Eight subjects had to be excluded because of missing clinical data. The remaining 50 were matched on age and severity of illness. Thus, our two subsamples
consisted of 50 subjects with simultaneous MDD and panic, and 50 matched subjects with only MDD. Table 1 presents the demographic and clinical data for both groups of patients. The sex distribution was similar in both groups ($\chi^2 = 0.184$, NS). Samples were adequately matched for age and severity. The small differences in the HRSD ratings disappeared when the adjusted HRSDs were analyzed. The HRSD ratings for psychic and somatic anxiety were consistently higher in the group with simultaneous panic and depression, while the item of guilt was significantly higher in the group with MDD alone. We also analyzed other clinical features, including number of previous episodes of endogenous depression, age at first episode of depression, number of previous suicide attempts, number of previous hospitalizations and number of weeks since current episode. The only significant difference occurred in the number of previous episodes of endogenous depression; patients with only MDD had a significantly higher number of episodes ($t = 10.23, p < 0.01$).

**Table 1. HRSD mean ratings for depression (total and some items) for MDD patients with or without panic attacks**

<table>
<thead>
<tr>
<th></th>
<th>(pairs)</th>
<th>Panic/ depression</th>
<th>Depression</th>
<th>SD</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50</td>
<td>35.26</td>
<td>35.50</td>
<td>2.83</td>
<td>NS</td>
</tr>
<tr>
<td>HRSD total</td>
<td>50</td>
<td>21.34</td>
<td>20.13</td>
<td>3.91</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted HRSD</td>
<td>50</td>
<td>16.85</td>
<td>17.04</td>
<td>2.66</td>
<td>NS</td>
</tr>
<tr>
<td>HRSD psychic anxiety</td>
<td>50</td>
<td>2.52</td>
<td>1.95</td>
<td>1.22</td>
<td>0.002</td>
</tr>
<tr>
<td>HRSD somatic anxiety</td>
<td>50</td>
<td>1.96</td>
<td>1.13</td>
<td>1.52</td>
<td>0.0008</td>
</tr>
<tr>
<td>HRSD depressed mood</td>
<td>50</td>
<td>2.41</td>
<td>2.59</td>
<td>0.96</td>
<td>NS</td>
</tr>
<tr>
<td>HRSD guilt</td>
<td>50</td>
<td>1.14</td>
<td>1.63</td>
<td>2.05</td>
<td>&lt; 0.04</td>
</tr>
</tbody>
</table>

HRSD = Hamilton Rating Scale for Depression.
MDD = major depressive disorder.

**Sleep EEG Results.** Seventeen of the 50 patients with simultaneous panic disorder and MDD, and 16 of the 50 with only MDD had sleep EEG tracings. Of the patients with panic and MDD, only four had secondary MDD. Results are presented in Table 2. Age and severity (HRSD and adjusted HRSD) were similar in both groups. Patients with simultaneous panic and MDD had significantly longer sleep latencies ($p < 0.02$), their sleep was less efficient ($p < 0.05$), their RLMA was longer ($p = 0.05$), and their time awake ($p = 0.06$) and REM latency ($p = 0.06$) approached significance. Other sleep variables failed to differentiate between the two groups.

The distribution of the REM latencies is shown in Fig. 1. Patients with simultaneous panic and MDD are distributed much less evenly than those with MDD alone. For all patients, REM latency grand mean was 68 minutes. To test if the distribution of the latencies around the grand mean was different between the groups, we performed a Fisher's exact test, which was significant at the 0.03 level. These various analyses suggest that patients with simultaneous panic and MDD are less uniform in their REM latency findings.
Table 2. Clinical variables and sleep measurements in MDD patients with and without panic attacks (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Panic/depression</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 16)</td>
<td>(n = 17)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>37.13 ± 8.66</td>
<td>32.94 ± 8.32</td>
<td>NS</td>
</tr>
<tr>
<td><strong>HRSD total</strong></td>
<td>19.26 ± 4.25</td>
<td>21.88 ± 4.27</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Adjusted HRSD</strong></td>
<td>16.06 ± 3.75</td>
<td>16.68 ± 3.92</td>
<td>NS</td>
</tr>
<tr>
<td><strong>EMA</strong></td>
<td>8.5 ± 12</td>
<td>6.74 ± 10.36</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SLEEP LAT</strong></td>
<td>25 ± 13.54</td>
<td>44.88 ± 32.17</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>AWAKE</strong></td>
<td>17.31 ± 14.02</td>
<td>30.65 ± 31.28</td>
<td>0.061</td>
</tr>
<tr>
<td><strong>TOT S/A</strong></td>
<td>357.88 ± 59.59</td>
<td>343.41 ± 60.37</td>
<td>NS</td>
</tr>
<tr>
<td><strong>RL</strong></td>
<td>54.78 ± 24.83</td>
<td>81.76 ± 63.57</td>
<td>0.061</td>
</tr>
<tr>
<td><strong>RLMA</strong></td>
<td>53.23 ± 24.01</td>
<td>77.34 ± 51.74</td>
<td>0.051</td>
</tr>
<tr>
<td><strong>REM %</strong></td>
<td>25.36 ± 5.13</td>
<td>23.18 ± 9.31</td>
<td>NS</td>
</tr>
<tr>
<td><strong>DELTA</strong></td>
<td>17 ± 21.40</td>
<td>17.76 ± 18.40</td>
<td>NS</td>
</tr>
<tr>
<td><strong>RD</strong></td>
<td>1.56 ± 0.44</td>
<td>1.53 ± 0.47</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SLEEP EFF</strong></td>
<td>87.58 ± 4.54</td>
<td>81.71 ± 11.56</td>
<td>0.051</td>
</tr>
</tbody>
</table>

EMA = Early morning awakening; SLEEP LAT = sleep latency; TOT S/A = time sleeping; RL = REM latency; RLMA = REM latency—awake; RD = REM density.

1. t for unequal variances.

Fig. 1. REM latencies in patients with MDD alone and simultaneous MDD and panic disorder (PD)

The distribution around the grand mean (68 minutes) is significantly different between the groups (Fisher's exact, p = 0.03).
Discussion

Seventeen percent of our sample of 336 patients with MDD also met DSM-III or RDC criteria for simultaneous panic disorder. These data replicate and extend other reports indicating that the coexistence of the two syndromes is relatively frequent (Lewis, 1934, 1966; Cassidy et al., 1957; Woodruff et al., 1967). Although this association between panic attacks and MDD has been known for over 30 years, only recently have authors begun to explore its clinical, therapeutic, prognostic, and psychobiological significance.

In their clinical profiles, patients with simultaneous panic and MDD scored consistently higher in HRSD ratings of somatic and psychic anxiety, and lower on guilt. Although patients with panic attacks might be expected to have high anxiety ratings, it should be remembered that depressed patients often report anxiety as a complaint. In our patients, we found no differences in age of the first episode of depressive illness, number of previous hospitalizations, number of previous suicide attempts, and number of weeks since episode began. The frequency of previous episodes of endogenous depression did differentiate between the groups; those without panic attacks had more episodes. It is unclear whether this difference suggests that patients with the joint syndrome have a higher frequency of chronic depression, as reported by some authors (Van Valkenburg et al., 1982).

Our sleep EEG recordings suggest that patients with simultaneous panic disorder and MDD are less homogeneous than those with MDD alone. Patients with panic and MDD had more difficulty in both falling asleep and remaining asleep, and the overall efficiency of their sleep was poorer; their REM latencies varied considerably. These data extend those reported in a preliminary communication (Grunhaus et al., 1984).

Dube et al. (1985) and Sitaram et al. (1984) reported recently on sleep EEG and arecoline infusion findings of patients with MDD and anxiety disorders. The patients were diagnosed with SADS/RDC criteria and divided into four groups: primary MDD, primary MDD with secondary anxiety disorder, primary anxiety disorder, and primary anxiety disorder with secondary MDD. The authors described significantly lower REM latencies and arecoline induction responses for both MDD groups, while the anxiety groups did not differ from normal controls. Their findings confirm previous suggestions that patients with primary depression (with or without anxiety) are significantly different from patients with secondary depressions (Kupfer, 1976; Kupfer et al., 1978). Unfortunately the authors included in the anxiety diagnosis patients with generalized anxiety disorder, panic disorder, and phobias, introducing confounding diagnostic variables whose impact on sleep recordings is difficult to assess. Their data also suggest that patients with MDD and anxiety, either primary or secondary, seem to constitute an "in-between" category, with REM latency in the primary MDD subjects being lower and in the primary anxiety subjects being higher.

Akiskal et al. (1984) similarly reported that chronic dysthymics had lower REM latencies and higher REM %, while anxious depressives had more disruptions in their sleep. Thus, lower REM latencies again were associated with the affective diagnosis.

These studies collectively appear to indicate that patients with primary depression who have a secondary diagnosis of panic disorder have higher REM latencies than
patients with only MDD. Perhaps the pathophysiology associated with the panic component may have a "normalizing" effect on REM patterns. Support for this suggestion comes from sleep studies in patients with generalized anxiety disorder (Reynolds et al., 1983) and panic disorder (Uhde et al., 1984). In both studies, anxious patients had REM latencies of 75 minutes and above. Further studies are indicated, ideally with all three groups. If findings remain consistent, this should be noted in future nosologic criteria for psychiatric research.

Differences in clinical profile may be of relevance in the treatment of anxious/panic/depressed patients. It has been reported that MDD patients with high anxiety ratings have poorer treatment outcome both with tricyclic antidepressant drugs and electroconvulsive therapy when compared to patients with lower anxiety ratings (Katz et al., 1982; Grunhaus et al., 1985). These effects of anxiety on treatment outcome of MDD patients also seem to apply to those with only panic disorder, suggesting that the associated panic disorder may be responsible for the poorer outcome (Van Valkenburg et al., 1982; Grunhaus et al., in press). Liebowitz et al. (1984) recently reported results of a placebo-controlled study on atypical depression; they found that patients with a history of panic attacks responded better to monoamine oxidase inhibitors. These data collectively suggest that patients with simultaneous panic and depressive disorders may prove to be more resistant to conventional tricyclic antidepressant regimens and may require more vigorous treatments or the use of monoamine oxidase inhibitors as drugs of preference.

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