Psychotropic Medications Affecting Biological Rhythm

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ÖZET:

Biyolojik ritmi etkileyen psikotrop ilaçlar

Birçok canlı organizmada, omurgalı ve memeli canlıda olduğu gibi insanda da biyolojik işlevler çeşitli aralıklarla salınan ritimlerle yürür. Sirkadyen, ultradien ve infradian ya da daha uzun aralıklarla salınan iç ritimlerimiz kendi iç düzenlerini her şartta devam ettiren, bağımsız biyolojik organizasyonlardır. Biyolojik olarak kendiliğinden işleyen, istikrarlı bir yol varsa da, gerek psikiyatrik hastalıklar ve gerekse de psikotrop ilaçlar bu iç ritimleri değiştirebilir. Psikotrop ilaçlar, etki düzeneklerindeki nörotransmmitter ya da nöromediatörler vasıtasıyla doğrudan veya daha uzun vadede hormonal ya da genetik değişikliklere neden olarak da biyolojik ritimler üzerine etkili olabilir. Biyolojik ritim düzensizliklerinin duygudurum bozuklukları açısından hem neden hem de sonuç olarak önemine dikkat çeken birçok çalışma vardır. Duygudurum bozukluklarının takip ve tedavisinde psikofarmakolojik ajanların biyolojik ritimlere olan muhtemel etkisi de değerlendirilmesi önemlidir.

Anahtar sözcükler: kronobiyotikler, psikotrop ilaçlar, biyolojik ritim

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ABSTRACT:

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There are many biological rhythms with various time oscillations regulating biological functions in living organisms, mammalians, and humans. Biological rhythms such as circadian, ultradian, and infradian or with longer cycles are independent biological organizations rather than dependent to the external stimulus. Although there is a sustained biological rhythmicity, psychiatric disorders and psychotropic drugs can change this process. The effects of psychotropics on biological rhythmicity can occur via possible neurotransmitter and neuromediator mechanisms within a relatively short time period on the other hand hormonal or genetic mechanisms can impact long term outcome. So far several studies suggested that biological rhythm disturbances play an important role in etiology and course of mood disorders'. Assessment of the possible effects of psychopharmacological agents on biological rhythm is important during the course of mood disorders.

Key words: chronobiotics, psychotropic medications, biological rhythm

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INTRODUCTION

Biological Rhythms

Many behaviors (e.g. sleep-wake, feeding) as well as physiological (e.g. body temperature, blood pressure) and endocrine (e.g. plasma corticosteroid concentration) events display a 24 h rhythmicity in mammals. These 24 h rhythms are induced by a timing system that is composed of central and peripheral clocks (1).The suprachiasmatic nucleus (SCN) of the hypothalamus is the central pacemaker or the master clock (2). The SCN receives input from many other brain areas and also has efferents towards many areas, several of them to the hypothalamus (3). Lesions of the SCN disturb circadian rhythmicity in a variety of behavioral, endocrine, and biochemical processes (4). Aside from the circadian endogenous rhythms, there are endogenous rhythms with shorter periods, ranging from seconds to hours, called ultradian rhythms, as well as longer rhythms lasting from a week or a month to a year. There are unsolved questions as to the role of the SCN in relation to these other rhythms. SCN lesions suppress some but not all ultradian rhythms. These lesions also modify the seasonal rhythm of reproduction of several mammals (5,6). SCN lesions in rats suppress the scale-invariant patterns of motor activity within a 4–24-hour time range, which suggests a general role of the SCN in rhythm generation, i.e. not only for circadian rhythms (7). Although light is the most important zeitgeber that directly influences the output of multiple oscillator systems, SCN together with peripheral clocks, enables a time-related homeostasis in case the

external time cues such as daylight are not available (5). Despite, there is a biological sustainability, psychiatric disorders and also psychotropic medications have important effects on synchronizations of biological clocks (8-11).

Biological Rhythms and Psychiatry

The major marked clinical feature in affective disorders is their periodic nature, in a large range from seasonal depression to rapid cycling of bipolar disorders (12). "In winter depression," the most common form of seasonal affective disorder, patients experience major depressive episodes beginning with the onset of winter, followed by remission or even hypomania in the spring (13,14). Also, many patients with non-seasonal depression show a regular daily pattern of symptoms, usually symptoms are more severe in the mornings (15). Suicide rates also show both diurnal and seasonal variations (16). Phase-advanced oscillations in plasma cortisol and norepinephrine compared to healthy subjects, and abnormal levels and patterns of melatonin secretion may reflect the fundamental signs of disturbed biological rhythms in depressed patients (17-19). There is clinical and epidemiological evidence that sleep disturbances in depression constitute a risk factor for poor clinical outcomes. Specifically, complaints of insomnia precede the onset and recurrence of depression (20). Some researchers found shortening in Rapid Eye Movement (REM) sleep latency in bipolar disorder not only in depressive episode but also in mania. Furthermore, there was great variability of sleep duration and increased nocturnal time awakening in remitted BPD outpatients (21). Some studies conducted on drug free patients, found that decreased sleep efficiency, reduced total sleep time, and elevated sleep latency in schizophrenia (22).

Chronopharmacology

Because it is not the main topic of this review, we only included brief information about definition and clinical importance to ensure familiarity with the concept of chronopharmacology. Even the amount of drug entering into the brain is the same, the effects may vary depending on the time of entry. This suggests presence of a rhythm in drug susceptibility of the brain (23).

Chronopharmacology is the investigative science that elucidates the impact of biological rhythms on medications from both chronopharmacodynamic and chronopharmacokinetic perspectives (24). For example, effects and side effects of Interferons (IFNs) may dramatically change with their administration time (25). IFNs have been widely used as antiviral and antitumor agents. IFNs can cause some neuropsychiatric side effects such as depression and in some research, their use was found related to higher suicide attempts (26,27). When IFNs are administrated in the morning they are rapidly removed from the plasma and their interactions with effector cells are decreased at the administration time. Furthermore, IFN may cause a secondary cortisol peak and related side effects about 6-8 hour after administration time (28,29). Similarly the effect of the 5-HT uptake blocker, clomipramine is stronger at noon in humans. This may be due to an increase in 5-HT release around noon time (30). Chronopharmacodynamic and chronopharmacokinetic factors also have important effects on efficacy and side effect profile of other psychotropic medications such as Valproic Acid (VA) (31).

Chronobiotics

Chronobiotic is defined as a substance that "adjusts the timing of internal biological rhythms" or "a substance that may adjusts or prevent the timing of the central biological clock" (32).

Psychotropic Drug Effects on Clock Genes

Clock genes have an important role on the regulation of circadian rhythms. These genes include Clock, Bmal1 (ARNTL), period genes (Per1, 2, 3), cryptochrome genes (Cry1, 2), casein kinase Ie (CSNK1e) and Rev-erb-a (Nr1d1) (33,34). The mRNA levels of numerous core clock genes change in depression including cryptochrome (CRY1, CRY2), period (PER1, PER2, PER3), BMAL1 (ARNTL), and CLOCK. A sleep deprivation study in BPD (Bipolar Disorder) depressed patients indicated a reduction in baseline CRY2 mRNA levels compared to controls (35,36). Following one night of sleep deprivation CRY2 mRNA levels increased 2-fold in controls but did not significantly change in depressed subjects (37). Mice with a mutation in Clock (Clock D19) have manic-like

behaviours which can be suppressed by lithium (38,39). A follow-up study in mice with a knockdown of Clock in the ventral tegmental area documented changes in activity which the investigators interpreted as a mixed state of manic and depressive behaviors. In these animals, locomotor activities were increased in response to novel stimuli yet overall activity in the home cage was decreased (40). It is challenging to report that the Clock mutation phenotype can be suppressed by melatonin (or the melatonin agonist, ramelteon) to stabilize circadian rhythms (41).

Effects of Antidepressants on Sleep

Before the assessment of the each antidepressant group, it is necessary to review possible effects of the major neurotransmitters on sleep. Serotonin is a major neurotransmitter that has modulatory effects on the regulation of sleep and wakefulness. Serotonergic systems have a substantial role on maintenance of wakefulness, the induction of sleep, and the changeover from Non Rapid Eye Movement (NREM) to REM sleep (42,43). It was assumed that the serotonergic neurons are active during the awareness, inactive during Slow Wave Sleep (SWS), and are particularly quiescent during REM sleep. As there are several types and subtypes of serotonin receptors in the receptor families, it is not easy to predict the exact effects of the serotonergic system on sleep (44). Under this circumstance, is it then correct to claim " the serotonergic system supports to initiation of sleep?" Although on one hand this opinion is correct, on the other hand "serotonergic system may induce a hypodopaminergic state, which can cause movement disorders and hence increased arousal and/or sleep onset insomnia." Noradrenaline (NA) and DA Dopamine (DA) are related to the awareness and DA also related with alertness. NA activity is highest level during the wakefulness, inactive during SWS, and extremely silent during REM sleep in that related with inactive muscle tone (45).

In this review, some psychotropic drugs with well known sleep inducing effects and commonly used effectively, such as benzodiazepines are excluded. Also some drugs such as Agomelatine mentioned briefly, because our main point was not just limited with chronotherapeutics.

Tricyclic Antidepressants (TCAs)

Although there are an individual differences, TCAs generally shorten sleep latency and improve sleep continuity in depressed patients, and their sleep inducing effects can cause daytime drowsiness. Most TCAs suppress REM sleep, increase REM latency and reduce the percentage of REM sleep, thus tending to normalize the disturbed sleep architecture seen in depressed patients (46). Amitriptyline and Doxepin increase sleep continuity and suppress REM sleep, and their sedative effects are distinct. Clomipramine has no significant sleep sustaining or sedative effect, but it has clearly suppressive effect on REM sleep (47). Until the late eighties, there are several published studies suggested that the antidepressant activity across different drugs was found to be related to their capacity to suppress REM sleep and suppression of REM sleep is the key mechanism of action of antidepressant drugs and REM sleep is depressogenic (48-51). At present, it is only possible to say that REM sleep changes with antidepressant medications may reflect underlying circadian effects (46).

Selective Serotonin Reuptake Inhibitors (SSRIs)

It has been suggested that SSRI use can reach degree of agitation and akathisia through the 5HT2A receptor sites in some patients (43). Approximately 25% of depressed patients enrolled in clinical trials with SSRIs reported subjective complaints of insomnia (47). SSRIs have dose dependent effect disruption of sleep continuity and daytime somnolence (52). Fluoxetine clearly suppresses REM this action commonly sustained to the 4 weeks of treatment. It also decreases to sleep efficiency, and increase number of awakenings (47,53). Fluoxetine produced resistant phase advances of the peak of SCN neuronal activity (54). Melatonin metabolized by CYP1A2 to 6-hydroxymelatonin and N-acetylserotonin with a minimal contribution of CYP2C19. Because of the both reactions were potently inhibited by Fluvoxamine, it can suggest that melatonin effects enhanced by Fluvoxamine (55). Paroxetine clearly suppresses REM sleep, both among healthy volunteers and depressed patients. Paroxetine suppresses REM, decreases total sleep time, and increases awakenings (47,53,56). Sertraline and Citalopram have less disruptive effects on sleep continuity because of their less activating effects (47,57).

Bupropion

It has effective via NA and DA reuptake inhibition. It decreases REM latency and increases total percentage of REM, and improve sleep efficiency (58).

Venlafaxine and Duloxetine

At lower doses, Venlafaxine has significantly sleep disturbing effects like SSRIs, and it caused by possibly effects of serotonin reuptake inhibition (47,59,60). Although 60 mg/day Duloxetine reduced to sleep continuity, 80 mg/day Duloxetine had significant improvement in sleep, and it has been emphasized that dose dependent change in SNRI effects on sleep continuity (61).

Mirtazapine

This special molecule has been opposite effects with SSRIs. SSRIs can cause to the behavioral activation, anxiety, sleep disturbances via 5-HT2A stimulation, whereas Mirtazapine has opposite effects on these dimensions. Similarly, Mirtazapine does not cause the irritability or loss of appetite via 5-HT2C stimulation, although SSRIs do it. Similar to the antihistaminic agents, Mirtazapine's sleep promoting effect is rapid, and it can cause daytime sedation. Although histaminergic blockage helps to rapid sleep onset, it is assumed that the effects on continuity is due to its 5HT2 and 5HT3 blocking effects (62,63).

Trazodone

There is no REM suppressive effect due to its weak 5-HT reuptake inhibition. Its hypnotic dose range is 50-200 mg, although antidepressant dosage should be three times more (64).

Melatonin and Melatonin Agonists

Melatonin is a hormone synthesized by the pineal gland. Its secretion occurs only at night in both diurnal and nocturnal mammals (65). Circadian rhythm regulation via SCN, depends on the regularly secretion of pineal melatonin and existence of healthy melatonin receptors in SCN as well (66). In healthy subjects, Dim-Light Melatonin Onset (DLMO) occurs 1–2 h before sleep onset. In depressed patients, DLMO is usually delayed and melatonin levels are decreased (67,68). In depressive patients there are some single nucleotide polymorphisms (SNPs) in the melatonin pathway such as arylalkylamine N-acetyltransferase (AANAT) (69) and a rate-limiting melatonin enzyme acetylserotonin methyltransferase (ASMT) (70). Melatonin is a prototype of chronobiotics and the chemical code of darkness (43). The effects of melatonin on SCN activity are mediated by at least two receptors; MT2 receptors that sensitive at dusk and dawn and causes phase shifts, and MT1 receptors that decreases the neuronal firing rate at early evening (71,72).

Ramelteon

It is a selective MT1 and MT2 receptor agonist. It has both sleep-promoting and chronobiotic effects (73).

Agomelatine

Agomelatine has no effects on pre or post synaptic 5 HT1A receptors and its mechanism of action is different from TCA and SSRIs. Agomelatine is significantly effective on a several behavioral models of antidepressant properties, such as forced-swim test (74), the learned helplessness paradigm in rats (75), the olfactory bulbectomized rat model (76), and the chronic mild stress test (77). In the chronic mild stress model, agomelatine remains effective independently of the administration time, shows that its antidepressant activity is not only due to its action at melatonergic receptors, but also related to the antagonistic activity at 5-HT2C receptors.

Mood Stabilizers

Carbamazepine

It was shown to increase SWS and decrease REM sleep. This study was conducted with 7 temporal lobe epilepsy patients and 9 healthy controls. In both groups, fragmentation of REM and increase in sleep shifts were observed (78). Another article reported increased SWS and sleep efficacy, decreased awakenings, and decreased sleep latency (79). However, there are some studies reporting no difference in sleep architecture with carbamazepine (80,81).

Valproic Acid (VA)

In a study, it was found that VA increases Stage 1, decreases stage 2 sleep, causes difficulty in initiating sleep, and reduces REM sleep (82), while the another study reported that VA has a little or no effect on sleep architecture (83).

Lithium

Lithium lengthens circadian rhythm period in plants, rodents, and mammalians including humans (84). Although the knowledge about the Lithium's efficacy in sustaining Sleep Deprivation Treatment (SDT) improvement is not new, current studies are more detailed and clarified the mechanism of action (85- 89). Benedetti reported that patients who had been treated with Lithium longer than 6 months showed more sustained improvement in SDT than drug free patients (88). It was also observed lithium treated patients with the short allele of the serotonin transporter gene (5-HTTLPR s/s variant) had better responses to SDT than those with the short allele and not treated with lithium (89). Although long term lithium treatment ineffective to prevent the recurrence major depressive episodes, it was able to sustain the clinical improvement associated with sleep deprivation (90).

Antipsychotics

Although dopamine plays an important role in generation of awakeness, some selective dopamine antagonists such as pimozide and sulpiride has little effect on the sleep of healthy subjects (91). The sedative and sleep-inducing effects of antipsychotics arise from their antiadrenergic, antihistaminergic and anticholinergic capacities (92). Atypical (such as Quetiapine or Olanzapine) and typical (such as Levopromazine or Chlorpromazine) antipsychotic effects on total sleep time are related to their serotonergic and histaminergic affinity. Olanzapine increases SWS and it has been associated with blockage of the 5HTC2 receptor sites (93). There is a controversial issue whether the atypical antipsychotics has special effects on prolactin peaks or not, although it has been known they clearly show increasing effects on prolactin levels (94,95). Systemic and intrahypothalamic prolactin increases REM sleep in cats, rabbits, and rats (96). On the other hand,

Table 1: Psychotropic medication effectson sleep										
Psychotropic Medications	S1	S2	SWS	REM	SL	RL	TST	SC	Arousals	Stage shifts
Antidepressants										
Amitriptyline (43,47,48)			↑	↓	↓	↑	↑	↑	↓	
Imipramine (43,46)			↑	↓	↑	↑	↓	–	↑	
Clomipramine (42,43)			↑	↓		↑		–		
Fluoxetine (47,53)			–	↓	↑	↑		↓	↑	
Paroxetine (47,53, 56)			–	↓	↑	↑		↓↑?	↑↓?	
Sertraline (47,57)			–	↓	↑	↑	↓	–	–	
Trazodone (64)			↑	–	↓		↑	↑	↓	
Duloxetine (61)				↓	↑			↑↓*		
Venlafaxine (47,59,60)	↑			↓		↑		↓	↑	
Mirtazapine (62,63)					↓		↑	↑	↓	
Anticonvulsants										
Valproic acid (82,83)	↑	↑↓?	↑	↓					–	N/A
Lamotrigine (42,43)	N/A	↑	↓	↑					↑	↓
Carbamazepine (42,43,78,79)	N/A	N/A	↑	↓	↓	↑	↑	↑	↓	↑
Antipsychotics										
Clozapine (42,43,92, 93,102)	↓	↑	–	↓			↑	↑		
Quetiapine (42,43,103)		↑		↓	↓	–	↑	↑		
Risperidone (42,43,92)		↓	↑			↑			↓	
Olanzapine (43,93,104)	↓		↑	↓	↓	↑	↑	↑	↓	
Haloperidol (43)					↓		↑	↑	↓	

S1: Stage1 sleep, S2: Stage 2 sleep, SWS: Slow Wave Sleep, REM: Rapid Eye Movement sleep, SL: Sleep latency, RL: REM latency, TST: Total Sleep Time, SE: Sleep Continuity, *: Depends to dose, ?: study results are inconsistent. N/A: data not available, ↑: Increase, ↓: Decrease, –: no change.

antiserum to prolactin decreases REM sleep in rats (96,97). In patients with hyperprolactinoma, SWS is selectively increased compared to the controls (98). Repetitive ghrelin administration increases SWS, and also GH, ACTH, and cortisol levels increase after ghrelin, in young men (99). Intrahypothalamic ghrelin increases feeding and wakefulness in rats (100). In a patient with night-eating syndrome, nocturnal ghrelin levels appeared to be elevated (101). Psychotropic medication effects on sleep are summarized at table 1.

CONCLUSIONS

Both known mechanism of action and every process within treatment are important in effects of psychotropic medications on biological rhythms. The psychotropic effects on rhythms can effectively be used in acute and chronic treatment of mood disorders and also in maintenance for their protective effect. The efforts to find effective chronotherapeutic agents in psychiatric disorders reflect unmet needs in psychopharmacological management of disorders. On the other hand, it is impossible to think about effects and side effects of a medication independent from biological rhythms. One may say that while planning a psychopharmacological treatment strategy, the need to consider biological rhythm and related results has increased.

Conflict of Interest

None of the authors had any conflict of interest to declare.

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