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Antidepressant and Antipsychotic Drugs

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I. Introduction

The antidepressant and antipsychotic drugs are a set of agents with a wide range of different pharmacologic effects. Many of these pharmacologic effects impact sleep-wake function. This can involve promoting sleep, promoting wakefulness, altering the amount or timing of sleep stages across the night and increasing the likelihood of restless legs syndrome and/or periodic movements of sleep which can disturb sleep. Depending on the time of day of administration, the pharmacokinetics of the drug, the dose of the drug, and the context, some of these effects may be therapeutic and some may be adverse effects. For example, when administered at bedtime to a patient with sleep difficulty, the sleep promoting effects of an antipsychotic medication can be therapeutic. However, if that medication is administered in the morning or if the combination of dosage and half-life of the medication result in next-day effects, the sleep promotion associated with this medication can be problematic. Some of the effects on sleep-wake function of these medications, such as altering the amount or timing of sleep stages, are of uncertain clinical significance but have long been of interest in terms of research pursuing whether these changes might be linked to therapeutic effects such as: antidepressant effects, sleep restoration, and improvement in negative symptoms in schizophrenia.

This chapter reviews the pharmacology and associated sleep-wake effects of the antidepressant and antipsychotic medications. It discusses factors relevant to these effects such as pharmacokinetic properties, dosing, therapeutic target, and key interactions. Comprehensive review of the clinical trials related to the use of these agents for the treatment of sleep-wake disorders are not covered in this chapter but are included in chapters in Part II of this volume.

II. Pharmacologic Mechanisms of Antidepressants and Antipsychotics Effects on Sleep-Wake Function

II. A. Promoting sleep by blocking the activity of wake promoting neurotransmitters

Sleep promotion occurs with antidepressants and antipsychotics that block receptors that mediate the wake promoting effects of a number of neurotransmitters including: the serotonin type 2 receptor (5HT₂), histamine receptors (H₁), muscarinic acetylcholine receptors (ACh), norepinephrine receptors (α_1), and dopamine receptors (DA).[1–6] These

effects can potentially improve sleep at night but also have the potential to cause daytime sedation.

II.A.1. 5HT2 antagonism—The serotonin (5HT) system and its effects on sleep are complex. However, there is some evidence to suggest that agents which selectively block 5HT2 receptors improve the ability to stay asleep in both human and animal studies.[7–10] The inconsistency of findings in such studies has led to the hypothesis that the sleep promoting effects of 5HT2 antagonism may depend on the ratio of effects on 5HT2A and 5HT2C receptor subtypes as well as other factors. However, these data along with the tendency of antidepressant and antipsychotic medications which have 5HT2 antagonist effects to enhance sleep has led to the general belief that 5HT2 antagonism is may be associated with sleep enhancement.

II.A.2. Histamine (H1) antagonism—Histamine is one of the most important wake promoting neurotransmitter systems in the brain. It mediates its effects by binding to the H1 histamine receptor.[1] Agents which increase histamine's release and binding to H1 receptors enhance wakefulness.[11] Many antidepressant and antipsychotic agents block these H1 receptors and, thereby, promote sleep.[12–13] Although there is ample experience with agents with H1 antagonism, few data exist on the sleep-wake effects of medications with H1 antagonism effects and minimal effects on other receptor systems. As a result, the understanding of the sleep-wake effects of H1 antagonism remains limited. However, recent studies have been carried out with doxepin dosed in the 1–6 mg range where this medication appears to be a relatively selective H1 antagonist (see III.A. below).[14–15] The data suggest that H1 antagonism may have its greatest sleep enhancing effects at the end of the night. In these studies, differences between doxepin and placebo were greatest in hours 7–8 of the night despite achieving peak blood level 1.5–4 hours after dosing.[14–15] These data suggest that the sleep enhancement of H1 antagonism is dissociated from blood level and may be more related to time of day. Further evidence to support this conclusion and to suggest that the sleep enhancing effects may be affected by activity level as well, is that doxepin in 1–6 mg was not associated with sedation when assessed after waking; just one hour after the peak, sleep enhancing effect was observed.[14–15]

II.A.3. Alpha 1 adrenergic antagonism—The wake promoting effects of norepinephrine in the central nervous system are well-established and are believed to be mediated at least in part by α_1 receptors.[1,16] This mechanism is believed to be responsible for some of the arousal achieved by stimulants such as d-amphetamine and methylphenidate.[16] On this basis, antidepressant and antipsychotic medications which block α_1 receptors are believed to have sleep-enhancing effects.[17–18]

II.A.4. Dopamine antagonism—Like norepinephrine, dopamine is also believed to be an important wake promoting neurotransmitter.[1] There is evidence that some of the wake promoting effects of the stimulants d-amphetamine and methylphenidate are mediated through increasing dopaminergic activity at both D1 and D2 receptor subtypes.[16] Antipsychotic medications block these receptors and are believed to be associated with some degree of sleep promoting effects as a result.[13]

II.A.5. Cholinergic antagonism—Acetylcholine is one of the most important neurotransmitters mediating arousal.[19] For example, cholinergic neurons form the core of the brain stem “reticular activating system”.[20] Some of the arousal effects of acetylcholine appear to be mediated via muscarinic cholinergic receptors which are blocked by any antidepressant and antipsychotic medications, resulting in a decrease in arousal and promotion of sleep.[21]

II. B. Promoting wakefulness by inhibiting the reuptake or metabolism of wake promoting neurotransmitters

Wake promotion may occur with antidepressants that block the reuptake or metabolism of neurotransmitters that bind to receptors which promote wakefulness including: the serotonin type 1 and type 2 receptors (5HT₂), norepinephrine receptors (α_1), and dopamine receptors. [1–6] This wake promotion may be therapeutic in many instances, however there is also the potential for these effects to lead to sleep disturbance.

II.B.1. NE reuptake inhibition—A number of antidepressants block the reuptake of norepinephrine including agents referred to as serotonin-reuptake inhibitors (SSRIs – fluoxetine, paroxetine, citalopram, escitalopram), serotonin-norepinephrine reuptake inhibitors (SNRIs-duloxetine, venlafaxine, desvenlafaxine), tricyclic antidepressants, (including: amitriptyline, desipramine, doxepin, trimipramine, imipramine) and bupropion a norepinephrine and dopamine reuptake inhibitor. While it might be expected that SSRIs only block 5HT reuptake and not NE, the data related to this issue suggest that SSRIs and SNRIs represent a continuum with respect to the capacity to block NE.[22] Some of these agents such as escitalopram have minimal NE reuptake inhibition at dosages typically used to treat depression, whereas others have relatively greater associated NE reuptake inhibition in antidepressant dosages (paroxetine, duloxetine, venlafaxine).[23–24] Norepinephrine reuptake would be expected to increase the amount of NE in the synapse, thereby increasing binding to α_1 adrenergic receptors, and promoting wakefulness.[1,16]

II.B.2. 5HT reuptake inhibition—Inhibition of 5HT reuptake occurs with SSRIs, SNRIs, tricyclic antidepressants, and the antidepressant trazodone and would be expected to promote wakefulness by increasing the binding to 5HT₁ and 5HT₂ receptors.[25–26] Consistent with the discussion earlier in this review, increasing the binding to 5HT₂ receptors would be expected to promote wakefulness and suppress non-REM sleep.[7–9] By increasing binding to 5HT₁ receptors, an increase in wakefulness may occur in association with suppression of REM sleep.[27] Daytime sedation has also been associated with inhibition of serotonin reuptake [serotonin-selective reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors [(SNRIs), TCAs], however, it is unclear if this is a primary effect or a secondary effect of sleep disruption occurring in conjunction with 5HT reuptake inhibition.[28–30]

II.B.3. Dopamine reuptake inhibition—Bupropion is the only antidepressant or antipsychotic agent that inhibits dopamine reuptake. Dopamine reuptake inhibition would be expected to have wake promoting effects.[1,16] This view is based to a degree on the fact that a number of stimulants also inhibit DA reuptake, however, a similar clinical profile cannot be assumed for bupropion due to differences in potency and potential regional specificity of dopamine reuptake.[31–32]

II.B.4. Inhibition of Monoamine Oxidase—Monoamine oxidase is the enzyme which breaks down biogenic amines including: NE, 5HT, epinephrine, melatonin, phenylethylamine, trace amines, and dopamine.[33] As a result, medications which inhibit this enzyme, monoamine oxidase inhibitors (MAOI), increase the available amount of NE, 5HT, epinephrine, and DA, and, much like agents which inhibit the reuptake of these neurotransmitters, MAOI may have some degree of wake promoting effects [34–36]. There are two forms of MAOI, one which is primarily involved in the metabolism of 5HT, NE, epinephrine, melatonin, and DA, referred to as MAO type A, while the other, MAO type B, primarily metabolizes DA, phenylethylamine, and trace amines and both have been associated with disturbances of sleep.[35] Daytime sedation is sometimes noted with MAOI, particularly with MAOA inhibitors, however, it is unclear if this is due to the MAO

inhibition or other of the many effects of these agents. It is unclear whether there are sleep/wake effects due to the inhibition of melatonin metabolism by MAOA inhibitors.

II. C. Suppression of REM sleep

Among antidepressant and antipsychotic agents, suppression of REM sleep appears to primarily derive from blockade of Ach receptors (occurs primarily with TCAs and a number of the antipsychotic agents) and increasing 5HT binding to 5HT_{1A} receptors, which occurs with TCAs, MAOIs, SSRIs, and SNRIs.[25,27,37–38] The significance of REM sleep suppression is unclear. Given the observation that REM latency is shortened in major depression and that depressed patients have an increase in the amount and intensity of REM sleep compared with healthy controls, the fact that REM suppression occurs with nearly all antidepressant medications has led to the hypothesis that suppression of REM sleep is a mechanism by which antidepressants have a therapeutic effect on depression.[39–43] However, this remains controversial as several agents which have consistently been demonstrated to have antidepressant effects appear to lack REM suppression (bupropion, mirtazapine, nefazodone).[44] Patients with schizophrenia also have shortened REM latency and an increase in the amount of REM sleep and this has been linked to greater severity of delusions, hallucinations and disorganization of thought and behavior.[44–45] However, there are no data available related to the question of whether the pharmacologic suppression of REM sleep is associated with therapeutic effects in patients with schizophrenia.[44]

II. D. Increasing Slow-Wave Sleep Time and Slow-Wave Amplitude

An increase in the amount of slow-wave sleep and in the amplitude of EEG slow waves in sleep occurs with antidepressants and antipsychotics that block 5HT₂ receptors.[7–10,46–50]. Though, some debate exists regarding the extent to which this effect is associated with different subtypes of 5HT₂ receptors. There is also debate about the clinical significance of this effect. As an increase in slow-wave sleep and slow-wave amplitude occurs in recovery sleep following sleep deprivation, some have hypothesized that these slow-wave effects might be associated with enhancing restoration from sleep.[51] It is also of note that slow-wave sleep is diminished in depressed patients.[39] Whether increasing slow-wave sleep and slow-wave amplitude has any beneficial effect in depression remains unclear. There is also evidence for diminished slow-wave sleep time and slow-wave amplitude in non-REM sleep in schizophrenia and that these changes are associated with greater functional impairment and deficits in cognitive and social deficits.[44–45,52] However, as with major depression, it remains unknown whether increasing slow-wave sleep time and slow-wave activity has therapeutic effects in patients with schizophrenia.[44]

II. E. Promoting Restless Legs Syndrome and Periodic Limb Movements of Sleep

A number of antidepressants and antipsychotics appear to have the potential to cause or exacerbate restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS) which can be associated with difficulties with sleep onset, sleep maintenance complaints, and/or daytime sleepiness.[53] A deficiency in iron, as indicated by serum ferritin at the low end of normal or below, can exacerbate this problem.[54] The mechanisms by which some antidepressant and antipsychotic medications promote RLS and PLMS are incompletely understood, however, this appears to be associated with increasing 5HT availability and dopamine receptor blockade [39,44,55]. On this basis it would be expected that SSRIs, SNRIs, tricyclic antidepressants, MAOIs, and all of the antipsychotics have the potential to increase RLS and PLMS. However, a recent review paper concluded that, of the antidepressants and antipsychotics those most strongly associated with drug-induced RLS in the published literature are: escitalopram; fluoxetine; mianserin; mirtazapine; and olanzapine, whereas those agents most strongly associated with PLMS are: bupropion, citalopram, fluoxetine, paroxetine, sertraline, and venlafaxine.[53] Of these medications, the

link of bupropion and PLMS is most controversial as some studies have not found any evidence of an association of PLMS and bupropion.[56]

III. Impact of Dose and Pharmacokinetics on Sleep-Wake Effects of Antidepressant and Antipsychotic Drugs

In addition to the pharmacologic considerations discussed above, whether sleep-wake effects occur with antidepressant and antipsychotic medications, and what type of effects are noted depend on a number of other factors including the dosage of the medication, the medication half-life, and the medication time to maximum concentration (tmax), an indicator of the speed of absorption. The data relevant to these issues for many antidepressant and antipsychotic medications appear in Table 2.

III A. Dose

Increasing dose generally increases the likelihood that a medication having a pharmacological effect will have an associated clinical effect and also increases the duration of clinical effects. It is important to note that changes in dosage may also alter the balance between different pharmacological effects associated with a given medication. One example of the effects of dosage on clinical effects is the antidepressant mirtazapine. Mirtazapine has a number of potent pharmacologic effects which promote sleep, however, it is also associated with antagonism of the alpha-2 adrenergic receptor, a presynaptic autoreceptor which inhibits NE release, and, as a result, blocking this receptor promotes wakefulness. It has been hypothesized that a decrease in sedation occurring with mirtazapine with increasing dosage is due to a relative increase in the importance of this alpha-2 antagonism at larger doses.[97] As discussed above, doxepin is another example of dose-dependent effects. Doxepin's most potent pharmacologic effect is histamine (H1) antagonism, and, as a result, if the dosage is dropped to a low-enough level, it is possible to achieve a predominant anti-histaminergic effect without the other effects which can occur with this medication including 5HT and NET reuptake inhibition, anticholinergic effects, anti-adrenergic and anticholinergic effects.[14–15] Recent studies suggest that at dosages from 1–6 mg (more than 10 times less than the usual antidepressant dosage) a unique profile of sleep-wake effects become apparent which are presumed to reflect this selective H1 antagonism including a predominant sleep-enhancing effect in the last third of the night without significant morning impairment.[14–15]

III. B. Half-life

Half-life plays an important role, along with dosage, in determining the duration of clinical effects. The longer the half-life the longer the effects are likely to last, though the recent data with low-dose doxepin just discussed suggest that factors other than the blood level of medications can affect the nature of sleep-wake effects observed.[14–15] In this regard, medications which promote sleep that are dosed at bedtime and that have longer half-lives are more likely to be associated with sleep enhancement towards the end of the night and with daytime sedation. Similarly, those with wake promoting effects dosed during the day that have longer half-lives are more likely to disrupt sleep.

III. C. Tmax

Tmax, the time until peak blood level occurs reflects the rate of absorption of a given medication and primarily affects the speed with which sleep-wake effects may become evident. For some medications with very long half-lives that maintain clinically significant serum levels throughout the day, Tmax is likely to have a minimal effect. However, for medications given as a single dosage or those with shorter half-lives, the Tmax can have a

substantial effect on the timing of sleep-wake effects. This is most likely to be apparent with sleep promoting medications given at bedtime where, if absorption is very slow (T_{max} is very long) significant blood levels may not be achieved in time to enhance sleep onset (e.g. olanzapine, ziprasidone, haloperidol).

IV. The Sleep-Wake Effects of Antidepressant Medications

In this section the specific properties of the antidepressant medications are reviewed. The following pharmacologically-based categories of agents are discussed: 1) tricyclic antidepressants; 2) trazodone; 3) mirtazapine; 4) selective serotonin reuptake inhibitors; 5) serotonin-norepinephrine reuptake inhibitors; and 6) bupropion; 7) monoamine oxidase inhibitors. The typical dosage, T_{max} , half-life, pharmacologic effects, and sleep-wake effects of these agents appear in Table 2.

IV. A. Tricyclic Antidepressants

IV.A.1. Pharmacology—The tricyclic antidepressants are a group of related compounds which have in common a cyclic chemical structure. These medications differ in terms of the side-chains which come off of this cyclic structure. All of the tricyclic antidepressants are thought to achieve their antidepressant effects via inhibition of 5HT and NE reuptake. As discussed above, this may be associated with wake promoting effects, suppression of non-REM sleep, suppression of REM sleep (5HT reuptake inhibition), RLS or PLMs (5HT reuptake inhibition). Doxepin and amitriptyline are associated with a relatively greater 5HT than NE reuptake inhibition. Desipramine is associated with relatively greater NE than 5HT reuptake inhibition and, as a result, may have a wake promoting effect. Trimipramine appears to have relatively minimal effects on both NE and 5HT reuptake. Other than NE and 5HT reuptake inhibition, the most important effects of the tricyclic antidepressants are H1 antagonism, muscarinic anticholinergic effects, and α_1 and α_2 adrenergic antagonism. Doxepin is the tricyclic antidepressant with the greatest relative H-1 antagonism potency and trimipramine is also a potent H1 antagonist. As discussed above this likely plays a role in sleep enhancement, particularly in the latter part of the night. Amitriptyline is the most anticholinergic of the tricyclic antidepressants. The anticholinergic effects are also likely to promote sleep to a degree as well as to suppress REM sleep. Amitriptyline, doxepin, and trimipramine are all associated with α_1 and α_2 adrenergic antagonism which is thought to enhance sleep.

Metabolism of tricyclic antidepressants involves a number of liver cytochrome P450 isoenzymes including CYP2C19, CYP2D6, CYP1A2, and CYP3A4.[98–100] As a result, blood levels of tricyclic antidepressants will be affected by factors which alter the function of these isoenzymes including polymorphisms in the population, age, grapefruit juice, and medications such as the antidepressants fluoxetine and paroxetine, the stimulant methylphenidate, and many antipsychotic medications (B 6,8).

The $T_{1/2}$ of the tricyclic antidepressants are all at least 10 hours. As a result, for those with sedating effects dosed at bedtime, there is significant potential for daytime sedation depending on the dosage. Agents which may have wake promoting effects, such as desipramine also have the potential to disrupt sleep at night when dosed in the morning. The T_{max} of these agents varies from 1.5–8 hours (see Table 2). On this basis effects on sleep onset may not be observed from single doses taken at bedtime of some of the tricyclic antidepressants.

IV.A.2. Studies of Sleep-Wake Effects—Studies of the effects of tricyclic antidepressants on sleep include trials of their use as antidepressants and a relatively small number of studies in patients with primary insomnia. Studies of the treatment of depression

have documented the sleep onset and maintenance effects of some tricyclic antidepressants including amitriptyline, doxepin, and trimipramine [12,41,103–106] and that desipramine and nortriptyline have minimal sleep enhancing effects.[41,102] Studies in primary insomnia patients document improvement in sleep quality and sleep efficiency (total sleep time divided by time in bed) but not sleep onset latency with trimipramine at dosages from 50–200 mg.[107–108] Sleep onset, maintenance, and quality effects versus placebo have been documented in studies of doxepin dosed at 25–50 mg.[109–112] As discussed above, doxepin has also been studied in dosages from 1–6 mg in primary insomnia patients where it has relatively selective H1 antagonism effects and been found to have sleep maintenance efficacy, particularly in the last third of the night and also sleep onset efficacy, though the latter effect was less consistently observed.[14–15,113]

In terms of effects of tricyclic antidepressants on sleep stages, doxepin and amitriptyline have been found to decrease the percentage of REM sleep and increase the latency to the onset of REM sleep, whereas no consistent effect on REM has been found for trimipramine. [41,103–105,108,114–115]

Although tricyclic antidepressants are reported to have the potential to cause or exacerbate PLMs and RLS, there is little systematic documentation of this. A recent review did not find any tricyclic antidepressants among those agents most strongly associated with RLS and PLMS.[53]

IV.B. Trazodone

IV.B.1. Pharmacology—Trazodone has a tetracyclic structure and its primary pharmacologic effects include antagonism of 5HT1A, 5HT2 receptors, α_1 adrenergic receptors, and H1 histamine receptors. Trazodone is also a weak inhibitor of 5HT reuptake. [6,116] The antagonism of 5HT1A, 5HT2, α_1 , and H1 receptors are thought to contribute to sleep enhancing effects of this agent. The 5HT2 antagonism would also be expected to lead to an increase in slow-wave sleep/EEG slow-wave activity. There is also the potential for 5-HT2C partial agonism to occur with trazodone therapy deriving from its active metabolite methyl-chlorophenylpiperazine (mCPP) which can lead to wake-promoting effects.[117–118] The degree of mCPP effect is quite variable because many factors affect the key routes of metabolism of trazodone and mCPP including genetic polymorphisms which occur commonly in the population.[117–118] The primary metabolic pathways of trazodone are CYP3A4 and CYP2D6.[2]

Trazodone is typically dosed in a range from 200–600 mg for the treatment of major depression and is dosed from 25 to 150 mg for the “off-label” treatment of insomnia.[2] It has a Tmax of 1–2 hours and a T1/2 of 7–15 hour.[2] As a result, it has the potential to lead to sleep onset and maintenance effects and daytime sedation when dosed just prior to bedtime.

IV.B.2. Studies of Sleep-Wake Effects—Despite the fact that trazodone is one of the most frequently administered insomnia therapies, there has been little systematic research on its sleep-wake effects. A few studies on the effects of trazodone on the sleep of healthy control subjects have been carried out and found efficacy of improvement in sleep time and sleep maintenance.[120] The majority of evidence that trazodone enhances sleep derives from studies of its use in the treatment of major depression.[121–123] Several placebo-controlled studies of the use of trazodone as adjunctive treatment to antidepressant medications also document sleep-enhancing effects with trazodone.[124–125] A placebo-controlled study of trazodone 50 mg in primary insomnia patients identified that a number of sleep parameters improved with trazodone therapy but the effect was only significant vs placebo in the first week of this two-week study.[126] A pilot placebo-controlled trial in

abstinent alcoholics with insomnia was also carried out and identified therapeutic effects on sleep maintenance with trazodone.[127]

Trazodone's effects on sleep stages appear to be limited primarily to an increase in slow-wave sleep and an increase in EEG Delta activity during non-REM sleep. [120–121,123,125,128–129]

In terms of RLS/PLMS, trazodone is not among the medications noted to be among those most commonly associated with drug-induced sleep-related movement difficulties.[53]

IV.C. Mirtazapine

IV.C.1. Pharmacology—The primary pharmacologic effects of mirtazapine are antagonism of 5HT₂, 5HT₃ receptors, α_1 and α_2 adrenergic receptors, and H₁ histaminergic receptors.[130] These effects would be expected to enhance sleep except for the α_2 antagonism which increases norepinephrine release and, on this basis, can promote wakefulness.[131]

Mirtazapine is dosed from 7.5–45 mg. It has a T_{max} of 0.25–2 hours and has a T_{1/2} of 20–40 hours.[2,130] On this basis possible effects include sleep onset effects, sleep maintenance effects, and daytime sedation when dosed at bedtime. The primary metabolism of mirtazapine occurs via CYP2D6, CYP3A4, and CYP1A2.[2]

IV.C.2. Studies of Sleep-Wake Effects—There are no published placebo-controlled trials of the mirtazapine treatment of insomnia. Evidence that mirtazapine has sleep enhancing effects include a double-blind trial comparing this agent with fluoxetine in depressed patients and open-label studies in healthy volunteers.[132–134]

Small polysomnographic studies of mirtazapine have been carried out in healthy volunteers and depressed patients and suggest that this agent improves sleep onset, sleep maintenance, total sleep time.[132,135] Mirtazapine led to an increased amount of slow-wave sleep in one of two of these studies and did not affect REM sleep.

Mirtazapine has been reported to be among the agents most associated with drug-induced RLS.[53]

IV.D. Selective Serotonin Reuptake Inhibitors (SSRIs)

IV.D.1. Pharmacology—As the name suggests, the primary pharmacologic effect of the selective serotonin reuptake inhibitors (SSRIs) is to inhibit 5HT reuptake. As a result, these agents would be expected to have the potential to disturb sleep, suppress REM sleep, and to cause or exacerbate RLS and PLMS. They also have varying degrees of norepinephrine reuptake inhibition which would also be expected to be associated with the potential for sleep disruption.[22–24]

T_{1/2} of the SSRIs varies from 21–144 hours suggesting that they have the potential to disturb sleep and to cause or exacerbate RLS and PLMs when dosed in the morning.

The SSRIs vary in terms of the primary liver cytochromes involved in their metabolism. Fluoxetine is primarily metabolized by CYP2D6 and CYP2C9, whereas fluvoxamine is primarily metabolized by CYP1A2 and CYP2D6, paroxetine is primarily metabolized by CYP2D6, and citalopram is metabolized primarily via CYP2C19.

IV.D.2. Studies of Sleep-Wake Effects—There are few placebo-controlled studies which focused on delineating the sleep-wake effects of SSRIs. Of note, one placebo-

controlled study in older insomnia patients was carried out with paroxetine and noted that a beneficial effect in terms of ratings of sleep quality, daytime alertness, and mood however, the authors concluded that paroxetine was not effective as they noted no effect vs placebo on sleep efficiency or categorical response rate.[136] It is important to bear in mind that SSRIs might have therapeutic effects on sleep via improving mood. However, given the complexity of central 5HT function it is possible that SSRIs might have a direct sleep promotion effect, at least in some individuals. As mentioned above, sedation is not infrequently observed with SSRIs, though it is unclear if this is a sleep promotion effect or consequence of disturbed sleep.[28–30] In this regard, the incidence of insomnia as an adverse event in trials of SSRIs in depressed patients is in the range of 7–22% as compared with 4–11% for placebo.[44] At the same time the frequency of somnolence as an adverse event is in the range of 4–24% for SSRIs compared with 4–11% in placebo subjects.[44] Thus, SSRIs appear to be associated with the potential for both sleep disturbance and sleep promotion. It remains unknown what determines when sleep disturbance, sleep enhancement or neither occurs or if they are related to each other. A factor which might be contributing to either sleep disturbance or the experience of daytime somnolence is PLMS and RLS which may be associated with SSRIs. In fact, SSRIs appear to be among the agents most strongly associated with drug induced RLS and PLMS.[53,56]

IV.E. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

IV.E.1. Pharmacology—The primary pharmacologic effects of the serotonin norepinephrine reuptake inhibitors (SNRIs) is a dose-dependent inhibition of 5HT and NE reuptake. On this basis, these agents would be expected to have the potential to disturb sleep, suppress REM sleep, and to cause or exacerbate RLS and PLMS. Compared with SSRIs, the SNRIs would be expected to have greater associated wake promotion owing to their relatively greater inhibition of norepinephrine reuptake. The SNRIs consist of 3 medications: venlafaxine, desvenlafaxine, and duloxetine.

The T_{1/2} of the SNRIs varies from 5–19 hours suggesting that they have the potential to disturb sleep and to cause or exacerbate RLS and PLMs when dosed in the morning.

The SNRIs are primarily metabolized by CYP2D6 and their elimination will be affected by factors which affect this isoenzyme.

IV.E.2. Studies of Sleep-Wake Effects—Few placebo-controlled studies have been carried out which focused on delineating the sleep-wake effects of SNRIs. One placebo-controlled study of the PSG effects of duloxetine was carried out in 24 healthy controls. [137] In this study, duloxetine was found to decrease the amount of REM sleep and increase the latency to the onset of REM sleep. The effects of duloxetine on sleep onset and maintenance were dependent upon the dosing regimen. A regimen of 60 mg twice per day of duloxetine led to a diminished capacity to stay asleep compared with placebo, whereas a regimen of 80 mg taken each morning improved the ability to fall asleep and maintain sleep vs placebo.

A placebo-controlled trial of the sleep effects of venlafaxine dosed up to a maximum of 225 mg/day was also carried out in depressed patients.[138] Compared with placebo, venlafaxine disturbed sleep in terms of a decrease in total sleep time and increase in wake time and also suppressed REM sleep in terms of an increase in REM latency and a decrease in total duration of REM sleep.

As with SSRIs data exist on the rate at which insomnia and sedation were reported as adverse effects in trials of SNRIs carried out in depressed patients. For venlafaxine the rate of insomnia reported as a side-effect is on the order of 4–23% vs 2–10% with placebo and

somnolence was reported by 5–23% vs 5–10% with placebo.[44] For duloxetine treated patients insomnia was reported by 8–16% of subjects vs 6–10% with placebo whereas somnolence was reported by 11–21% of subjects receiving duloxetine as compared with 3–8% of placebo-treated subjects. While these data seem to suggest a comparable rate of insomnia and sedation as seen with SSRIs, studies systematically assessing sleep and wake function are needed in order to characterize the relative wake and sleep promoting effects of the SNRIs and how this compares with SSRIs. One factor to consider here is dosage as there may be relatively greater noradrenergic reuptake inhibition with greater dosages of the SNRIs and a greater prevalence of insomnia as an adverse effect has been reported with higher dosages of venlafaxine.[44]

In terms of effects on PLMS and RLS, there is relatively less clinical experience with the SNRIs than the SSRIs, however, the SNRI that has been available for the longest period of time in the U.S., venlafaxine, is one of the agents most frequently associated with PLMS. [53] Presumably this reflects the 5HT reuptake inhibition of this agent.

IV.F. Bupropion

IV.F.1. Pharmacology—Bupropion's principal pharmacologic effects are inhibition of norepinephrine and dopamine reuptake. As a result, this medication would be expected to promote wakefulness. No substantive effects on sleep stages or RLS/PLMS would be expected from this pharmacologic profile.

The half-life of bupropion is approximately 21 hours and it is most commonly prescribed in the U.S. in an extended release formulation. On this basis, there is the potential for the disturbance of night time sleep with morning dosing.

Primary metabolism of bupropion occurs via CYP2B6.

IV.F.2. Studies of Sleep-Wake Effects—Data on the sleep-wake effects of bupropion primarily derive from adverse events rates in placebo-controlled depression trials with this agent. These data suggest a rate of insomnia that is comparable to that of SSRIs and SNRIs with a lower rate of somnolence. Insomnia has been reported as an adverse event in 5–20% of bupropion treated patients as compared with 2–8% of patients treated with placebo.[44] The somnolence rate with bupropion was 1–7% vs 2–7% among placebo treated patients suggested minimal potential for sleep enhancement.[44]

There have also been a number of studies examining the PSG effects of bupropion in depressed patients.[56,138–143] Taken together these studies suggest that bupropion has no consistent effect on sleep stage distribution and does not appear to suppress REM sleep.[44]

A few studies have been carried out examining the effects of bupropion on PLMS. These studies suggest that bupropion does not increase PLMS, however a recent review concluded that bupropion is among those agents with a relatively strong association with drug-induced PLMS.[44,53]

IV.G. Monoamine Oxidase Inhibitors (MAOI)

IV.G.1. Pharmacology—Monoamine oxidase is involved in breaking down a number of neurotransmitters that have sleep-wake effects. As described above, there are two types of monoamine oxidase, types A and B. Those which inhibit type A, including phenelzine, isocarboxazid, and tranylcypromine (See Table 2) increase the availability of 5HT, NE, epinephrine, melatonin and DA and would be expected to be associated with wake promotion, REM suppression, and the potential for increasing RLS/PLMS. The monoamine oxidase type B inhibitors primarily increase the availability of DA, phenylethylamine, and

trace amines and would be expected to be primarily associated with wake promotion. The MAOIs also can have anticholinergic effects which would be expected to promote sleep and suppress REM activity and many also block adrenergic receptors and have antihistaminergic effects which may promote sleep.

The T_{max} of the MAOI vary from 0.5–5 hours and their T_{1/2} is 2.5–10 hours. Those with shorter half-lives, such as phenelzine, isocarboxazid, and tranylcypromine would be relatively less likely to disturb sleep if dosed in the morning than selegiline which has a 10 hour half-life.

In terms of the metabolism of MAOIs, phenelzine is inactivated hepatically by acetylation. The metabolism of tranylcypromine occurs via ring-hydroxylation and N-acetylation. The metabolism of selegiline primarily occurs via liver cytochromes CYP2B6 and CYP3A4 with CYP2A6 playing a minor role.

IV.G.2. Studies of Sleep-Wake Effects—Few controlled trials document the sleep/wake effects of MAOIs. Disturbance of sleep has been observed with phenelzine, tranylcypromine, and isocarboxazid and suppression of REM sleep has been reported to occur with phenelzine and tranylcypromine.[4] Phenelzine:

V. The Sleep-Wake Effects of Antipsychotic Medications

In this section the properties of the antipsychotic medications are reviewed. The antipsychotic effects of these medications are primarily believed to be mediated by antagonism of DA receptors. [66,71,144] In this section we discuss these agents employing as a framework the two traditional categories: ‘typical’ antipsychotics, an older group of agents that do not block serotonin receptors, and ‘atypical’ antipsychotics, which do block serotonin receptors in addition to having antidopaminergic effects. [64,71,145] The typical dosage, T_{max}, half-life, pharmacologic effects, and sleep-wake effects of these agents appear in Table 2.

V.A. Typical Antipsychotics

V.A.1. Pharmacology—In addition to antagonism of DA receptors, typical antipsychotics may also have anticholinergic, anti-histaminergic, and antiadrenergic effects. All of these effects would be expected to be sleep enhancing. Of the atypical antipsychotics, those with the greatest antihistaminergic effects relative to their other pharmacologic effects include chlorpromazine and thioridazine.[70,146,147] Of note, these agents, though classified as ‘typical’ antipsychotics, also have some degree of 5HT₂ antagonism and would be expected to be among the most sedating ‘typical’ antipsychotics owing to this 5HT₂ antagonism and strong H₁ blocking effects. Given their 5HT₂ antagonism they would also be expected to increase the amount of slow-wave sleep and increase slow-wave activity. Chlorpromazine and thioridazine also have relatively high anticholinergic activity which has the potential to lead to a suppression of REM sleep. Those agents which are most potent for blocking dopamine receptors, such as, haloperidol, pimozide, and thiothixene have relatively greater potential for triggering leg restlessness and PLMS which can interfere with the ability to fall or stay asleep. [54,148] These higher potency DA antagonists also have anticholinergic effects which carries with it potential suppression of REM sleep.

The T_{max} of thiothixene, thioridazine, and chlorpromazine is on the order of 2–4 hours (see Table 2), suggesting that, when delivered as a single bedtime dose, a sleep onset effect is relatively less likely with these agents than with agents with shorter T_{max}. The likelihood of an effect on sleep onset is even less with haloperidol as it has a T_{max} of 4–6 hours. As the half-lives of these agents is 10–36 hours, there is the potential for sleep maintenance effects

and daytime sedation with bedtime dosing and long-lasting daytime sedation when administered in the morning.

The primary metabolism of the “typical” antipsychotics occurs via the liver cytochromes CYP1A2 (haloperidol), CYP2D6 (haloperidol, thioridazine, and chlorpromazine), and CYP3A4 (haloperidol and pimozide).

The ‘typical’ antipsychotics vary in their side-effect profiles as a function of the relative potency of dopamine antagonism to blockade of other receptor subtypes. Those with highest dopamine antagonist potency, including haloperidol, pimozide, and thiothixene, are the most strongly associated with a set of movement-related adverse effects referred to as “extrapyramidal” side-effects including Parkinsonian symptoms and tardive dyskinesia.[70] With greater dopamine antagonist potency, these agents can achieve an antipsychotic effect with relatively lower levels of other types of pharmacologic effects such as antihistaminic, antiadrenergic, and anticholinergic effects, though these side-effects may still be experienced by some individuals treated with these higher potency agents and are dose dependent.

IV.A.2. Studies of Sleep-Wake Effects—There are few data derived from studies focusing on the sleep-wake effects of ‘typical antipsychotics’. In one open-label study, the PSG effects of clinical dosing of thiothixene and haloperidol were compared in 14 medication-free schizophrenia patients.[87] Compared to baseline, both agents led to improvement in sleep onset latency, wake time after sleep onset, and total sleep time. An increase in REM latency and a small increase in slow-wave sleep time were noted with both medications, though no other effects on REM or slow-wave sleep were observed. A similar study comparing PSG sleep indices in those treated with haloperidol and the ‘atypical’ antipsychotic risperidone found that risperidone led to a greater increase in slow-wave sleep.[91]

In terms of the frequency with which sleep-related effects have been reported as adverse effects in placebo-controlled studies of ‘typical’ antipsychotics, chlorpromazine and thioridazine are associated with the highest rate of reported somnolence (33–57%), whereas 23% of haloperidol-treated patients were noted to have somnolence.[13] Interestingly, insomnia is noted in roughly a quarter of patients treated with haloperidol and thioridazine.[13] It seems likely that this insomnia is due, at least in part to RLS or PLMS being triggered by these medications. In this regard, PSG evidence of an increase in PLMS frequency has been noted with haloperidol.[149–150] It is also possible that PLMS is responsible for the somnolence reported with at least some of the ‘typical’ antipsychotics.

V.B. Atypical Antipsychotics

V.B.1. Pharmacology—The ‘atypical’ antipsychotics differ from the ‘typical’ antipsychotics in terms of having 5HT₂ antagonism in addition to antagonism of DA receptors. On this basis, it might be expected that these agents might be associated with greater sleep enhancement, greater increase in slow-wave sleep, greater increase in slow-wave activity, and perhaps greater weight gain associated with them than ‘typical’ antipsychotics. Olanzapine, risperidone, clozapine, and ziprasidone are the most potent 5HT₂ antagonists of the “atypical” antipsychotics.[13] In addition to the 5HT₂ and DA antagonist effects, ‘atypical’ antipsychotics also have varying degrees of anticholinergic, anti-histaminergic, and antiadrenergic effects, all of which would be expected to enhance sleep to some degree. Of the ‘atypical’ agents, olanzapine and clozapine appear to have the greatest anti-histaminergic and anti-cholinergic effects, [68] while risperidone is a relatively potent α_1 adrenergic antagonist.[69] Quetiapine is a relatively low-potency DA antagonist, and, as a result, it is administered in higher dosages leading to more significant clinical

antihistaminergic and adrenergic effects than other 'atypical' antipsychotics which are more potent antagonists at these receptors.[64] Ziprasidone and aripiprazole are somewhat unique among the 'atypical' antipsychotics as they are 5HT1A agonists which would be expected to be associated with wake promotion and suppression of REM sleep.[13] Aripiprazole is relatively potent as a dopaminergic antagonist and has relatively minor effects on adrenergic and histaminergic receptors at typical clinical dosages.[151] Overall, on the basis of antihistaminergic and anti-adrenergic effects the 'atypical' antipsychotics with the greatest sleep enhancement would be expected to be: olanzapine, clozapine, and quetiapine, however, in terms of 5HT2 antagonist effects, olanzapine, risperidone, ziprasidone, and clozapine would be expected to enhance sleep to the greatest degree.[13] The greatest degree of REM suppression would be expected with ziprasidone and aripiprazole on the basis of their 5HT1A agonist effects and with olanzapine and clozapine due to the associated anticholinergic effects.[13]

From a pharmacokinetic point of view, quetiapine and risperidone that have Tmax of 1–2 hours are most likely to have effects on sleep onset when dosed as a single dose at bedtime (see Table 2), whereas this is least likely with ziprasidone and olanzapine that have Tmax in the range of 4–6 hours.[13] Quetiapine with an elimination half-life of 7 hours is least likely to be associated with daytime sedation with nighttime dosing and will be affected by factors which alter the CYP3A4 and CYP2D6 liver enzymes.[13] The elimination of risperidone is also dependent upon liver cytochromes CYP2D6, CYP3A4, however, its T1/2 is substantially more variable suggesting that a wide range of variation in duration of sedation across the night and during the daytime is likely to be seen with this agent.[13] Ziprasidone metabolized primarily by CYP3A4 and to a lesser degree by CYP1A2 has a relatively short T1/2 of 4–10 hours and, therefore, has a relatively low likelihood of daytime effects when dosed at bedtime. Olanzapine has an elimination half-life which is affected by factors which alter CYP1A2 and CYP2D6, and, as the Tmax is in the range of 25–50 hours this agent is relatively likely to be associated with daytime effects.[13] Aripiprazole and clozapine both have half-lives that exceed 15 hours and, as a result, have the potential for long-lasting effects.

IV.B.2. Studies of Sleep-Wake Effects—Several polysomnographic trials of the sleep-wake effects of 'atypical' antipsychotics have been carried out in healthy volunteers and in those with mood disorders or schizophrenia. Two of these were placebo-controlled cross-over studies comparing sleep on an undisturbed night and a night where subjects were exposed to noise. In one of these studies (N=14), quetiapine dosed at 25 and 100 mg was associated with significant effects on sleep onset latency, total sleep time, sleep efficiency, and sleep quality and led to suppression of REM sleep.[93] In the other study, ziprasidone dosed at 40 mg was associated with significant effects on total sleep time, sleep efficiency, number of awakenings, as well as reported sleep quality.[94] In this study ziprasidone was also found to significantly decrease the percentage of REM sleep and REM density, and increase REM latency and slow-wave sleep time.[94] Small PSG studies of olanzapine in healthy controls and in patients with mood disorders and schizophrenia suggest that this agent improves sleep latency, wake time after sleep onset, sleep efficiency, and sleep quality and increases slow-wave sleep time. [88,153–158] Quetiapine dosed in a range from 25–75 mg has also been studied in an open-label study in patients with primary insomnia and was noted to improve self-reported sleep onset latency, sleep efficiency, and total sleep time. [159] Open-label PSG studies of the treatment of patients with schizophrenia with 10 mg of olanzapine have been carried out and confirm that this agent decreases the number of awakenings, increases total sleep time, and increases the percentage of slow-wave sleep. [88–89] Two small studies of clozapine in medication-free schizophrenia patients have been carried out indicating that this agent decreases wake time and awakenings, improves sleep time, and increases slow-wave sleep time. [85,90] A PSG study of the effects of risperidone

0.5–1 mg in a small number of depressed patients was also carried out and indicated that this medication decreased wake time after sleep onset and decreased the amount of REM sleep. [92] In a study comparing clinical treatment with haloperidol and risperidone, risperidone led to significantly greater slow-wave sleep time.[91]

Adverse effects data suggest that the highest rates of sedation among the ‘atypical’ antipsychotics occur with clozapine (52%), followed by risperidone (30%) and olanzapine (29%).[13] The agent with the lowest rate of somnolence as an adverse effect in placebo-controlled trials was aripiprazole which is associated with somnolence in approximately 12% of cases.[13] Quetiapine and ziprasidone both are associated with somnolence as an adverse event in 16% of subjects.[13] In interpreting these data it is important to bear in mind that the rate of sedation as an adverse effect reflects both the sleep enhancement of the medication as well as its pharmacokinetic properties.

Insomnia reported as an adverse effect was most common with aripiprazole, reported by 24% of subjects.[13] Risperidone and olanzapine are associated with insomnia as an adverse event in 17–18% of subjects, whereas quetiapine and ziprasidone have been associated with a 9% rate of insomnia.[13] As noted above, it is impossible to determine the extent to which RLS/PLMS might be contributing to the rates of insomnia or daytime sedation observed. Few studies have looked at the association of RLS/PLMS with ‘atypical’ antipsychotic medications. However, the few that have studied this relationship have reported an association of PLMS with olanzapine and risperidone among the ‘atypical’ antipsychotics [149–150] suggesting that at least some of the insomnia reported with these agents may have been PLMS-related.

VII. Summary and Conclusions

This chapter has reviewed the pharmacology and associated sleep-wake effects of the antidepressant and antipsychotic medications. Although the available data on the sleep-wake effects of these medications is limited, the data that exists suggests a clear correspondence between the pharmacology of these agents and their varying effects on sleep-wake function. In this regard, antidepressants tend to be associated with inhibition of the reuptake of 5HT or NE (and DA in the case of bupropion) or have 5HT₂ antagonism. The 5HT reuptake inhibition appears to be associated with a tendency towards wake promotion, suppression of REM sleep and triggering of RLS/PLMS. Sedation and some of the sleep disturbance seen with 5HT reuptake inhibitors may be a direct pharmacologic effect or secondary to eliciting RLS/PLMS. The NE reuptake inhibition appears to primarily be associated with wake promotion while 5HT₂ antagonism may be associated with a tendency towards sleep promotion, slow-wave sleep enhancement, and possibly weight gain/insulin resistance. The antipsychotics may also be antagonists of 5HT₂ receptors, particularly the ‘atypical’ antipsychotics, though their antipsychotic effect appears to derive from dopamine antagonism which appears to increase the risks of RLS/PLMS and may be sleep promoting. The other sleep-wake effects of the antidepressants and antipsychotics derive from pharmacologic effects not related to their antidepressant or antipsychotic mechanisms including cholinergic antagonism (sleep promotion and suppression of REM sleep), histaminergic antagonism (sleep promotion, possibly increase in appetite), adrenergic antagonism (sleep promotion and orthostatic hypotension), and 5HT_{1A} agonist effects (wake promotion, suppression of REM sleep). This chapter also discusses how pharmacokinetic and dosing factors also play a key role in determining the varied sleep-wake effects of these medications. It is hoped that this review of these principles will provide a basis for understanding the sleep-wake effects of antipsychotic and antidepressant medications that will be of utility both for research and for clinical practice.

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Table 1
Pharmacologic Mechanisms of Sleep Wake Effects of Antidepressants and Antipsychotics

Mechanism	Sleep Promotion	Wake Promotion	REM Suppression	Increases SWS	Promotes RLS/PLMS
H1 Antagonism	✓				
Ach Antagonism	✓		✓		
5HT2 Antagonism	✓			✓	
α_1 Antagonism	✓				
α_2 Antagonism		✓			
D1/D2 Antagonism	✓				✓
5HT Reuptake Inhibition		✓	✓		✓
NE Reuptake Inhibition		✓			
DA Reuptake Inhibition		✓			
MAO Inhibition		✓	✓		✓
5HT1A Agonism		✓	✓		

Table 2

Key Attributes of Antidepressant and Antipsychotic Medications

Medication	Type	Dosage*	Tmax (hrs)	T1/2 (hrs)	Mechanisms of Sleep Effects	Possible Sleep Effects
ANTIDEPRESSANTS						
Amitriptyline	Tricyclic	10–300 mg	2–5	10–100	Antagonism of NE, HA, Ach, 5HTT, NET	↑Sleep, ↓REM ↑RLS/PLMS
Doxepin	Tricyclic	25–300 mg	1.5–4	10–50	Antagonism of NE, HA, Ach, 5HTT, NET	↑Sleep, ↓REM ↑RLS/PLMS
Doxepin	Tricyclic	3–6 mg	1.5–4	10–50	Antagonism of HA	↑Sleep
Trimipramine	Tricyclic	25–300 mg	2–8	15–40	Antagonism of NE, HA, Ach	↑Sleep, ↑RLS/PLMS
Trazodone	Phenylpiperazine	25–600 mg	1–2	7–15	Antagonism of 5HT2, NE, HA, 5HTT	↑Sleep, ↓REM ↑RLS/PLMS, ↑SWS
Mirtazapine	Tetracyclic	7.5–45 mg	0.25–2	20–40	Antagonism of 5HT2, HA	↓Sleep, ↓REM ↑RLS/PLMS
Fluoxetine	SSRI	10–80 mg	6–8	96–144	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Paroxetine	SSRI	10–50 mg	6–10	21	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Sertraline	SSRI	25–200 mg	8	24	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Citalopram	SSRI	20–60 mg	4	35	Antagonism of 5HTT	↓Sleep, ↓REM ↑RLS/PLMS
Escitalopram	SSRI	10–20 mg	5	27–32	Antagonism of 5HTT	↓Sleep, ↓REM ↑RLS/PLMS
Venlafaxine	SNRI	75–225 mg	2–5.5	5–11	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Desvenlafaxine	SNRI	50–400 mg	0.5	11	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Duloxetine	SNRI	40–60 mg	6	9–19	Antagonism of 5HTT, NET	↓Sleep, ↓REM ↑RLS/PLMS
Bupropion XL	Aminoketone	150–450 mg	1.5	21	Antagonism of NET and DAT	↓Sleep
Phenelzine	“Irreversible” MAOI	15–90 mg	2–4	2.5	MAO A and B Inhibition	↓Sleep, ↓REM ↑RLS/PLMS
Isocarboxazid	“Irreversible” MAOI	10–40 mg	3–5	2.5	MAO A and B Inhibition	↓Sleep, ↓REM ↑RLS/PLMS
Tranylcypromine	“Reversible” MAOI	30–60 mg	1–3	2.5	MAO A and B Inhibition	↓Sleep, ↓REM ↑RLS/PLMS

Medication	Type	Dosage*	Tmax (hrs)	T1/2 (hrs)	Mechanisms of Sleep Effects	Possible Sleep Effects
Selegiline	"Reversible" MAOI	5–10 mg	0.7–1.5	10	MAO B Inhibition	↓ Sleep
Selegiline Transdermal	"Reversible" MAOI	6–12 mg	Rapid	10	MAO B Inhibition	↓ Sleep
ANTIPSYCHOTICS						
Olanzapine	Thio-benzodiazepine	2.5–20 mg	4–6	20–54	Antagonism of HA, NE, Ach, 5HT ₂ , DA	↑ Sleep, ↑ SWS, ↑ RLS/PLMS
Quetiapine	Dibenzo-thiazepine derivative	25–300 mg	1–2	7	Antagonism of HA, NE, Ach, 5HT ₂ , DA	↑ Sleep, ↓ REM ↑ RLS/PLMS
Risperidone	Benzisoxazole derivative	1–8 mg	1	3–20	Antagonism of DA, 5HT, NE, HA	↑ Sleep, ↓ REM ↑ RLS/PLMS, ↑ SWS
Ziprasidone	Benzo-thiazolyl-piperazine derivative	20–160 mg	5	4–10	Antagonism of DA, 5HT, NE, HA, 5HTT, NET	↑ Sleep, ↓ REM ↑ RLS/PLMS, ↑ SWS
Aripiprazole	Benzisoxazole derivative	10–30 mg	3–5	75	Partial DA, 5HT _{1A} Agonist; Antagonist of 5HT _{2A} , NE, HA	± Sleep, ? REM ↑ RLS/PLMS, ? SWS
Clozapine	Dibenzo-diazepine	12.5–500 mg	3	16	Antagonism of DA, Ach, 5HT, NE, HA	↑ Sleep, ↑ RLS/PLMS, ↑ SWS
Thiothixene	Thioxanthene Derivative	2–60 mg	2–4	34	Antagonism of DA, Ach, NE	↑ Sleep, ↓ REM ↑ RLS/PLMS, ↑ SWS
Thioridazine	Piperidine Phenothiazine	10–800 mg	2–4	10	Antagonism of DA, NE, Ach, 5HT, HA	↑ Sleep, ? REM ↑ RLS/PLMS, ? SWS
Chlorpromazine	Dimethylamine Phenothiazine Derivative	10–2000 mg	2–4	15–30	Antagonism of DA, Ach, 5HT, NE, HA	↑ Sleep, ? REM ↑ RLS/PLMS, ? SWS
Haloperidol	Butyrophenone	0.5–100 mg	4–6	12–36	Antagonism of DA, NE, HA	↑ Sleep, ↓ REM ↑ RLS/PLMS, ↑ SWS

* Refers to daily dosage

OH=Orthostatic Hypotension; NE=Norepinephrine; Ach=Acetylcholine; GLU=Glutamate; GABA=gamma-amino-butyric acid; 5HT₂=Serotonin Type 2 Receptor. Table based on the following references:
[2,56–96]