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Kupfer D J. REM latency: a psychobiologic marker for primary depressive disease. *Biol. Psychiat.* 11:159-74, 1976.
[Univ. Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, PA]

Previous investigations have indicated that one of the most consistent EEG sleep findings in depressive patients has been a shortened REM latency. On the basis of these studies, we have concluded that, with the exception of drug withdrawal states (such as CNS depressant or amphetamine withdrawal and narcolepsy), shortened REM latency points to a strong affective component in the patient's illness. Furthermore, this psychobiologic marker is a persistent, rather than a transient, phenomenon and can be observed over a period of several weeks unless a patient's condition becomes more favorable through clinical intervention. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 225 publications, making it the most-cited paper from this journal.]

REM Latency and Depressive Disorders

David J. Kupfer
Department of Psychiatry
University of Pittsburgh
School of Medicine
Western Psychiatric Institute and Clinic
Pittsburgh, PA 15213-2593

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When I finished my clinical research fellowship at the National Institute of Mental Health in 1969, I returned to Yale University imbued with a strong desire to pursue psychobiological research in psychiatry with a strong emphasis on the use of electroencephalographic sleep. Several active years of investigative work at Yale led to our *Lancet* 1972 publication proposing that shortened REM latency (time from the onset of sleep until the onset of the first REM period) was a key EEG sleep feature found in hospitalized depressed patients.[1] After relocating our research group to the University of Pittsburgh, a new set of studies stimulated us to suggest that REM latency was associated with depressive illness sufficiently frequently to represent a "marker" of the illness. With an appropriate mixture of naïveté and determination, this manuscript was submitted for the A.E. Bennett Award offered by the Society of Biological Psychiatry in 1975. Much to our amazement, we won the first prize in clinical science, and the manuscript was published in 1976 in *Biological Psychiatry*.

This report directly spawned a cottage industry of EEG sleep research in depressive illness. The research finding itself went through several phases at other universities. The first phase of initial replication with high specificity was followed by a second phase of less specificity, with somewhat similar findings appearing in other psychopathological entities, usually related to affective illness. For us, perhaps the most significant aspect of this 1976 report was that it represented the high watermark of the notion of a simple, single-feature sleep abnormality in depression. Indeed, the subsequent 14 years have been highlighted by a widening of the net to include other EEG sleep features in depression and an increasing integration with neuroendocrine parameters and other biological rhythms.

Although the initial focus was placed on the cross-sectional aspects of the depressive episode itself, the more interesting but more difficult longitudinal approach has provided the necessary modification of the term "marker" and has led investigators to grapple directly with the state/trait question and the issue of markers of vulnerability to illness as well as markers of illness itself. While the finding of 1976 has not disappeared from our world view, recent publications such as "Two roads to rapid eye movement latency"[2] and "Social zeitgebers [timers] and biological rhythms: a unified approach to understanding the etiology of depression"[3] represent a broader view of the relationship of EEG sleep and other circadian abnormalities to affective illness and describe future research directions.

I am both amused and intrigued that the 1976 report has been cited as frequently as it has. At one point, I thought it was being cited frequently only by us. The apparent widespread interest in this work probably reflects the tremendous desire to develop a psychobiological perspective of major psychiatric disorders. Although it is likely that disorders such as depression represent heterogenous disorders, the view that clinical and basic neuroscience will lead to the pathogenesis of at least some forms of depressive disorder is a reassuring one. One would hope that the next 14 years would shed even more light on these questions through study of both short-term and long-term therapeutic maneuvers so that these treatments could be based on a firmer understanding of the biology of the disorder.

1. **Kupfer D J & Foster G.** Interval between onset of sleep and rapid-eye-movement sleep as an indicator of depression. *Lancet* 2:684-6, 1972. (Cited 100 times.)
2. **Kupfer D J & Ehlers C L.** Two roads to rapid eye movement latency. *Arch. Gen. Psychiat.* 46:945-8, 1989.
3. **Ehlers C L, Frank E & Kupfer D J.** Social zeitgebers and biological rhythms: a unified approach to understanding the etiology of depression. *Arch. Gen. Psychiat.* 45:948-52, 1988.