DEAR EDITOR,

We spend our lives in three completely different states of being: Wakefulness (W), Rapid Eye Movement (REM) sleep and Non-REM (NREM) Sleep. Each of these states has its unique neuroanatomical, neurophysiologic, neurochemical and neuropharmacological correlates. The reason it took so long to determine that sleep is actually a bimodal process are

a. Superficially and from a distance REM and NREM sleep look similar and
b. These two states cycle back and forth giving the illusion of homogeneity.

Brain activity is coordinated to produce various stages of sleep. Electrophysiological recordings of human brain reveal three distinct state of existence: wakefulness, rapid eye movement (REM) sleep, and non-REM (NREM) sleep. The distinction between sleep and wakefulness is attributed to the synchronization and desynchronization of thalamocortical circuits [1,2]. Wake-like or “desynchronized” (low-amplitude and high-frequency) electroencephalographic (EEG) activity with clusters of REM and very low levels of muscle tone characterize REM sleep.

As much as one third of the adult population reports difficulty sleeping [3]. Disturbed sleep is a common finding in psychiatric illnesses. Some patients will even attribute their daytime psychiatric symptoms to abnormal sleep and believe that improved sleep will solve their problems. Another point is that alterations of sleep by psychiatric conditions are likely to have underlying brain neuro-transmitter dysfunction directly involved in the pathophysiological process of the disease.

Whether drugs induce wakefulness (“waking drugs”) or sleep (“hypnosedative drugs”) depend on their liability to stimulate or inhibit wake- or NREM sleep-promoting neurons.

Medications can interact with neurotransmitters and brain-processes to produce adverse or therapeutic effects. The effects of medicines are sometimes desirable, such as the ability of a sedative to induce sleep. However, they are sometimes undesirable. For example the same sedative lasts for a longer time, inducing groginess in the morning and thereby increasing the risk of an accident.

At times medications used to treat conditions totally unrelated to sleep disorders induce adverse or beneficial effect on sleep, such as insomnia induced by an anti depressant or sleep induced by an antihistamine. Commonly used medications in sleep medicine include stimulants for excessive sleepiness, and sedatives and hypnotics for insomnia. Dopamine agonists and certain benzodiazepines also are used for movement disorders and parasomnias.

Stimulants

This class of drugs includes amphetamines and related compounds such as methylphenidate, modafinil and Pemoline. Xantheine derivatives such as caffeine and theophylline are also considered CNS Stimulants. Stimulants, as a rule, increase wakefulness, decrease total sleep time and slow wave sleep and increase sleep latency. All of them uniformly decreases sleep continuity, slow wave sleep, and REM sleep, and it increases sleep latency.

Hypnotics and Sedatives

Benzodiazepines are the major drugs in this category. They are agonists of the GABAA receptor. They are sedating and increase stage 2 sleep and sleep spindles. They generally reduce sleep latency and increase sleep continuity, and they reduce REM and slow wave sleep. The shorter acting benzodiazepines usually improve sleep in the first part of the night but cause sleep disruption and fragmentation during the second part of the night. They produce dependence, and there is usually rebound insomnia when these medications are stopped [6,7].

ADVERSE EFFECTS OF MEDICATIONS ON SLEEP

Antidepressants

There are various subgroups in the antidepressant category. The major ones being Tricyclic Antidepressants (TCA’s), specific Serotonin Reuptake Inhibitors (SSRI’s).The Serotonin Norepinephrine Reuptake inhibitors (SNRI’s) etc. The Tricylic’s usually act by preventing reuptake of both Serotonin and Norepinephrine. Amongst these two neurotransmitters reuptake of Serotonin is more affected than Norepinephrine. The various TCA’s affect sleep by reducing sleep latency and increasing sleep continuity. They act uniformly to reduce REM sleep. Slow wave sleep is usually unaffected. Periodic leg movements I sleep may increase. Tricylic’s are the most sedating amongst the Antidepressants.

They also produce antagonism at α1, M1, and H1 receptors. Imipramine is similar in action to Amitriptyline. However,
Nortryptiline is less sedating and only reduces REM Sleep [8,9]. Selective serotonin reuptake inhibitors are more likely to produce insomnia, which may improve with continuing dose of the medication. The compounds included in this group induce vivid dreams. They uniformly affect REM sleep by

1. Increasing sleep latency and
2. Decreasing sleep continuity

Slow wave sleep may or may not be reduced.

The mechanism of action varies between the different Specific Serotonin reuptake inhibitors (SSRI's). The more 'pure' in action the SSRI, the less effect it will have on NREM Sleep architecture. Therefore Citalopram which is an exclusive serotonin reuptake inhibitor will not affect sleep continuity or sleep latency. It however decreases REM sleep. It produces insomnia.

Fluoxetine in addition to preventing reuptake of Serotonin also acts to prevent reuptake of Norepinephrine and stimulates the 5-HT2C receptor. Fluoxetine decreases slow wave sleep, REM sleep, and sleep continuity. Sleep latency is increased by both Sertaline and Paroxetine. Both will also reduce REM sleep. Escitalopram usually has the least effect on sleep architecture [8,10]. Venlafaxine is a Serotonin and Norepinephrine reuptake inhibitor. It also inhibits dopamine reuptake. It reduces sleep continuity, slow – wave sleep and REM sleep. It does not induce insomnia and has no effect on sleep latency [8,11].

Antipsychotics

Traditional Antipsychotics like Haloperidol and Chlorpromazine are sedatives and increase sleep continuity. These drugs may impair performance.

Haloperidol is a dopamine (D2 receptor), serotonin (5-HT2), and α1 antagonist. It increases sleep continuity and is mildly sedating. Its effect on REM and NREM Sleep is still not clear and requires more studies.

Aripiprazole acts by antagonizing the serotonin (5HT2A) receptors. It produces partial agonism at Dopamine D2 receptor and Serotonin 5-HT1A receptor. It is unlikely to impair performance. It does cause Insomnia.

Clozapine and olanzapine are markedly sedating and impair performance. Clozapine also increases REM density. Both of these Antipsychotics increase sleep continuity, decrease sleep latency, and decrease total REM sleep [8,12].

Anxiolytics

In this group, Benzodiazepines (Alprazolam and Lorazepam etc.) are the most widely used, as of today, in clinical practice. They are all uniformly sedating. They decrease sleep latency, slow wave sleep, and REM sleep and increase stage 2 sleep. They also increase sleep continuity. They produce agonism at the GABA-Α receptor [6].

Antiepileptic

There are various classes of Anti Epileptics used. Perhaps the most widely used is Phenytion Sodium. It acts as a Sodium Channel Blocker. It has sedating properties and acts by reducing REM sleep and increasing the NREM phase. It also reduced sleep onset time.

Carbamazepine is used for treating partial seizures. It is a norepinephrine agonist and a partial adenosine agonist. It decreases sleep latency and REM sleep and increases sleep continuity and slow wave sleep [4,8].

Regards,

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REFERENCES