Disturbed Circadian Rest-Activity Cycles in Schizophrenia Patients: An Effect of Drugs?

by Anna Wirz-Justice, Hans-Joachim Haug, and Christian Cajochen

Abstract

The circadian rest-activity cycle of schizophrenia patients stabilized for more than a year on monotherapy with a "classical" neuroleptic (haloperidol, flupentixol) or with the atypical neuroleptic clozapine was documented by continuous activity monitoring for 3–7 weeks. In this pilot study, the three patients treated with clozapine had remarkably highly ordered rest-activity cycles, whereas the four patients on classical neuroleptics had minor to major circadian rhythm abnormalities. This is the first documentation of circadian rest-activity cycle disturbances in schizophrenia related to class of drug.

Keywords: Circadian rest-activity cycle, schizophrenia, neuroleptics, clozapine.

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Mammalian circadian rest-activity or sleep-wake cycles are generated by the circadian pacemaker in the suprachiasmatic nuclei (SCN) of the hypothalamus and synchronized to the external light-dark cycle by retinal input (Turek and Zee 1999). Hypothalamic damage in this area has been shown to disrupt the human circadian sleep-wake cycle as well as cognitive and behavioral functioning (Cohen and Albers 1991).

We previously measured the circadian rest-activity cycle in a schizophrenia patient over 7 months, documenting an arrhythmic pattern that appeared to be a result of the sedative action of haloperidol treatment, since it improved with dose reduction and even more after a switch to treatment with clozapine (Wirz-Justice et al. 1997). Other circadian rhythms measured in this patient (melatonin, cortisol, core body temperature) were of normal amplitude, albeit advanced in phase, suggesting that circadian pacemaker function was intact. This single case was used to model putative effects of neuroleptic drugs on sleep regulation (Daan et al. 1984). When simulating decreased arousal (in this model by reducing the level of the upper circadian threshold delimiting sleep onset), the rest-activity cycle first showed ultradian (napping) patterns and later became arrhythmic. The difference between the two drug treatments in a single patient led us to infer that rest-activity cycle integrity was related to the type of drug, since no other factors changed during the period of observation.

Strong sleep-consolidating effects have been described for clozapine (Hinze-Selch et al. 1997). However, with respect to the circadian rhythm organization of sleep, it may be relevant that in the brain, clozapine shows the highest specific binding in the SCN itself (Lovenberg et al. 1993). This area is characterized by a high concentration of $5HT_7$ receptors (and D_4 receptors). It has been shown that selective serotonergic antagonist binding to the $5HT_7$ receptor potentiates photic-induced circadian phase shifts (i.e., increases sensitivity to light) (Rea et al. 1995). Thus, the improved circadian rhythmicity after clozapine treatment in our patient may have been related to these specific serotonergic antagonist actions in the SCN.

The hypothesis arising from this case study is that the circadian rest-activity cycles of clozapine-treated schizophrenia patients should be normal and those of patients treated with classic neuroleptics may be disturbed.

Until now there have been very few actigraphy studies in schizophrenia, and these have measured the rest-activity cycle for periods insufficiently long to analyze rhythm disturbances in detail (3–4 days). Both normal (Scheinfeld et al. 1995) and abnormal (Martin et al. 2001; Yu and Campbell, unpublished data) rest-activity cycles have been found. In a small study, haloperidol-treated patients manifested less robust circadian activity patterns and more daytime sleep than patients treated with risperidone (which also has serotonergic antagonist actions) (Martin et al. 2001). We initiated this pilot study to gather

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individual rest-activity data over a longer period to ascertain whether such abnormalities existed, and if they might be indeed related to the type of drug.

Methods

Seven schizophrenia patients who had received monotherapy for at least 1 year prior to the study participated. All except one with a schizotypal disorder (patient 4; ICD–10: F 21.0) were diagnosed as having paranoid schizophrenia (F 20.0). Five were hospitalized, one was a day patient (patient 3), and one was ambulatory (patient 4). Their clinical characteristics, treatment, and Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and Brief Psychiatric Rating Scale (Overall and Gorham 1962) scores are presented in table 1.

Patients were asked to wear an activity monitor (model Gähwiler, Zürich) on the nondominant wrist, day and night; compliance was remarkably good after the apparatus, its function, and an actogram had been carefully explained. Informed consent was obtained from each patient. Patients agreed to participate in the study and abstain from alcohol. The duration of activity monitoring varied from 3 to 7 weeks.

The activity monitors stored hand movements summed over 1-minute intervals; the 24-hour rhythm was double-plotted in a raster format that permits better visualization of the patterns. Circadian rhythms were subjected to periodogram analysis, which extracts all statistically significant rhythmic components, usually the main peak at 24 hours with its harmonics at 12 hours and 36 hours, as well as any at an unusual period. The "best tau" estimates the fit of the data to the 24-hour day, and the "best omega" is a measure of amplitude of the 24-hour peak (Klemfuss and Clopton 1993).

Results

The patients' clinical state, as reflected in PANSS and BPRS scores evaluated before and after activity monitoring, did not change. Negative symptoms were found only in patients treated with classical neuroleptics (table 1). Individual actograms are presented in figure 1. The most striking finding is that each patient on classical neuroleptics (patients 1–4) had some circadian abnormality in the rest-activity cycle. This was also noticeable in the average 24-hour patterns of activity (figure 2), with higher nocturnal movement and a less clear definition of activity onset in the morning and offset in the evening. In contrast, patients treated with clozapine (patients 5–7) had an extraordinarily synchronized and highly replicable rest-activity cycle.

Periodogram analysis of the activity data is presented in figure 2 and table 2 and can be summarized as follows. All patients were synchronized (entrained) to the external 24-hour day and social environment ("zeitgebers"), as demonstrated by the "best tau" value of 24 hours. The "best omega" value indicates the amplitude of the 24-hour peak: in healthy subjects this is quite high (e.g., in one of our control groups, $n = 7$ men, 0.70 ± 0.08, standard deviation). Normal values were found in five patients, but two patients treated with flupentixol were only half as high (patients 1 and 4). Although the main peak frequency was always 24 hours (and usually with harmonics at 12 hours and 36 hours), other significant components were present to a lesser degree (figure 2).

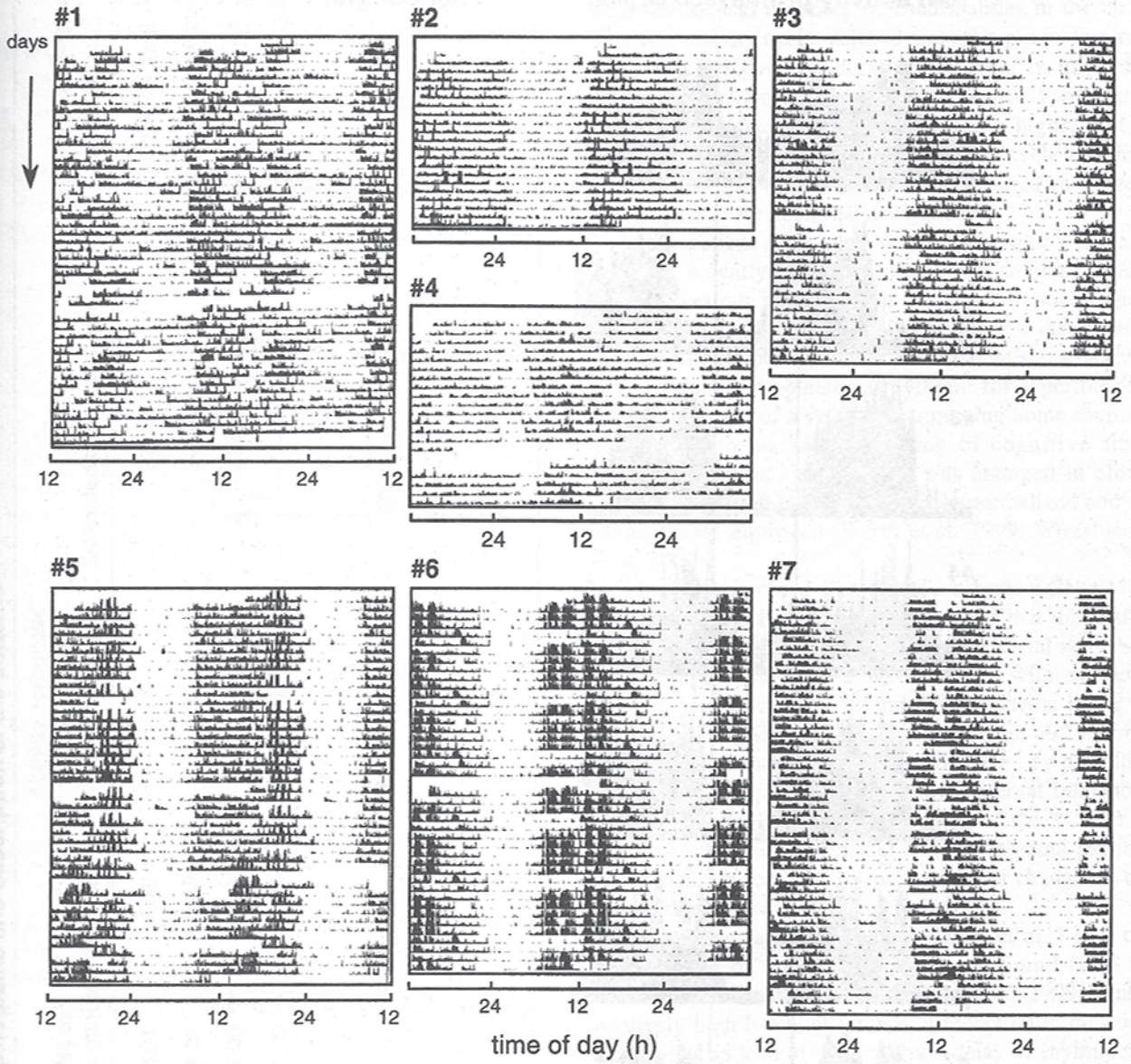
Patient 1 showed the most abnormal rest-activity cycle, with a circabidian component (double-length, approximately 48 hours), as well as free-running components (peaks at 42 hours and 46 hours). Patient 2 was a long sleeper with a delayed sleep phase syndrome. Patient 3, a day patient, was also a long sleeper, presenting with the most regular rest-activity cycle of this group, but this patient had many nocturnal awakenings. Patient 4, an ambulatory patient, had a very short sleep period of about 4 hours and showed changing bedtimes and wakeup times, i.e., "relative coordination" of the rest-activity cycle. In contrast, the three clozapine-treated patients had very rigidly entrained rest-activity cycles and distinctive onset and offset of activity. In particular, the remarkable pattern

Table 1. Clinical characteristics of the seven schizophrenia patients

Patient	Year of birth	Sex	ICD–10 diagnosis	Year of first diagnosis	PANSS score[1]	BPRS score	Drug and dose
1	1948	M	F 20.0	1972	–9	33	Flupentixol, 8 mg/day
2	1956	M	F 20.0	1977	–8	38	Haloperidol, 8 mg/day
3	1945	M	F 20.0	1962	10	45	Flupentixol, 13 mg/day
4	1944	M	F 21.0	1970	1	44	Flupentixol, 8 mg/day
5	1943	M	F 20.0	1964	4	64	Clozapine, 250 mg/day
6	1952	M	F 20.0	1969	2	27	Clozapine, 250 mg/day
7	1962	F	F 20.0	1978	4	36	Clozapine, 300 mg/day

Note.— PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale.
[1]PANSS scores are combination scores (positive type, score > 3; negative type, score < 8).

Figure 1. Actograms of 7 schizophrenia patients on monotherapy for at least a year[1]



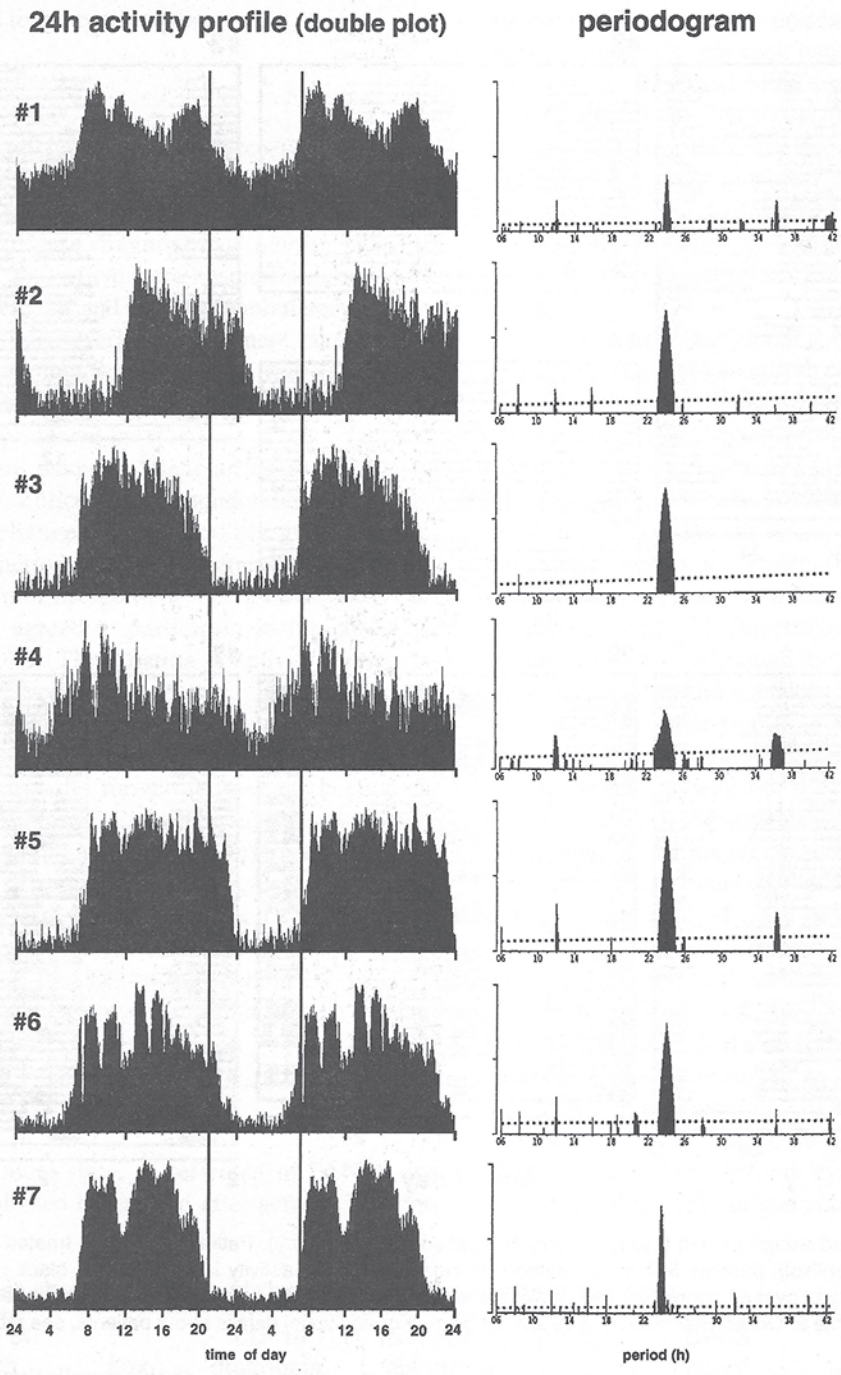
[1] All patients were hospitalized except patient 3 (day patient) and patient 4 (ambulatory). Patients 1–4 were treated with classical neuroleptics (haloperidol or flupentixol); patients 5–7 were treated with clozapine. Motor activity is registered in black (1-minute bins) and graphed as a double 24-hour plot over 48 hours (first line = days 1 and 2, second line = days 2 and 3, etc.). The number of days registered (vertical lines) are noted in table 2. Occasional missing data are left blank. For additional details about patients, see table 1.

of patient 6 appears to mirror precisely, week after week, the pattern of ward activities during the week, followed by less structured days and sleeping late on weekends.

Discussion

These schizophrenia patients treated over a year with a single antipsychotic medication showed a dichotomy of circadian rhythm organization. Major limitations to this pilot study are the small number of patients, without any pretreatment baseline or the possibility (for ethical reasons) of taking the patients off drugs. We postulate that the differences found are related to the type of drug, with *of course the caveats appropriate to possible individual* differences in illness, other factors that may have modified the response to treatment per se, and the myriad number of uncontrolled variables in such an observational trial. As a group selected only by the criteria of being on stabilized monotherapy and compliant with respect to actimetry, these patients may not be representative of

Figure 2. Averaged circadian rest-activity cycle profile



Left side: The activity profile over 24 hours (1-minute bins, double-plotted over 48 hours for better visualization) was averaged from data collected for each patient (number of days analyzed, table 2). The vertical line at 21 hours indicates the usual bedtime on the ward; the line at 7 hours, the usual wakeup time. This permits the sleep/rest period between these times to be judged as quiet/interrupted by movement, early/late (e.g., the delayed wakeup time in patient 2). The day-to-day replicability in the clozapine-treated patients is reflected in the sharp peaks and troughs of the average pattern (e.g., the midday nap in patients 6 and 7). Fuzziness throughout the average day and night reflects changing day-to-day patterns (e.g., the very abnormal pattern, including circabidian days in patient 1).

Right side: Periodogram analyses of sections of the patients' actograms. The sloping horizontal line delineates the significance level at $p < 0.01$. The main peak at 24 hours reflects entrainment to the 24-hour day, with occasional harmonics at 12 hours and 36 hours. The periodogram was calculated from the following number of days for each patient: patient 1, 48 days; patient 2, 20 days; patient 3, 20 days; patient 4, 14 days; patient 5, 20 days; patient 6, 21 days; patient 7, 51 days.

Table 2. Periodogram analysis of the actograms and description of the patterns

Patient number	Days studied	Days analyzed	Best tau (hours:minutes)	Best omega	Activity acrophase (time of day, hours:minutes)	Estimated timing of sleep	Description of circadian phenomena
1	48	48	24:01	0.38	13:10	21–7h	Circabidian days
2	20	20	24:02	0.68	17:17	2–12h	Delayed sleep phase
3	39	20	24:00	0.79	12:49	21–7h	
4	22	14	24:00	0.39	11:02	~ 24–4h	Free running (relative coordination)
5	44	20	24:01	0.76	15:03	23–7h	
6	43	21	24:00	0.74	13:54	22–6h	Nap 11–13h
7	52	51	24:01	0.72	13:34	21–7h	Nap 11–13h

schizophrenia patients as a whole. However, a certain consistency was apparent: patients treated with classical neuroleptics had a variety of abnormalities in the circadian rest-activity cycle: delayed circadian phase, free running with relative coordination, circabidian days, and enhanced or reduced amount of rest compared with activity. Patients treated with clozapine had a highly regular and reproducible circadian rest-activity cycle synchronized at the appropriate phase to the external social zeitgebers, and fewer nocturnal disturbances.

In a patient with early-onset Alzheimer's disease, we have recently observed remarkably similar changes that support our interpretation that this chronobiological finding may be drug- and not illness-related. After initiation of haloperidol treatment, this patient's rest-activity cycle became completely arrhythmic for a period of 2 months (in spite of a very regular nursing home routine), together with marked worsening of cognitive state. When the patient's medication was changed to clozapine, the circadian rest-activity cycle normalized and the clinical state improved (Werth et al. 1999; Wirz-Justice et al. 2000).

It may be argued that there is a basic SCN-related disturbance in schizophrenia patients and that this disturbance could be "masked" by the regular social zeitgebers and the light-dark cycle so as to present with an apparently intact rest-activity rhythm. That patients living on the same ward, with the same daily activities and environment, showed such different patterns (e.g., as patients 1 and 6) argues against masking from external influences. No evidence exists so far for a lesion of the SCN or an abnormal circadian pacemaker in schizophrenia patients; rather, other factors may be responsible for changes in circadian sleep-wake cycle organization.

The sleep regulation model (Daan et al. 1984) can simulate all of the patterns we have found (D.G.M. Beersma, personal communication, June 30, 1999). Under relatively high levels of arousal, a reduction in circadian amplitude can lead to, first, a phase delay of rhythmicity, then relative coordination, and then possibly circabidian patterns. In contrast, a reduction in arousal per se leads to ultradian rhythmicity and arrhythmia, as previously observed (Wirz-Justice et al. 1997). Thus, from these preliminary data, it may be the drugs and not the illness that change certain circadian characteristics: classical neuroleptics might decrease circadian amplitude and/or arousal level (dependent on individual response/dosage), whereas clozapine enhances synchrony of the rest-activity cycle with the external 24-hour day (whether through increasing sensitivity to light or circadian amplitude in the SCN). In these chronically ill patients, we cannot stop treatment to see if this rhythm abnormality is reversible; however, in two case studies, one patient with schizophrenia (Wirz-Justice et al. 1997) and one with Alzheimer's

disease (Wirz-Justice et al. 2000), we have been able to restore circadian rest-activity cycle integrity (as well as improve clinical state) by changing medication from haloperidol to clozapine.

Given these patterns, and the lack of negative symptoms in the clozapine-treated patients, we are now investigating a larger group of schizophrenia patients to see if there is a relationship between the integrity of the circadian rest-activity cycle, type of drug, and, just as important, the clinical course.

References

Cohen, R.A., and Albers, H.E. Disruption of human circadian and cognitive regulation following a discrete hypothalamic lesion: A case study. *Neurology,* 41:726–729, 1991.

Daan, S.; Beersma, D.G.M.; and Borbély, A.A. Timing of human sleep: Recovery process gated by a circadian pacemaker. *American Journal of Physiology,* 246:R161–R178, 1984.

Hinze-Selch, D.; Mullington, J.; Orth, A.; Lauer, C.J.; and Pollmächer, T. Effects of clozapine on sleep: A longitudinal study. *Biological Psychiatry,* 42:260–266, 1997.

Kay, S.R.; Fiszbein, A.; and Opler, L.A. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin,* 13(2):261–276, 1987.

Klemfuss, H., and Clopton, P.L. Seeing tau: A comparison of six methods. *Journal of Interdisciplinary Cycle Research,* 24:1–16, 1993.

Lovenberg, T.W.; Baron, B.M.; De Lecea, L.; Miller, J.D.; Prosser, R.A.; Rea, M.A.; Foye, P.E.; Racke, M.; Slone, A.L.; Siegel, B.W.; Danielson, P.E.; Sutcliffe, J.G.; and Erlander, M.G. A novel adenylyl cyclase-activating serotonin receptor ($5HT_7$) implicated in the regulation of mammalian circadian rhythms. *Neuron,* 11:449–458, 1993.

Martin, J.; Jeste, D.V.; Caliguiri, M.P.; Patterson, T.; Heaton, R.; and Ancoli-Israel, S. Actigraphic estimates of circadian rhythms and sleep/wake in older schizophrenia patients. *Schizophrenia Research,* 47:77–86, 2001.

Overall, J.E., and Gorham, D.R. The Brief Psychiatric Rating Scale. *Psychological Reports,* 10:799–812, 1962.

Rea, M.A.; Barrera, J.; Glass, J.D.; and Gannon, R.L. Serotonergic potentiation of photic phase shifts of the circadian activity rhythms. *NeuroReport,* 6:1289–1292, 1995.

Scheinfeld, C.; Treves, I.; Neumann, M.; and Dagan, Y. Objectively measured sleep-wake patterns in schizophrenic patients [Abstract]. *Sleep Research,* 24A:277, 1995.

Turek, F.W., and Zee, P.C., eds. *Regulation of Sleep and Circadian Rhythms.* Vol. 133. Lung Biology in Health and Disease, Lenfant, C., ed. New York, NY: Marcel Dekker, 1999.

Werth, E.; Savaskan, E.; Fontana Gasio, P.; van Someren, E.J.W.; Hock, C.; Kaiser, H.; and Wirz-Justice, A. Rest-activity cycle and light exposure of hospitalized Alzheimer's patients. [Abstract]. *Sleep,* 22(Suppl):S265, 1999.

Wirz-Justice, A.; Cajochen, C.; and Nussbaum, P. A schizophrenic patient with an arrhythmic circadian rest-activity cycle. *Psychiatry Research,* 73:83–90, 1997.

Wirz-Justice, A.; Werth, E.; Savaskan, E.; Knoblauch, E.; Fontana Gasio, P.; and Müller-Spahn, F. Haloperidol disrupts, clozapine reinstates the circadian rest-activity cycle in a patient with early-onset Alzheimer's disease. *Alzheimer Disease and Associated Disorders,* 14:212–215, 2000.

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