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## A schizophrenic patient with an arrhythmic circadian rest-activity cycle

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### Abstract

A haloperidol-treated patient with chronic schizophrenia had a near-arrhythmic circadian rest-activity cycle, whereas rhythms of 6-sulphatoxy-melatonin and core body temperature were of normal amplitude and phase-advanced. Sleep electroencephalography measured throughout a 31-h 'constant-bedrest' protocol revealed a phase-delayed sleep-wake propensity cycle, low sleep continuity (ultradian 'bouts'), and very little slow-wave sleep and slow-wave activity (0.75–4.5 Hz). Switching treatment to the atypical neuroleptic clozapine improved both the circadian organization of the rest-activity cycle and the patient's clinical state. This observation can be conceptualized in terms of the two-process model of sleep regulation. High-dose haloperidol treatment may have lowered the circadian alertness threshold, whereas clozapine augmented circadian amplitude (perhaps through its high affinity to dopamine D4 and serotonin 5HT7 receptors in the suprachiasmatic nuclei). Measurement of the circadian rest-activity cycle may be a useful non-invasive method to follow functional consequences of neuroleptic treatment. © 1997 Elsevier Science Ireland Ltd.

**Keywords:** Haloperidol; Clozapine; Circadian rhythms; Sleep; Polysomnography

### 1. Introduction

The circadian pacemaker in mammals has been identified in the suprachiasmatic nuclei (SCN) of

the hypothalamus. The SCN drive all known circadian rhythms (e.g. the temporal organisation of the rest-activity or sleep-wake cycle, the core body temperature rhythm and the nocturnal secretion of the pineal hormone melatonin) and are synchronised to the external light-dark cycle by retinal input (Klein et al., 1991). In rodents with SCN lesions, the rest-activity cycle is arrhythmic.

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In humans, tumors in the anterior hypothalamus have been shown to result in highly disturbed, near-arrhythmic rest–activity cycles (e.g. Cohen and Albers, 1991). We report an example of a rest–activity cycle that is near-arrhythmic in the presence of a functioning circadian pacemaker, with clinical consequences.

## 2. Case history

A male patient (born 1955) was first hospitalised at the age of 19. From 1982 onwards, his diagnosis was clearly schizophrenia (ICD 9: 295.20; ICD 10: 20.20), with symptomatology that shifted from paranoia in the early years to more depressive phases later on. The patient suffered from recurrent catatonic episodes — once being found sitting completely stiff in the snow at  $-10^{\circ}\text{C}$ . The most severe and debilitating attack with hyperthermia occurred after haloperidol had been withdrawn preparatory to a clinical trial with a new neuroleptic. Over the years he had been hospitalized 14 times, with short intervals of sufficient improvement to permit placement in a special outpatient home. He had received depot and oral haloperidol treatment since 1982. His neurological status was normal and there were no deviant values in the clinical chemistry examination. The nursing staff noted increasing apathy, mutism and aberrations in his sleep–wake cycle (he dozed throughout the day and was only communicative, if at all, during the night). Because of this behavioral pattern, the patient was referred to the chronobiology laboratory.

## 3. Experimental procedure and results

Since this was an exploratory study, each procedure developed out of the preceding findings. Informed consent was obtained at each step.

### 3.1. Actimetry

For 220 days (with some interruptions), beginning on 23 April 1993, he wore an actigraph (Gähwiler®, Zürich) under his usual ward living conditions. Treatment had been stabilized with

depot haloperidol (200 mg i.m., last given on 14 April 1993); haloperidol p.o. (20 mg/day); and levomepromazine p.o. (25 mg/day), together with biperiden (depot 4 mg, 2 mg p.o./day). During this first measurement period (Fig. 1A), he had a near-arrhythmic rest–activity cycle, with weak ward-related zeitgebers such as lunch and 1- to 2-h naps in the afternoon and around dawn. This pattern had persisted for weeks and was thus not an artifact of the monitoring situation itself. In the periodogram analysis (Klemfuss and Clopton, 1993), the unusual actogram had only a very weak 24-h component, with an additional small but significant period of 38.5 h. The best omega — a measure of amplitude of this peak — was 0.18; that is, extremely low compared with that from a group of similarly aged normal volunteers in our laboratory ( $n = 7$ ,  $0.70 \pm 0.08$ , range 0.56–0.79). The abnormal actogram suggested a disturbance in the SCN area, but the patient refused to undergo a magnetic resonance imaging examination to evaluate this possibility. Complete ophthalmologic testing was then carried out, with normal results. We offered the use of light therapy as a possible entraining agent (1 h morning and evening), but it was inconsistently used during this time and did not lead to improvement in the rest–activity cycle (Fig. 1A from 22 July 1993).

### 3.2. Melatonin rhythm

Urine was collected by the ward staff at approximately 4-h intervals over 48 h. Measurement of the major melatonin metabolite 6-sulphatoxymelatonin (Aldhous and Arendt, 1988) revealed a robust rhythm at a somewhat early nocturnal phase: cosinor-fitted peak at 02.39 h, compared with 04.40 h and 06.45 h for two groups of healthy men (Deacon and Arendt, 1994; Kräuchi and Wirz-Justice, 1994). This was viewed as evidence for intact rhythmic SCN function (Fig. 2). Urinary cortisol was also assayed, but high stress-related values on the first day precluded its reliable use as a circadian marker, although a normal amplitude rhythm was seen on the second day with an early peak in the 19.30–22.00 h aliquot (data not shown).

### 3.3. Sleep EEG and temperature

To differentiate rest–activity from sleep–wake periods, an experimental protocol was designed to measure the sleep electroencephalogram (EEG) under conditions that would reveal a circadian rhythm in sleep propensity, if present. The patient agreed to participate in a ‘constant bedrest’ protocol (Zulley, 1992). He was kept in bed, in a room in which both temperature (22°C) and light (< 10 lx) were controlled, and permitted to sleep ad libitum. Meals were available on demand, as was a selection of video cassettes. Members of his ward nursing staff looked after him in a shift schedule. Continuous measurements of the EEG and rectal temperature were carried out for a period of 31 h from 10.00 h on the first day until 17.00 h on the following day. The sleep EEG was scored according to Rechtschaffen and Kales (1968).

The first few hours of the ‘constant bedrest’ represented an adaptation to the unusual laboratory conditions, and the patient withdrew and slept during most of this time. He was continuously awake from 17.27 h to 02.19 h with a few minutes of stage 1 sleep between 22.00 and 23.00

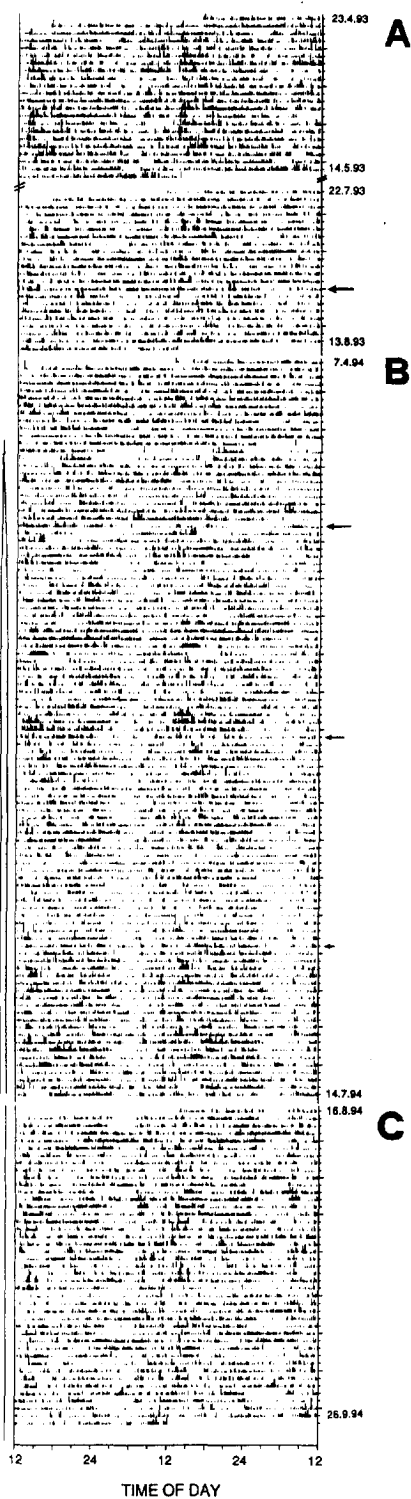


Fig. 1. Double plot of the circadian rest–activity cycle (2-min values, log-transformed). Day 1 and Day 2 are plotted consecutively (48 h) and beneath one another to enhance visualization of the patterns. (A) Initial period in spring and summer 1993 under haloperidol treatment: The horizontal arrow on the right ordinate indicates depot injection (200 mg i.m.); in addition the patient was treated with oral haloperidol, levomepromazine and biperiden. From 22 July to 13 August 1993, he additionally received light therapy (1 h in morning and evening). (B) Slow change of medication in spring and summer 1994: The black arrow on the left indicates reduction of haloperidol, p.o., from 15 mg to no further tablets. Depot haloperidol was injected i.m. (arrows on the right-hand side of the actogram) in decreasing doses from 150 mg, 100 mg, 50 mg to zero at the end of the period illustrated. Clozapine treatment (open arrow on the left) began on 14 April with 25 mg p.o. and was stabilized at 300 mg. (C) Last part of the actogram in autumn 1994, on clozapine treatment alone (300 mg).

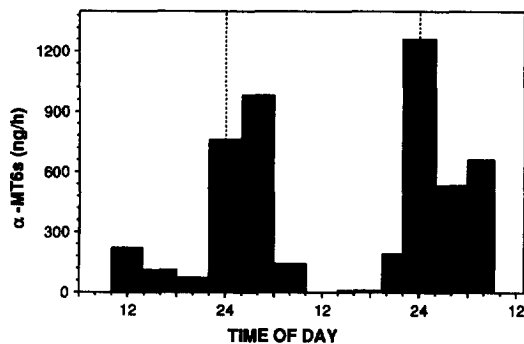


Fig. 2. Forty-eight-hour profile of the rate of urinary 6-sulphatoxy-melatonin ( $\alpha$ -MT6s) secretion measured every 4 h.

h. EEG data clearly documented a circadian propensity for sleep, but at a delayed phase, as had first been noted by the ward staff (Figs. 3 and 4). The distribution of rapid eye movement (REM) sleep followed the characteristic circadian pattern with highest propensity in the morning. Sleep was abnormal in a number of ways: (a) there was practically no slow-wave sleep (SWS) (no stage 4 and only 7 min of stage 3); (b) 'bouts' of sleep occurred at short intervals (20–70 min in length) throughout the 'sleep phase', similar to the bouts of rest noted in the actogram; (c) spectral analysis revealed low power ( $59.6 \mu\text{V}^2$ ) in the delta band (0.75–4.5 Hz) in non-REM sleep compared with values for normal volunteers from our laboratory ( $n = 10$ ,  $181.6 \pm 9.1 \mu\text{V}^2$ ; range = 84–290  $\mu\text{V}^2$ ) and no evidence of declining slow-wave activity throughout the 'sleep' period as is usually found (Achermann and Borbély, 1987).

Rectal temperature showed a circadian rhythm with a minimum during the night (Fig. 4). Towards the end of the constant bedrest protocol, the patient developed an abnormal continuous rise in core body temperature. At this time (approx. 11.00 h on Day 2), the nurses observed development of catatonia. Such hyperthermia is reminiscent of the early observations by Gjessing 1932, Fig. 6, p. 350). Therefore analysis of the 24-h and 12-h components of the circadian rhythm were made after removing the linear trend [for method, see Kräuchi and Wirz-Justice 1994)]. The circadian minimum was calculated to be at 00.25

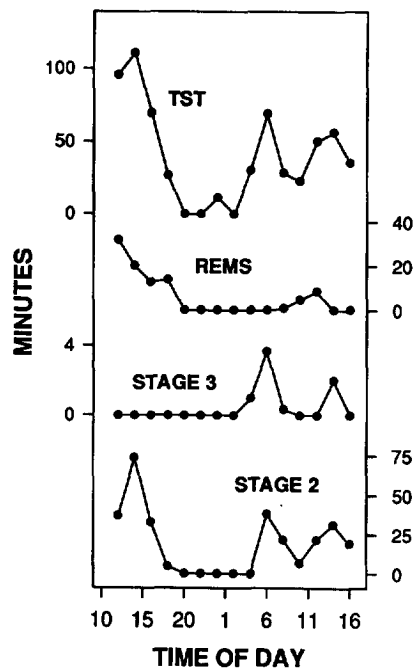


Fig. 3. Distribution of total sleep and sleep stages during a constant bedrest protocol (2-h mean values in minutes). TST, total sleep time (stages 1, 2, 3 and rapid eye movement sleep; REMS, rapid eye movement sleep). The patient had no stage 4 sleep.

h, which is earlier than the temperature minimum at 05.19 h measured in healthy men under a constant routine (Kräuchi and Wirz-Justice, 1994), and can be interpreted as supporting the findings of an earlier phased 6-sulphatoxy-melatonin rhythm.

### 3.4. Initiation of clozapine treatment

The above findings of an apparently functioning circadian pacemaker combined with a near-arrhythmic rest-activity cycle led to conceptualisation of these observations within the two-process model of sleep regulation (Daan et al., 1984). In this model, extreme lowering of the vigilance threshold leads to ultradian or arrhythmic rest-activity cycles. Thus, we considered the high dose of neuroleptic medication rather than the illness itself as probably causative of these abnor-

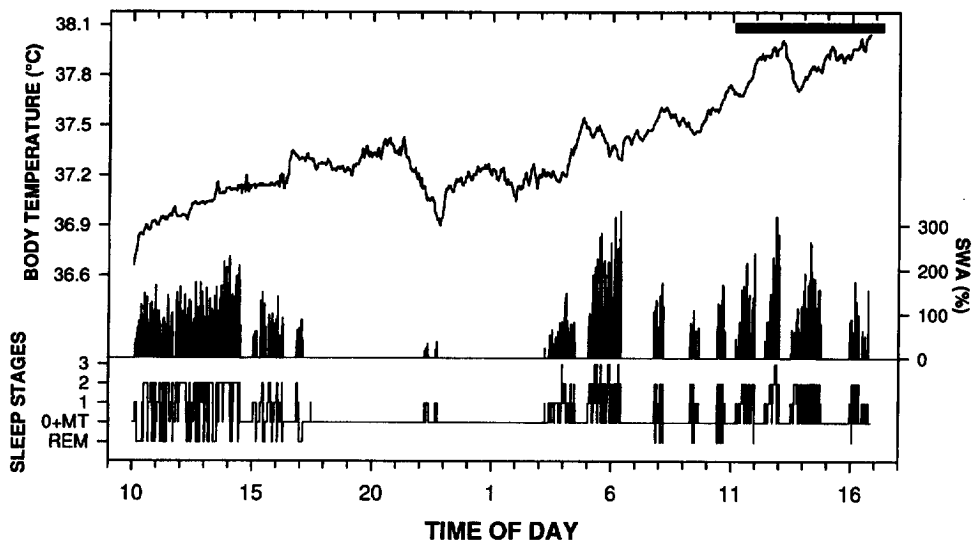


Fig. 4. Time course of rectal temperature (in minute intervals), SWA (slow wave activity; EEG power density in the 0.75–4.5 Hz range; 100% = 59.6  $\mu V^2$ ) and vigilance stages (0, wake, MT, movement time) during a constant bedrest protocol of 31 h. SWA is expressed as a percentage of the mean SWA in non-REM sleep.

malities. Together with the psychiatrist responsible for treatment, we initiated a change from haloperidol to the atypical neuroleptic clozapine.

The haloperidol washout (begun on 4 April 1994) was carried out very slowly, concomitant with slowly increasing doses of clozapine (Fig. 1B). First levomepromazine was stopped and oral haloperidol reduced, followed by biperiden reduction to 2 mg p.o./day. A change in circadian characteristics of the rest–activity cycle began as soon as oral neuroleptics were reduced and clozapine treatment began (an apparent free-running rhythm component of 31.2 h was present in the periodogram, best omega 0.26; with additional small but significant periodicities at 19 h, 47 h and 50 h). When the clozapine dosage was stabilised at 300 mg/day and no further haloperidol tablets were taken, the circadian rest–activity cycle was somewhat restored, albeit not of high amplitude. Depot haloperidol dosage was incrementally reduced and the rest–activity cycle remained quite stable with a visibly longer and more consolidated sleep period than had previously been observed (Fig. 1B, lower part, increased 24-h component in the periodogram, best

omega 0.34; no free-running components). Clinically, negative symptoms improved. The patient had more social contacts and was more communicative, which the ward staff considered a real improvement in his quality of life. It was the first time in years that the possibility of moving to live in a sheltered community could be discussed. After 1 month of clozapine treatment alone, the rest–activity cycle was again less clear (Fig. 1C, 24-h component in the periodogram, best omega 0.21; additional small free-running components at 16 h, 18 h, 27.2 h and 39.5 h). In spite of this deterioration of the rest–activity cycle, the patient's clinical state was still improved (though he remained hospitalized) and clozapine treatment has been maintained. Catatonic episodes still occur. The patient finally got tired of wearing the actigraph, so no further measurement under long-term clozapine was possible, nor would he carry out a second bedrest protocol.

#### 4. Comment

The rest–activity cycle of this schizophrenic patient was not congruent with his circadian

rhythms. Although his actogram was near-arrhythmic, a sleep–wake propensity cycle was revealed under environmentally protected constant bedrest conditions. The sleep–wake propensity cycle was phase-delayed, with a relatively short consolidated wake period of 9 h beginning at 17.27 h. In contrast, the circadian rhythms of melatonin and cortisol secretion and core body temperature were both phase-advanced compared with rhythms found in normal subjects.

Explanations must be sought on a number of levels. It is clear that there is no way of separating the phenomena observed here into psychiatric illness vs. pharmacological treatment. The delayed sleep–wake propensity cycle may be considered psychologically as a way of coping with the stress of difficult social interactions under hospitalised conditions. In the night — where he was awake, if not always active — contact with individual nursing personnel was possible. The timing of his sleep–wake propensity (which was nearly at an inverse phase to the endogenous circadian rhythms of melatonin secretion and temperature) was therefore not determined by his circadian clock, but by this ‘avoidance’ behaviour. This social characteristic has often been observed in schizophrenic patients [see Zarcone and Benson (1994), p. 915].

There is very little circadian rhythm research in schizophrenia. Free-running experiments in two schizophrenic patients suggested ‘too short a day’, which would predict advanced phase-position under entrained conditions (Mills et al., 1977), as found in this patient. A possible explanation may be that neuroleptics induce supersensitivity to light, which also results in an advanced phase position. To test this would require a specialized ophthalmologic investigation, such as we have carried out in patients chronically treated with lithium, who show retinal subsensitivity (Wirz-Justice et al., 1997) and phase-delayed circadian rhythms (Wirz-Justice, 1982). However, endocrine rhythms in untreated schizophrenic patients showed normal circadian timekeeping (Van Cauter et al., 1991). Further chronobiologically focused studies in schizophrenia appear warranted.

SW activity was abnormally low and there was no exponential decline in intensity during sleep, as normally found (Achermann and Borbély, 1987), perhaps related to the fragmented sleep episodes, which themselves may be an epiphenomenon of haloperidol treatment. These new behavioural observations (ultradian ‘bouts’) may be linked to our old, until now inexplicable observations in rats, that the rhythm of dopamine receptor binding in the striatum changed frequencies from circadian to ultradian after 2 weeks of depot fluphenazine treatment (Naber et al., 1982).

Several studies have shown that sleep architecture is changed in schizophrenia [reviewed in Zarcone and Benson (1994)]. Specifically, deficits in SWS and alterations in the amount of REM sleep, as well as reductions in REM latency, have often been observed. Neuroleptic treatment, although sedating, does not change SWS (Zarcone and Benson, 1994, p. 921). Clozapine, which also has sedative properties, has marked sleep-consolidating effects (Hinze-Selch et al., 1996), which may be related to the observed improvement in circadian amplitude.

We therefore postulate that the abnormal rest–activity cycle in this schizophrenic patient is most likely to have been induced by high-dose haloperidol, since it improved on dose reduction, concomitant with a change to clozapine treatment. In the sleep-regulation model (Daan et al., 1984), haloperidol would be considered to have lowered the upper threshold (i.e. vigilance). Such a low amplitude between the circadian thresholds delimiting wake and sleep results in ultradian rhythms and even arrhythmia. It may be relevant that the patient described his condition very precisely as a continuous ‘Dämmerzustand’, i.e. a twilight zone of never attaining proper wakefulness.

The antipsychotic effects of neuroleptics are considered to be mediated by the blockade of dopamine D2 receptors. A principal property of clozapine, which is believed to contribute to its atypical profile, is its higher affinity for D4 receptors (Mrzljak et al., 1996) and 5HT2 receptors (Meltzer, 1989). The ratio of affinities to 5HT2/D2 receptor binding sites may delineate

the atypical properties of neuroleptics (Meltzer et al., 1989). The serotonergic antagonist activity modifies the pattern of DA release, increasing dopaminergic activity in the frontal cortex. It may also contribute to the improvement in negative symptoms (Lieberman et al., 1994), also found in our patient after clozapine treatment.

What may be relevant to our interpretation is that the highest concentration of serotonin outside the raphé nuclei is found in the SCN, that this area is characterised by a high concentration of 5HT7 receptors (and D4 receptors) and that the highest binding of clozapine is found in this region (Lovenberg et al., 1993). Functionally, a selective serotonergic antagonist binding to the 5HT7 receptor has been shown to potentiate photic circadian phase shifts, i.e. increase sensitivity to light (Rea et al., 1995). Thus, improved circadian rhythmicity after clozapine in this patient may be related to its specific serotonergic antagonist actions in the SCN.

This is the first case, as far as we are aware, of long-term documentation to reveal the complex pattern of the rest–activity cycle in a treated schizophrenic patient. Previous actigraph studies have measured only 3–4 days, which may or may not reveal such abnormalities. One study found no difference in rest–activity or melatonin excretion rhythms between treated schizophrenic patients and control subjects (Scheinfeld et al., 1995), whereas in another series of studies in older schizophrenic patients, disruptions in the rest–activity cycle were attributed to the sedating effects of neuroleptics (Martin et al., 1995, 1996). Unpublished actigraphic data from Yu and Campbell (personal communication) support our contention that there are important differences between classical neuroleptics and clozapine on the organization of circadian rest–activity cycles.

We have shown that a chronic schizophrenic patient treated with haloperidol had circadian rhythms of normal amplitude and advanced in phase, even though the rest–activity cycle was nearly arrhythmic. A switch to the atypical neuroleptic clozapine improved circadian rhythmicity, although the normalizing effect was not maintained. We have no explanation for this relapse; perhaps after longer-term monotherapy, the

rhythm would have stabilized. The hypothesis arising from these observations is that the rest–activity cycles of schizophrenic patients treated with clozapine should be normally entrained, whereas those of patients treated with typical neuroleptics should be disturbed. Indeed, a subsequent small pilot study has shown a marked difference that supports this dual conceptualization. Three clozapine-treated patients all had rigidly organised, high-amplitude circadian rest–activity cycles, whereas three out of four patients treated with typical neuroleptics had disturbed ones, albeit not as extreme as in this first patient. The rhythm abnormalities were individually different (phase-delayed, free-running, or circadian rest–activity cycles) (Haug et al., 1996). Is development of an abnormal rest–activity cycle related to drug dosage, to sedation, to predilection for later dyskinesias, to clinical course, or to lack of improvement of negative symptoms? Activity monitoring may provide a non-invasive method to answer these questions of experimental psychopathology and may ultimately offer useful information in the selection of the most appropriate antipsychotic medication and dose for an individual schizophrenic patient.

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