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Review article

Sleep and circadian rhythm dysregulation in schizophrenia

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ABSTRACT

Sleep-onset and maintenance insomnia is a common symptom in schizophrenic patients regardless of either their medication status (drug-naive or previously treated) or the phase of the clinical course (acute or chronic). Regarding sleep architecture, the majority of studies indicate that non-rapid eye movement (NREM), N3 sleep and REM sleep onset latency are reduced in schizophrenia, whereas REM sleep duration tends to remain unchanged. Many of these sleep disturbances in schizophrenia appear to be caused by abnormalities of the circadian system as indicated by misalignments of the endogenous circadian cycle and the sleep–wake cycle. Circadian disruption, sleep onset insomnia and difficulties in maintaining sleep in schizophrenic patients could be partly related to a presumed hyperactivity of the dopaminergic system and dysfunction of the GABAergic system, both associated with core features of schizophrenia and with signaling in sleep and wake promoting brain regions. Since multiple neurotransmitter systems within the CNS can be implicated in sleep disturbances in schizophrenia, the characterization of the neurotransmitter systems involved remains a challenging dilemma.

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1. Introduction

Schizophrenia is characterized by positive symptoms, such as delusions and hallucinations, together with negative symptoms, mainly lack of motivation and interest, flattened affect and social withdrawal. Insomnia is a common feature in schizophrenia, although it is seldom the predominant complaint (Anonymous, 2000). As comorbid insomnia, it belongs to the most frequent type of insomnia (McCrae and Lichstein, 2001). According to the

Abbreviations: AANAT, (Alkylamine N-Acetyl Transferase); ASMT, (Acetylserotonin methyl transferase formerly HIOMT); BZD, (Benzodiazepine); CRY, (Cryptochrome); N2, (Non REM Sleep Stage 2); N3, (Non REM Sleep Stage 3); PER, (Period); REMOL, (Rapid Eye Movement Sleep Onset Latency); SCN, (Suprachiasmatic Nuclei); SNP, (Single Nucleotide Polymorphism).

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Diagnostic and Statistical Manual of Mental Disorders (Anonymous, 2000), comorbid insomnia is related to a mental disorder, to another sleep disorder, to a general medical condition, or to the effects of medication or of drugs of abuse. Studies of sleep in schizophrenia, however, have not provided consistent results (Benca et al., 1992; Keshavan et al., 1990).

As indicated by Van Kammen et al. (1986), sleep disturbances in schizophrenia can be sufficiently severe to warrant clinical attention. Ritsner et al. (2004) studied the relationship between subjective quality of sleep and perceived quality of life among schizophrenic patients; patients with insomnia reported lower mean scores on all quality of life domains and these were independent of comorbid depression, side-effects related to antipsychotic medication, or distress. Although treatment of the underlying disorder with antipsychotic drugs tends to improve insomnia in patients with schizophrenia, drug administration does not always result in better sleep (Monti, 2004). Benzodiazepine (BZD) and non-BZD hypnotics are often used adjunctively to improve sleep in this patient group.

2. Temporal disorganization and dysfunctional circadian rhythms in schizophrenia

Sleep is a prominent part of the 24-h circadian cycle and is regulated by a complex interplay of sleep and wake promoting and inhibiting brain areas. The regulation of sleep and wakefulness can be conceptualized by the two-process model (Borbély, 1982), which comprises the circadian process and the homeostatic process. The circadian component describes the intrinsic circadian timing and synchronization of body functions to the light–dark cycle of day and night. The homeostatic or evoked component regulates the "need for sleep" which builds up during wakefulness and dissipates during sleep.

Several studies have documented abnormalities in the circadian organization of sleep–wake cycles in patients diagnosed with schizophrenia, which can result in difficulties in initiating and maintaining sleep. These circadian misalignments range from delayed and advanced sleep phase, free running rest–activity patterns to irregular sleep–wake patterns (Bromundt et al., 2011; Wirz-Justice et al., 1997, 2001; Wulff et al., 2006, 2012).

Melatonin profiles, commonly used as an endocrine marker of the individual's circadian rhythm, help to detect circadian misalignments with the sleep–wake cycle or lack of entrainment, i.e. the desynchronization to the light–dark cycle. A recent ambulatory study using saliva samples to determine melatonin and wrist actimetry for assessing circadian rhythms has found circadian misalignments of sleep timing with bedtime earlier than the melatonin onset and fragmented sleep epochs in some schizophrenic patients, with the consequence of significantly worse cognitive performance than in patients with synchronized circadian rhythms (Bromundt et al., 2011). Another study in schizophrenic patients has reported markedly delayed and/or free-running melatonin phases and sleep–wake cycles, and therefore the circadian rhythms were badly entrained to the light–dark cycle (Wulff et al., 2012).

A circadian phase advance of the melatonin profile was reported by Rao et al. (1994) in schizophrenic patients, and in isolation experiments a remarkable shorter circadian period of 23.7 h was revealed in two patients suffering from schizophrenia (Mills et al., 1977). A case study under controlled "constant bed rest" laboratory conditions for more than 30 h has also shown a phase advance of melatonin secretion and core body temperature, but a delayed rhythm for sleep propensity (Wirz-Justice et al., 1997).

In a recent study including 34 schizophrenia outpatients and 34 healthy subjects, saliva melatonin was collected under dim light conditions hourly from 20:00 h to 23:00 h. Wrist actimetry recordings and a sleep diary were used for sleep–wake cycle assessment (Afonso et al., 2011). Schizophrenic patients showed a reduced sleep efficiency, longer sleep latencies and increased number of nighttime awakenings. In addition, there was a loss of the negative correlations of saliva melatonin levels with sleep latency and total sleep time and positive correlations with sleep efficiency that were present in controls indicating an interference with endogenous melatonin sleep-promoting action in schizophrenia (Afonso et al., 2011).

Thus, schizophrenic patients often show a change in the circadian phase angle, i.e. the difference among the timing of the circadian melatonin profile, the timing of the major sleep and wake episodes and the external day–night cycle. Along these lines goes the finding that schizophrenic patients can have a blunted circadian variation of melatonin secretion (Bersani et al., 2003; Ferrier et al., 1982; Monteleone et al., 1992; Robinson et al., 1991). However, these latter studies were not controlled for prior light history that may have confounded the results. It should be noted that circadian rhythm disruptions are common, but are not specific to this patient group.

The mammalian circadian timing apparatus comprises oscillators that are found universally at a cellular level and a central pacemaker generator located in the hypothalamic suprachiasmatic nuclei (SCN) (Dibner et al., 2010). Circadian rhythms are driven by the self-regulatory interaction of a set of clock genes and their protein products (Ko and Takahashi, 2006; Mazzoccoli et al., 2012). Expression of proteins from one positive and one negative loop oscillates, forming a circadian rhythm. The positive drive to the daily clock is constituted by helix–loop–helix, PAS-domain containing transcription factor genes (*Clock* and *Bmal1*). The negative loop consists mainly of *Per* and *Cry* proteins, which provide a negative feedback signal on *Clock*/*Bmal1* drive to complete the 24-h cycle (Mazzoccoli et al., 2012). Since dopaminergic signaling through D_2 receptors appears to be associated with increased *Clock*:*Bmal1* activity (Yujnovsky et al., 2006), a possible link between the dopaminergic hypothesis of schizophrenia and circadian abnormalities in these patients is worth exploration.

Evidence linking circadian clock gene polymorphisms with schizophrenia is limited. In one study, SNP analysis of the *Clock* gene demonstrated that T3111C polymorphism showed a transmission bias in a sample of 145 Japanese schizophrenic subjects relative to healthy controls (Takao et al., 2007). The authors suggested that this SNP, which may be associated with aberrant dopaminergic transmission at the SCN, presumably underlies the pathophysiology of schizophrenia. *Per3*, but not *Per2* abnormalities were associated with schizophrenia in another study (Mansour et al., 2006). Post-mortem studies have shown decreased expression of the *Per1* mRNA in the temporal lobe of schizophrenic subjects compared with age-matched normal controls (Aston et al., 2004). Another circadian gene, *Cry1* was hypothesized to be a candidate gene for schizophrenia based on its location near a linkage hotspot for schizophrenia on chromosome 12q24 (Peng et al., 2007). The fact that *Cry1* is expressed in dopaminergic cells in the retina and that its expression influences the effects of psychoactive drugs lends support to this hypothesis.

However, the association between clock genes and schizophrenia is not undisputed, since positive studies had smaller samples (around 150 patients) than those needed for genetic association studies (Mansour et al., 2006; Takao et al., 2007; Zhang et al., 2011). Moreover, larger studies have failed to confirm those initial findings (Kishi et al., 2009; Purcell et al., 2009; Stefansson et al., 2009), thus the possible association between a specific subtype of schizophrenia and any of the clock genes is far from resolution.

Another protein that has been implicated in schizophrenia is SNAP-25. Decreased levels of SNAP-25 have been reported in the hippocampus (Fatemi et al., 2001; Thompson et al., 2003a; Young et al., 1998) while increased levels have been reported in the cerebrospinal fluid (Thompson et al., 1999, 2003b). Genetic studies also implicate SNAP-25 in schizophrenia (Arinami et al., 2005; Carroll et al., 2009; Fanous et al., 2010; Lewis et al., 2003). It has been reported that in vitro treatment of rat SCN with SNAP-25 at CT (circadian time) 14 h

or CT20 induced phase delays or advances respectively (Ding et al., 1994). Moreover, there is a circadian rhythm of expression of SNAP-25 in rat SCN (Panda et al., 2002). In vitro administration of botulinum toxin A blocks exocytosis and compromises circadian gene expression in the rodent SCN (Deery et al., 2009). Based on these findings studies were done of the blind-drunk mouse which has a dominant mutation in SNAP-25 and has been used as a model of schizophrenia (Oliver et al., 2012). Despite normal retinal inputs and clock gene rhythms in the SCN, rest–activity rhythms were disrupted and the 24-h rhythms of arginine vasopressin in the SCN and plasma corticosterone were both markedly phase advanced. Thus, there is a link between circadian activity disruption and synaptic dysfunction caused by SNAP-25 disruption. Taken together these findings suggest that alterations in SNAP-25 function may underlie some of the symptoms in schizophrenia and especially those related to sleep–wake timing.

3. Potential therapeutic value of melatonin and its analogs in schizophrenia

Several studies have shown the importance of melatonin both for the initiation and for maintenance of sleep (see for a recent review Cardinali et al., 2012). As melatonin exhibits both hypnotic and chronobiotic properties, it has been used for treatment of age-related insomnia as well as of other primary and secondary insomnia (Leger et al., 2004; Zhdanova et al., 2001). A recent consensus report of the British Association for Psychopharmacology on evidence-based treatment of insomnia, parasomnia and circadian rhythm sleep disorders recommended melatonin as the first choice treatment when a hypnotic is indicated in patients over 55 years (Wilson et al., 2010).

Because of the well-established role of melatonin in sleep entrainment and enhancement, studies have been done of polymorphisms of melatonin related genes in schizophrenia. No studies of the alkylamine N-acetyl transferase (AANAT) gene, the gene responsible for the timing of melatonin secretion (Brown et al., 2009) have been reported. Acetylserotonin methyl transferase (ASMT, formerly HIOMT), the gene responsible for the amount of melatonin produced (Brown et al., 2009), was reported to show no difference in activity between autopsied pineals from schizophrenics and controls (Owen et al., 1983). However study of XY homologous genes found a triplication in an area related to ASMT in an XX schizophrenic patient, a polymorphism that was not found in other patients (Ross et al., 2003). A systematic study of other ASMT gene polymorphisms has yet to be done. Because neither of these genes have been examined in detail it is not known whether the reported alterations in timing or quantity of melatonin may be due to polymorphisms in these genes.

An association of polymorphism in the promoter of the MT_1 melatonin receptor gene with schizophrenia and with insomnia symptoms in schizophrenia patients has been reported (Park et al., 2011). The authors genotyped two promoter single nucleotide polymorphisms using direct sequencing in 289 schizophrenia patients and 505 control subjects. One of these single nucleotide polymorphisms was found associated with schizophrenia. It was also associated with insomnia symptoms of schizophrenia but not with hypersomnia symptoms. The authors concluded that the MT_1 melatonin receptor gene may be a susceptibility gene for schizophrenia and may be associated with insomnia symptoms exhibited in schizophrenia patients (Park et al., 2011). This genetic polymorphism might reduce the effect of endogenous melatonin thus lending support to the use of melatonin supplementation.

It is of considerable interest that several studies have shown melatonin produces inhibition of dopamine release (Dubocovich, 1983; Zisapel and Laudon, 1982), reduced dopamine content (Alexiuk and Vriend, 1993; Jaliffa et al., 2000), increased turnover (Alexiuk and Vriend, 1991, 2007; Alexiuk et al., 1996) and alteration of dopamine receptor activation (Alexiuk and Vriend, 2007; Hamdi, 1998; Iuvone and Gan, 1995; Khaldy et al., 2002; Zisapel, 2001) in areas of the mammalian brain (retina, hypothalamus, hippocampus, medulla-pons, and striatum). In mouse striatum the circadian rhythm of dopamine has been shown to be linked to the melatonin rhythm (Khaldy et al., 2002). It has also been shown that the MT_1 receptor mediates changes in clock gene expression in the mouse striatum; an action that may be relevant to the pathobiology of dopaminergic mediated behaviors (Imbesi et al., 2009). Positron emission tomography (PET) studies of dopamine function using 18F-DOPA as a ligand reveal seasonal changes in presynaptic dopamine synthesis in the caudal putamen (Eisenberg et al., 2010; Kaasinen et al., 2012). In the human MT_1 and MT_2 receptors have been localized widely in central nervous system and retina (Brunner et al., 2006; Savaskan et al., 2002, 2005, 2007; Scher et al., 2002; Song et al., 1997). MT_1 receptors are localized on dopaminergic neurons in the human retina (Scher et al., 2002) and MT_1 receptors have a regional and cellular expression profile in the human central dopaminergic system, being present in regions of Brodmann's area 10 (prefrontal cortex), putamen, caudate nucleus, nucleus accumbens, substantia nigra, amygdala and hippocampus (Uz et al., 2005). Alterated effects of melatonin on these systems may be related to the pathophysiology of schizophrenia.

In addition melatonin has protective effects on dopaminergic systems both as a direct free-radical scavenger and as an indirect anti-oxidant (Hardeland et al., 2011). Several studies have shown that melatonin is protective against dopaminergic neurodegeneration in rat model systems (Singhal et al., 2012). Moreover it attenuates dopamine decreases in the nigrostriatal system in the zitter rat, a species with age related degeneration of the dopaminergic system (Hashimoto et al., 2012). Thus decreases in melatonin may be relevant to the neurodegeneration thought to occur in schizophrenia (Meyer-Lindenberg, 2011).

As mentioned above, the majority of patients with schizophrenia suffer from disturbed sleep and the usual treatment of these patients is the supplementation of antipsychotics with BZP. However, prolonged BZP administration is associated with numerous adverse reactions including sedation, cognitive impairment, risk of falls, development of tolerance, physical and psychological dependence, and rebound insomnia (Wilson et al., 2010). Moreover, BZP treatment is associated with reduced secretion of melatonin (Hajak et al., 1996; Kabuto et al., 1986) presumably acting via BZP receptors present in human pineal gland (Lowenstein et al., 1984) or via those in the SCN (Strecker et al., 1999; Wan et al., 1999), and the association of increased risk of death in schizophrenia patients treated with a combination of antipsychotics and long-acting BZP has been reported (Baandrup et al., 2010).

Therefore, melatonin could be an alternative to treat sleep disturbances in psychiatric patients with circadian misalignments. Three studies have been published on the clinical use of melatonin in schizophrenia patients. In a randomized, blinded, cross-over study measuring urinary melatonin output in patients with chronic schizophrenia and assessing the effects of melatonin replacement on their sleep quality, Shamir et al. (2000a) reported that melatonin (2 mg, controlled release) improved sleep efficiency as evaluated by wrist actimetry (see Table 1). In a second study 19 patients with DSM-IV schizophrenia received the normal treatment regimen and melatonin or placebo for 2 treatment periods of 3 weeks each with 1 week washout between treatment periods (Shamir et al., 2000b). For measuring endogenous melatonin production, urine was collected from each patient every 3 h between 9:00 p.m. and 9:00 a.m. All patients had low melatonin output. Melatonin replacement significantly improved rest-derived sleep efficiency and increased REM sleep latency compared with placebo and this improvement was significantly greater in low-efficiency than high-efficiency sleepers. The authors concluded that melatonin improves sleep efficiency in patients with schizophrenia whose sleep quality is poor. Suresh Kumar et al. (2007) reported that melatonin improved the subjective quality of sleep in a randomized, double-blinded, placebo-controlled trial including 40 stable DSM-IV schizophrenic outpatients with initial

Table 1
Abnormalities in the circadian rhythms in schizophrenic patients and use of melatonergic ligands.

Variable	Reference(s)
Abnormalities in the circadian organization	
– delayed and advanced sleep phase	Wirz-Justice et al. (1997, 2001),
– free running rest-activity patterns	Wulff et al. (2010, 2012),
– irregular sleep-wake patterns	Bromundt et al. (2011)
– circadian misalignments	
Melatonin profiles	
– circadian phase advance of melatonin secretion	Rao et al. (1994), Wirz-Justice et al. (1997)
– loss of negative correlation of saliva melatonin levels with sleep latency and total sleep time and positive correlation with sleep efficiency	Afonso et al. (2011)
Melatonin and agomelatine administration	
– melatonin (2 mg controlled release/night) improved sleep efficiency	Shamir et al. (2000a,b)
– melatonin (3–12 mg/night) improved the quality and depth of nighttime sleep	Suresh Kumar et al. (2007)
– agomelatine (25 mg/day) allowed a patient (case report study) with chronic schizophrenia and severe insomnia to completely suspend benzodiazepine hypnotic medication	Morera-Fumero and Abreu-Gonzalez (2010)

insomnia of at least 2 weeks' duration. Patients were randomly assigned to augment their current medications with either flexibly dosed melatonin (3–12 mg/night; N = 20) or placebo (N = 20). Relative to placebo, melatonin (modal stable dose 3 mg) significantly improved the quality and depth of nighttime sleep, reduced the number of nighttime awakenings, and increased the duration of sleep without producing a morning hangover. A randomized clinical trial to examine whether prolonged-release melatonin has a role in withdrawing long-term benzodiazepine administration in schizophrenia patients is currently under way (Baandrup et al., 2011).

Since melatonin has a short half-life (less than 30 min) it is effective in sleep entrainment but its efficacy in maintaining sleep has not been consistently demonstrated. Thus prolonged release preparations of melatonin or melatonin agonists with a longer duration of action on sleep regulatory structures in the brain are being developed (Turek and Gillette, 2004). Slow release forms of melatonin (e.g., Circadin®, a 2 mg-preparation developed by Neurim, Tel Aviv, Israel, and approved by the European Medicines Agency in 2007) and the melatonin analogs ramelteon, agomelatine, tasimelteon and TK-301 are examples of this strategy.

Ramelteon (Rozerem®, Takeda Pharmaceuticals, Japan) is a melatonergic hypnotic analog approved by the FDA for treatment of insomnia in 2005. It is a selective agonist for MT_1/MT_2 receptors without significant affinity for other receptor sites (Miyamoto, 2009). Because there is increasing information on the involvement of melatonin and MT_1/MT_2 receptors in the regulation of several aspects of the metabolic syndrome (Cardinali et al., 2011) a recent study tested whether ramelteon is effective to reverse the multiple metabolic abnormalities associated with antipsychotic agents in the schizophrenia population such as insulin resistance, hyperlipidemia, inflammation, obesity, and fat distribution (Borba et al., 2011). A double-blind, placebo-controlled, 8-week pilot trial was conducted, adding ramelteon 8 mg/day to 45 stable outpatients with schizophrenia. Ramelteon did not improve anthropometric measurements, glucose metabolism, and inflammatory markers but it decreased total cholesterol and ratio of cholesterol to high-density lipoprotein, as well as showing a trend toward reduction in fat in the abdominal and trunk areas.

Agomelatine (Valdoxan®, Servier, France) is a recently introduced melatonergic antidepressant that acts on both MT_1 and MT_2 receptors with a similar affinity to that of melatonin and also acts as an antagonist to 5-HT_{2C} receptors at a three-fold higher concentration. In a case report study on a patient with chronic simple schizophrenia and severe insomnia and depression who only had a partial response to high doses of BZP and sedating antipsychotics, treatment with agomelatine (25 mg/day) allowed the patient to completely suspend BZP (Morera-Fumero and Abreu-Gonzalez, 2010).

Several other compounds are being investigated with relatively more selective activity on melatonin receptor subtypes, therefore heralding an interesting future era for melatonin agonist research and their potential use in schizophrenia (Hardeland, 2010; Spadoni et al., 2011).

4. Antipsychotic agents and their effects on sleep architecture and circadian sleep–wake cycle

Antipsychotic medications impact on the patients' sleep and rest–activity patterns. First and second generation antipsychotics, except risperidone, are consistently associated with an increase in total sleep time and sleep efficiency in both patients and normal controls (Cohrs, 2008). The first and second generation antipsychotics vary in showing an increase in slow wave sleep in both patients and control groups while the two second generation drugs olanzapine and ziprasiadone both clearly demonstrate an increase and clozapine shows a decrease. The circadian cycle of patients stabilized for more than a year on monotherapy with a classical antipsychotic (haloperidol, fluphenazine) or with the atypical antipsychotic clozapine was documented by continuous activity monitoring for 3–7 weeks (Wirz-Justice et al., 2001). Patients treated with clozapine had remarkably highly ordered rest-activity cycles, whereas patients on classical antipsychotics such as haloperidol or flupentixol had minor to major circadian rhythm abnormalities. This observation can be conceptualized in terms of the two-process model of sleep regulation mentioned above. High-dose haloperidol treatment may have lowered the circadian alertness threshold, initiating polyphasic sleep episodes, whereas clozapine increased circadian amplitude (perhaps through its high affinity to dopamine D_4 and serotonin 5-HT_7 receptors in the SCN), thereby improving entrainment.

5. Methodological shortcomings

In contrast to studies of patients with anxiety or mood disorders, studies of sleep in schizophrenia patients have failed to generate consistent findings. More specifically, methodological shortcomings may contribute to this inconsistency (see Table 2).

In a review of all-night PSG sleep studies of never-medicated or previously treated schizophrenia patients (Monti and Monti, 2004), never medicated schizophrenia patients showed increases of N2 sleep onset latency, wake time after sleep onset, and an increase in the number of nocturnal awakenings, whereas total sleep time and sleep efficiency were reduced. Very low levels of N3 sleep in both the patients and the controls but REM sleep duration remained almost unchanged. The REM onset latency (REMOL) showed a pronounced decrease in the schizophrenia patients.

Circadian rhythm sleep disorders can be evaluated by using wrist actimetry recordings (Morgenthaler et al., 2007). Moreover, urine or blood as well as saliva collection in the evening hours, commonly five samples at one hour intervals under dim light to determine the melatonin onset, are used as a circadian phase marker (Benloucif et al., 2008). Both actimetry and saliva collection are well accepted by the patients, but they require high compliance, since rest–activity cycles have to be recorded for at least 2 weeks and preferably in real life under habitual conditions to exclude the effect of dictated time schedules, e.g. clinic routines. Therefore, mostly antipsychotic treated patients have been included in circadian studies so far. Studies on melatonin secretion in medicated people with schizophrenia have to be interpreted with caution, since the effect of antipsychotic medication per se on melatonin levels are not yet fully known, with the

Table 2
Methodological shortcomings in sleep in schizophrenia studies.

Items	Shortcoming Criteria	Reference(s)
1	Very small number of clinical subjects (N)	Stern et al. (1969) Gillin et al. (1974) Ganguli et al. (1987) Thaker et al. (1990)
2	Heterogeneity of subjects, ascribed to the failure to divide patients into consistent subcategories (paranoid, catatonic, undifferentiated) or to ascertain that patients are in similar phases of the clinical course (acute, sub-acute, sub-chronic, chronic).	Jus et al. (1973) Brambilla et al. (1983) Lauer and Krieg (1998)
3	Control groups that include patients with neurologic or somatic diseases.	Jus et al. (1973)
4	Outdated scoring methods used in some sleep studies.	Feinberg et al. (1964) Brannen and Jewett (1969) Stern et al. (1969)
5	Confound of age, which is of concern because of the well-known fact that the prevalence of sleep apnea and periodic limb movement disorder increases with age.	Jus et al. (1973)
6	Confound of gender: females are more likely than males to experience symptoms of insomnia and to use prescription and over-the-counter sleep aids.	Brambilla et al. (1983)
7	First-night effect: in several studies apparently normal young controls failed to show REM sleep, stage 4 sleep, and slow wave sleep values corresponding to the usual values for their age; accordingly, the values for mean percentage or duration of REM sleep, N3 sleep, or slow wave sleep for control subjects were found to be far below the values reported for comparable control populations using similar scoring techniques; as a result the observed differences in stage 4 sleep and REM sleep between controls and schizophrenia patients were not significant.	Ganguli et al. (1987) Tandon et al. (1992) Lauer et al. (1997) Lauer and Krieg (1998).
8	Confound of medication: the effects of medication have been of great concern to investigators involved in the study of sleep in schizophrenia patients; in this respect, it has been pointed out that chronic treatment with neuroleptics, as well as their withdrawal, have profound effects on sleep maintenance, NREM sleep structure, and several features of REM sleep.	Ganguli et al. (1987) Baldessarini (1996) Lauer et al. (1997)
9	Lack of screening in many studies for the presence of primary sleep disorders.	Jus et al. (1973)

exception of a study showing that olanzapine did not significantly alter melatonin levels in individuals with schizophrenia who had predominantly negative symptoms (Mann et al., 2006). Moreover, antipsychotic medication can increase daytime sleepiness and affect sleep–wake patterns per se (Kluge et al., 2012).

Compared with controls, previously treated schizophrenic patients showed increases in N2 sleep onset latency and wake time after sleep onset, while in contrast total sleep time and sleep efficiency were reduced. N3 sleep was reduced in five studies and remained unchanged in two studies. Nevertheless, a strict correlation could not be established between the reduction of N3 sleep and the duration of the drug-free period preceding the study. REM sleep was diminished in two studies but unchanged in eight studies. The REMOL was shortened in five studies but unmodified in the four studies in which the drug-free period ranged from 3 to 4 weeks. Overall, sleep disturbances of either never medicated or previously treated schizophrenic patients was characterized by sleep-onset and maintenance insomnia. Regarding sleep architecture, the majority of studies indicate that N3 sleep and REMOL were reduced whereas REM sleep duration tended to remain unmodified.

6. Sleep of schizophrenic patients according to the phase of the clinical course

To date, there have been only four studies which have investigated exclusively schizophrenic patients who were experiencing a first episode or an acute exacerbation of their illness

N2 sleep latency was increased whereas total sleep time was reduced in four studies. In the report by Poulin et al. (2003), N3 sleep was markedly decreased in the schizophrenic patients relative to the controls. In contrast, a decrease of N3 sleep was not noted by either Lauer et al. (1997) or Lauer and Krieg (1998). However, it should be pointed out that in these three studies values of N3 sleep were abnormally low in both the controls and the patients, thus suggesting an incomplete adaptation to the sleep laboratory. REM sleep duration showed non-significant changes in all four studies; in contrast, schizophrenic patients experiencing their first episode demonstrated short REM latencies (Table 3).

Circadian rhythm sleep disruptions are independent of illness duration (Bromundt et al., 2011; Wulff et al., 2012), and are most frequently observed during the prodromal phase or prior to psychotic relapse.

6.1. Schizophrenic patients studied during the chronic phase of their illness

In chronic patients, N2 sleep onset latency was found to be significantly increased in five studies (Monti and Monti, 2004), whereas total sleep time was reduced in four studies. N3 sleep was decreased in three studies (two missing values), whereas REM sleep duration remained unchanged in seven studies. The REMOL was significantly reduced in three studies (one missing value). Thus, available evidence tends to indicate that sleep onset and maintenance is disrupted in schizophrenia patients irrespective of the phase of the illness or the length of the drug-free period prior to the polysomnographic study. Neither does the phase of illness substantially influence values of N4 sleep, REM sleep duration, or REMOL.

It can be concluded that sleep-onset and sleep maintenance insomnia is a characteristic feature of schizophrenia patients regardless of the medication status or the phase of the clinical course. The REM sleep duration tended to remain unaltered although REMOL was decreased in 50% of the studies. Because no increase in REM sleep was found in these studies, although there was a reduction in REMOL, a rebound phenomenon can be eliminated as an explanation.

7. Mechanisms involved in the circadian and sleep disruptions in schizophrenic patients

What are the mechanisms involved in the sleep onset and maintenance insomnia of schizophrenia patients? According to the original dopamine hypothesis of schizophrenia formulated in the 1960s, the symptoms of schizophrenia depend on the over-activity of the dopaminergic system (Carlsson and Lindquist, 1963). It had been proposed that an increase in the synthesis and release of dopamine and in the density of D_2 receptors was associated with the positive symptoms

Table 3
Polysomnographic features in schizophrenia.
From: Stern et al. (1969), Gillin et al. (1974), Ganguli et al. (1987), Kempenaers et al. (1988), Tandon et al. (1992), Nofzinger et al. (1993), Lauer et al. (1997).

Sleep efficiency ↓
Sleep onset latency ↑
Wake time after sleep onset ↑
Total sleep time ↓
Slow wave sleep (non-REM sleep stages 3 & 4) ↓
REMOL ↓
REM Sleep ↓

of schizophrenia, whereas the negative and the cognitive symptoms would arise from a deficit of dopamine in the dorsolateral prefrontal cortex (Abi-Dargham, 2004; Carlsson et al., 2001). However recent evidence from positron emission tomography (PET) studies with high affinity ligands provide no convincing evidence for a D_2 receptor abnormality in schizophrenia (Ginovart and Kapur, 2012). Thus the abnormality in dopamine seems to be confined to increased synthesis and release in the striatum and deficit in both synthesis and release in the dorsolateral prefrontal cortex, which are related to positive and negative symptoms of schizophrenia respectively. In this respect, an increased responsiveness of the nigrostriatal pathway has been shown with a pharmacological stress model and single photon emission computed tomography (Abi-Dargham et al., 1998; Breier et al., 1997; Laruelle et al., 1996). On the other hand, the dopamine transporter and the D1 receptor are normal.

Based on these findings, the hypothesis that the insomnia of schizophrenic patients is related to an over-activity of the dopamine system can be advanced; indirect evidence derived from pharmacological studies supports this contention. For instance, the D_2 receptor agonists apomorphine, bromocriptine, and pergolide have been shown experimentally to enhance wakefulness and to reduce sleep at doses that interact with postsynaptic D_2 receptors (Monti et al., 1988). In contrast, YM-09151-2, a substituted benzamide and selective D_2 blocking agent, increases light sleep (Monti et al., 1989). However, there is the possibility that insomnia in schizophrenic patients is not exclusively dopamine dependent but that other neurotransmitter systems are also involved in its disruption. In this respect, post-mortem human brain studies (binding and cell-counting studies, axon terminal immunoreactivity, glutamic acid decarboxylase [GAD] activity) and animal models indicate a reduction of GABA activity (Wassef et al., 1999, 2003), which may play a role in the pathophysiology of schizophrenia, including the sleep and circadian disruptions. However, it is unclear at the present time how alterations of the GABA system interact with dopamine dysregulation in schizophrenia.

It is also worth considering the possible roles of melatonin in these symptoms. Inadequate inhibition of dopamine synthesis and release in the striatum by melatonin could be a factor that is related not only to the insomnia but also exacerbate the positive symptoms of schizophrenia (Dubocovich, 1983; Zisapel et al., 1982). Further studies will be necessary to clarify this issue. In this context, a recent report on schizophrenic outpatients with insomnia treated with melatonin in a double blind, placebo-controlled study states that in addition to improving a variety of sleep parameters, patients displayed heightened freshness on awakening, improved mood and improved daytime functioning (Suresh Kumar et al., 2007). This finding warrants further study.

Interestingly, reductions in REMOL are characteristic findings of narcolepsy. A short REMOL is also a frequent finding in patients with major depressive disorder. Regarding the pathophysiological mechanisms underlying REM sleep abnormalities in narcolepsy, they seem to be related in great measure to a deficiency of the hypocretin (orexin) neurotransmitter system, located in the lateral hypothalamus (Taheri et al., 2002). On the other hand, the cholinergic–aminergic imbalance hypothesis proposes that either enhanced cholinergic neurotransmission or diminished serotonergic and noradrenergic neurotransmission accounts for the REM sleep changes in depressed patients (Janowsky et al., 1972). The imbalance hypothesis is supported by findings showing that under normal conditions REM sleep is facilitated by cholinergic and inhibited by serotonergic and noradrenergic neurons located in the brainstem (Hobson et al., 1998). The available evidence does not support a role for acetylcholine, catechol- and indoleamines, orexin, or GABA in the reduction of REMOL in schizophrenia patients. Thus, further studies are needed to identify the neurotransmitter system(s) involved in the reduction of REMOL in schizophrenia.

Aetiological mechanisms that might contribute to circadian abnormalities include dysfunction of neurotransmitter systems such as dopamine and glutamate (Lisman et al., 2008), both of which are involved in the complex interaction of sleep and wake mechanisms. Internal desynchronization of circadian rhythms and lack of entrainment with the 24-h light–dark cycle may be credited to the psychopathology itself, but also to secondary, weak zeitgeber effects, e.g. abnormal light–dark exposure and disrupted social behavior in these patients (Wirz-Justice et al., 2009; Wulff et al., 2010). Moreover, recent studies suggest a link between circadian clock gene polymorphisms or dysregulation and schizophrenia (Mansour et al., 2006; Zhang et al., 2011). Molecular mechanisms that constitute the circadian clock have also been associated with the dopaminergic hypothesis of schizophrenia. Signaling mediated by the dopamine D_2 receptor increases clock gene expression by enhancing the transcriptional capacity of the *Clock:Bmal1* complex (Yujnovsky et al., 2006).

8. Conclusions

In conclusion, sleep-onset and maintenance insomnia is a characteristic feature of schizophrenic patients regardless of either their medication status or the phase of the disorder. The majority of studies show that slow wave sleep and REMOL are reduced in schizophrenia, whereas REM sleep duration tends to remain unchanged. Sleep disturbance in schizophrenia may be partly related to the presumed over-activity of the dopaminergic system, although the GABAergic system may also be involved. Both neurotransmitters have effects on sleep and wake promoting brain areas which can explain sleep disturbances due to circadian rhythm disruptions frequently observed in these patients. Moreover, polymorphisms or dysregulation of certain clock genes were linked to schizophrenia and may cause disturbances of sleep–wake patterns. Circadian misalignments leading to sleep–wake disruption may also be credited to secondary effects such as insufficient light exposure and weak social zeitgebers that lead to circadian desynchronisation and lack of entrainment. Deficits in melatonin may cause overactivity of the striatal dopamine system leading both to insomnia and to increased positive symptoms. Preliminary studies with melatonin suggest that it may be a useful treatment for sleep disturbances in schizophrenia and further investigation of its utility in treating schizophrenic symptoms is warranted.

In general, much remains to be elucidated regarding sleep disturbances in schizophrenia. Studies that avoid the aforementioned shortcomings of existing sleep studies are needed, as well as clinical and basic neuroscience studies of other neurotransmitter abnormalities in schizophrenia. Such information could provide treatments that ameliorate symptoms of sleep disturbances experienced by schizophrenic patients, and thereby improve their quality of life.

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