Sleep Medicine Reviews (2004) **8**, 19–30

ELSEVIER

SLEEP MEDICINE reviews

www.elsevier.com/locate/jnlabr/ysmrv

CLINICAL REVIEW

# Treatment of insomnia associated with clinical depression

**Ripu D. Jindal***, **Michael E. Thase**

*Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA*

**KEYWORDS**
Insomnia; Depression; Sleep; Antidepressant therapy; Behavioral management

**Summary** Sleep disturbances are almost always present in patients with depression. Though sleep disturbances generally abate with the resolution of depression, some patients continue to report poor sleep. Since a number of studies have demonstrated that insomnia increases the risk of new-onset depression and recurrence of depression, optimal management of insomnia associated with depression becomes an important clinical goal. Antidepressant agents have variable effects on sleep and in fact, some antidepressants seem to worsen sleep in patients with depression. This article reviews various treatment options in the management of patients presenting with insomnia and depression, including single agents, combination strategies and behavioral interventions.


Poor sleep is such a fundamental aspect of depression that one needs to be careful in making a diagnosis of depression in the absence of sleep complaints. Sleep disturbances in depression include insomnia, the more common form, and hypersomnia. In fact, some patients fluctuate between hypersomnolence and insomnia during the course of an episode of depression. These different patterns of sleep disturbances reflect the psychobiological heterogeneity of depressive syndromes. The onset, depth, duration, and restorative quality of sleep also are influenced by an age-dependent interplay of serotoninergic, noradrenergic, cholinergic, and peptidergic neurotransmission systems. Some of the sleep disturbances associated with depression are of prognostic value, predicting poorer response to some forms of therapy as well as relapses and recurrences. This article will address management of insomnia associated with the depressive disorders, including bipolar depression, major depressive disorder, and dysthymia. After briefly reviewing the epidemiology and pathophysiology of difficulties initiating and maintaining sleep, the strategies used to treat insomnia in depression will be discussed, beginning with the simplest 'monotherapy' strategies and moving on to the various adjunctive approaches.

## Clinical correlates

The incidence and severity of sleep disturbances associated with depression are partly dependent on factors such as age, sex, and the subtype and severity of the depressive syndrome. As is generally true for the non-depressed, aging is associated with greater difficulty maintaining sleep in depression. Hypersomnolence, by contrast, is more common

*Corresponding author. Present Address: Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA. Tel.: +1-412-624-3568; fax: +1-412-624-4000.
*E-mail address:* jindalr@msx.upmc.edu (R.D. Jindal).

1087-0792/03/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S1087-0792(03)00025-X

earlier in life and may be nearly as prevalent as insomnia among younger depressed women.[1,2] Bipolar depression[3] and seasonal (Fall/Winter pattern) depression[4] are also associated with a relatively higher prevalence of hypersomnia. Astute clinicians also watch for a sudden decrease in sleep in bipolar depression as an indicator of the transition to mixed, psychotic or manic episodes.[13]

Insomnia associated with depression is generally described by three overlapping presentations: difficulty falling asleep (DFA), difficulty staying asleep or sleep continuity disturbances (SCD), and early morning awakening (EMA). Although none of these disturbances is pathognomonic of depression, DFA is usually viewed as the least specific (i.e. very common in many other disorders) and EMA as the most specific. The most severe insomnias are associated with recurrent, melancholic depressive episodes and psychotic depressions, which are also the conditions more likely to occur among older adults.[5–7] Comorbid anxiety associated with depression also increases the likelihood of worsening insomnia. In turn, the severity of depressive insomnia has been linked to suicidality[8,9] and poorer response to various forms of antidepressant treatment.[10–12]

Sleep disturbances also represent antecedents or risk factors for subsequent depressive episodes. For example, among both younger adults and those at mid-life, insomnia is associated with a 2–4 fold increased risk for depression during longitudinal follow-up.[13–15] The re-emergence of insomnia similarly can herald a new episode of recurrent depression.[16] Similarly, improvement in subjective insomnia is closely related to global improvement in depression.[17] Together, these observations suggest that insomnia is a form fruste of at least some forms of mood disorder.

## Pathophysiology

The polysomnogram has, for 50 years, been the principal tool for investigating the pathophysiology of sleep disturbances. The discovery of rapid eye movement (REM) sleep (and it's relation to dreaming) presaged a period of intense investigation of sleep as a dynamic process involving both circadian and ultradian rhythms.

At the electrophysiological level, a night of healthy sleep can be thought of a series of progressions through 5 states of brain activity, including both 4 arbitrarily defined stages of nonREM sleep and 3–6 periods of REM sleep. The stages 3 and 4 of nonREM sleep, also known as slow wave sleep, are characterized by the predominance of delta (slow) waves, as well as the lowest levels of spontaneous movement and arousability. Slow wave sleep also has been shown to be associated with the lowest absolute rate of brain glucose metabolism[18,19] and there is increasing certainty that slow wave sleep is biologically necessary.[20]

High amplitude delta waves are concentrated in the first half of the night. The first nocturnal period of slow wave sleep also is normally paired with the circadian surge in secretion of growth hormone. The amount of slow wave sleep decreases across a night and, after adolescence, is progressively less across each subsequent decade of longevity. The decline in the amount of slow wave sleep associated with normal aging is further accelerated by most serious general medical and mental illnesses.[21] Slow wave sleep thus can be thought of as a general health indicator.

Most people have 3–6 periods of REM sleep across the night, occurring at approximately 90-minute intervals. Defined by the characteristic eye movements and faster electroencephalographic activity, about 90% of dreaming occurs in REM sleep. Most experts now agree that REM sleep is associated with consolidation of new knowledge and integration of waking affective experiences.[22,23] Not surprisingly, this psychologically complex stage of sleep is associated with increased blood flow and glucose metabolism in limbic regions.[24] REM sleep has an ultradian pattern that is reciprocal to slow wave sleep: REM periods typically increase in length and 'intensity' (i.e. number of eye movements per unit of time) as the night progresses.

Various changes in REM sleep have been demonstrated in different depressive states.[25] At the least specific level, states of heightened generalized arousal tend to inhibit the onset of REM sleep,[21] an effect mimicked by psychostimulants.[26] By contrast, affectively charged states, including depressive dysphoria, mania, and the flashbacks of post-traumatic stress disorder, have been associated with increased REM sleep indices.[21,27,28] However, depressive syndromes associated with general medical disorders may be characterized by either decreased REM time or reduced REM intensity.[21,29] Some abnormalties in REM sleep especially reduced REM latency were widely thought to be specific to depression. However, a subsequent meta-analysis demonstrated that none of abnormalities in REM sleep is unique to depression.[27]

Apart from the changes in REM sleep, other common polysomnographic features of patients with depression are reduced sleep efficiency, increased sleep latency, frequent awakenings,

increases in stage 1 and 2 sleep and reduced slow wave sleep.[30] Some but not all of these polysomnographic features tend to normalize with the resolution of depression.[31]

Sleep patterns in depression have consistently shown age effects in different studies. For example, EEG sleep studies of depressed children and adolescents have not revealed the same magnitude of changes as seen in adults.[32] Lauer and colleagues (1991) have also demonstrated that there is no difference in REM latency between the depressed and the controls until the middle of the fourth decade of life.[33] Similarly, elderly patients with depression do not tend to show significant differences in their sleep patterns as compared to age-matched controls. One possibility is that due to the age-related decline in sleep variables like slow wave sleep, elderly patients have very little (in terms of sleep) to lose.[27,30] It is also possible that depression in the very young and the very old has a different etiopathogenesis than in those in their middle years.

All antidepressant medications have some effects on sleep architecture.[34] Suppression of REM sleep with the treatment of depression was such a consistent finding in early studies that it was seen as essential for the antidepressant action. This belief was further supported by the evidence of correlation between clinical response and REM suppression as well as temporal relationship between the onset of clinical response and REM suppression. However, some of the latter studies suggested that REM suppression is not necessary for antidepressant action. For example, some studies show evidence of no change[35–37] or even an increase in REM sleep[38] with the treatment of depression. Recently, Landolt and colleagues (2001) have also demonstrated that antidepressant response to phenelzine treatment does not depend on elimination of REM sleep or inhibition of slow wave activity in non-REM sleep.[39] However, the generalizibility of some of these studies is limited by their small sample sizes.

## Insomnia with depression: treatment choices

Before initiating treatment of the insomnia associated with depression, it is important to rule out primary sleep disorders such as sleep apnea and periodic leg movement syndrome. Patients with sleep apnea and PLMS have higher rates of depression than the general population.[40–42] Furthermore, there is evidence that effective treatment of sleep apnea improves mood in these patients.[41,43,44] It is not clear if treatment of PLMS offers similar benefits.

Another reason for ruling out primary sleep disorders is that some of the agents used in the treatment of insomnia associated with depression are known to worsen primary sleep disorders. For example, some, but not all antidepressant agents are associated with worsening of PLMS.[45] Similarly, there is evidence that hypnotics may worsen obstructive sleep apnea syndrome.[46] However, some studies suggest that hypnotics may improve sleep without affecting breathing in patients with mild sleep apnea.[47] Thus, a cautious and 'case by case' approach is recommended in prescribing hypnotics in patients with sleep apnea. In our practice, we also try to avoid serotonergic antidepressant agents in patients with significant PLMS.

### Prescription of a single agent

Use of a single agent at bedtime simplifies adherence and minimizes cost and the risk of drug-drug interactions. The effects of tertiary tricyclic antidepressants (e.g. amitriptiline, doxepin, trimipramine), selective serotonin reuptake inhibitors (fluoxetine, sertraline, paroxetine, citalopram), trazodone, nefazodone, mirtazapine, bupropion and venlafaxine have been studied as single agents in the treatment of depression and insomnia. Among the tricyclic antidepressants (TCAs), both amitriptyline and trimipramine have been shown to improve mood and sleep in well-controlled studies.[48–50]

The TCAs have REM suppressing effects, which range from modest (i.e. a 20% reduction in REM time) to marked (i.e. a 75% reduction in REM time).[51] REM suppression is typically greater during the first 3 to 4 h of sleep [52] and there is some accommodation to these effects with extended therapy.[53] In fact, the intensity of REM sleep during the final hours of sleep may actually increase over time to a level greater than at pretreatment.

The degree of suppression of REM sleep early during TCA monotherapy has some predictive effects on subsequent antidepressant response.[54,55] This effect, which is largely independent of sedative effects, is probably a direct consequence of monoamine reuptake inhibition in brainstem serotoninergic and/or noradrenergic nuclei.

Due to their more troublesome side effect profile and potential for lethality in overdose, the TCAs have been largely replaced by the selective serotonergic agents (SSRIs) as the most commonly used antidepressants throughout much of the world. SSRIs are generally considered to be less

sedating than most of the TCAs and, in fact, seem to be activating.[56] For example, reduced sleep continuity has been documented in the PSG recordings with the use of various SSRIs.[37,56–60] Despite this apparent worsening of sleep, many patients report improvements in subjective sleep during SSRI therapy.[37,61] This is explained partly by the fact that people (with or without depression) are likely to underestimate the number of short awakenings[62,63] and partly by the alleviation of the negative cognitive set associated with depression. Nevertheless, a sizable minority of patients report either persistent or worsening insomnia with the use of an SSRI.[64]

In one study, the effects of venlafaxine on sleep architecture more or less paralleled those of the SSRIs.[65] However, that study only employed lower doses of venlafaxine, doses in which it acts predominately as a serotonergic agent. It will be interesting to study the effects of venlafaxine on sleep in doses commonly used in clinical practice.

Though there is very limited data on the effect of bupropion on sleep,[36] it also is generally considered an activating antidepressant. Because of their activating effects, a number of patients taking SSRIs, venlafaxine or bupropion are coprescribed benzodiazepines or sedating antidepressants, and yet others are switched to sedating antidepressants. Some physicians even choose agents such as TCAs, trazodone, nefazodone or mirtazapine ahead of the SSRIs, venlafaxine and bupropion in the treatment of depressive insomnia. Due to the paucity of comparative studies regarding the superiority of one antidepressant over the other, treatment choices are driven by individual preferences. The recommendations that we usually make to our patients are summarized in Fig. 1.

There is evidence that monotherapy with trazodone, nefazodone and mirtazapine (in moderate doses) relieves depressive insomnia. Among these, trazodone is seldom used now as an antidepressant, though two studies have documented the improvement in clinical parameters of depression as well as on the polysomnographic variables with trazodone monotherapy.[66,67] Nefazodone has definite beneficial effects on self-report and PSG measures of depressive insomnia when used as a monotherapy.[37,68,69] In a large multi-center trial, nefazodone therapy also had significantly more rapid and greater ultimate improvement of depressive insomnia than those treated with psychotherapy despite the two interventions having similar overall antidepressant effects by the end of the acute phase.[70] Nefazodone is also much less likely to cause orthostasis than its predecessor, trazodone, and

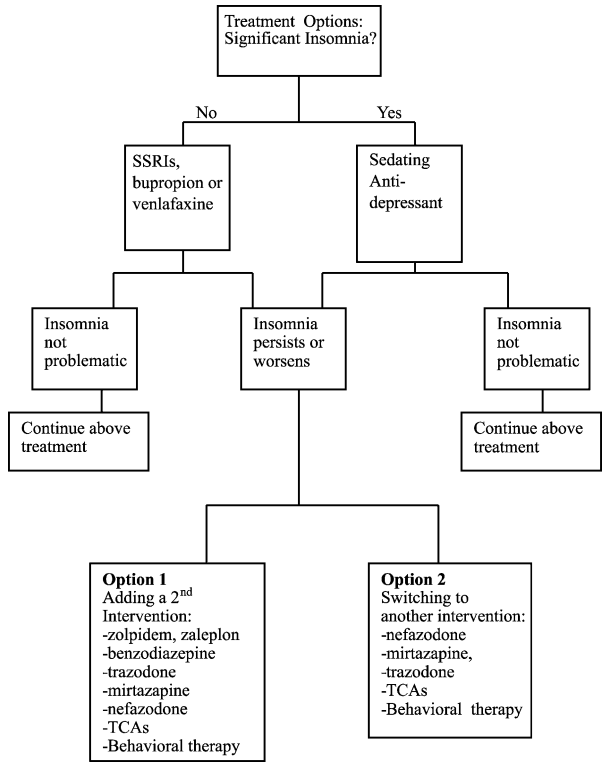


**Figure 1** A proposed treatment decision-tree.

(to date) there have been no reports of priapism among nefazodone-treated men.

Mirtazapine is a tricyclic-like compound that is virtually devoid of effects on monoamine reuptake or cardiac conduction. Mirtazapine is a potent blocker of 5-$HT_2$, 5-$HT_3$, and histamine receptors and, among the newer antidepressants, it has the strongest initial sedative effects.[71,72] These effects cause daytime sedation in about 50% of patients during the first two weeks of mirtazapine monotherapy.[72]

There are several small studies of the effects of mirtazapine on PSG profiles that document modest REM suppression and significant reductions of nocturnal awakenings and awake time.[73] In one such study, six depressed patients treated with mirtazapine had a rapid improvement in subjective depression scores and objective sleep parameters.[74] Moreover, sleep architecture and daytime alertness were preserved. Further polysomnographic study of mirtazapine in larger groups of depressed patients is needed.

## Co-prescription of antidepressants

Persistent insomnia during antidepressant treatment also can be dealt with by prescription of a second antidepressant medication. Although we know that this strategy is commonly used, the actual frequency of this practice is not well-quantified.

Typically, compounds such as trazodone, doxepin, trimipramine, amitriptyline, nefazodone, or mirtazapine are used to capitalize on sedative effects associated with blockade of histamine or 5-$HT_2$ post-synaptic receptors. This practice has several advantages, foremost being avoidance of concerns of abuse, dependence, or tolerance associated with other sedative-hypnotics if longer-term therapy is required. Other strengths include the possibility of synergistic or adjunctive antidepressant effects and, with the exception of nefazodone and mirtazapine, the availability of relatively inexpensive generic formulations.

One important shortcoming of the antidepressant co-prescription strategy is a relative lack of good data on the effectiveness of these strategies. One study demonstrated an improvement in subjective sleep with the addition of trazodone in depressed patients treated with either fluoxetine or bupropion.[75] However, that study did not employ PSG recording.

To our knowledge, there are no PSG studies of co-prescription of TCAs with SSRIs, venlafaxine, bupropion, or reboxetine: experience with the tricyclics as concomitant medications is thus anecdotal. The TCAs most widely chosen are strongly antihistaminic, although it is possible that 5-$HT_2$ blockade also may be implicated. Of course as the effects on TCAs alone, even at modest doses have been studied systematically in the sleep laboratory, some inferences can be drawn.

A second area of concern centers on safety. Potential problems include drug-drug metabolic interactions (e.g. elevated TCA plasma levels because of inhibition of CYP P450 $2D_6$ or $3A_4$ isoenzymes), blood level related TCA effects on cardiac conduction, and orthostatic hypotension, which can occur even at lower TCA doses. The TCAs also can be lethal in overdoses as small as 1,000 mg of amitriptyline or its equivalent and such lethality may be increased if the concomitant antidepressant affects TCA metabolism or sedation thresholds.

Although not yet studied in the sleep laboratory, co-prescription of mirtazapine (15–30 mg) and a SSRI, venlafaxine, bupropion, or reboxetine could be expected to have beneficial effects on persistent insomnia. Mirtazapine, unlike the TCAs, does not have metabolic interactions with other newer antidepressants and also could be expected to lessen other treatment-emergent 5-$HT_3$ -mediated gastro-intestinal side effects.[74] Beyond initial daytime sedation, the major adverse effects attributable to mirtazapine therapy are increased appetite and weight gain (both ranging between 20 and 30% in acute phase trials).[74] It is not clear if co-prescription of a second antidepressant would lessen or worsen weight gain.

Some physicians also co-prescribe nefazodone (50–200 mg/q.h.s.) to treat persistent insomnia during SSRI therapy. In our experience, it is less useful than trazodone as a co-therapy. One concern about adding nefazodone to ongoing SSRI therapy pertains to anecdotal reports of poor tolerability.[76] This could result from inhibition of both CYP P450 $2D_6$ (selected SSRIs) and $3A_4$ (nefazodone), including the possibility of significant increases in the nefazodone metabolite meta-chlorophenylpiperazine (mCPP). This metabolite can paradoxically worsen depression and cause feelings of tenseness (anxiety).[77]

## Co-prescription with benzodiazepines

Evidence from drug utilization data-bases suggests that 30–40% of patients treated with SSRIs receive concomitant benzodiazepines (BZ).[78] In our experience, about one-half of such co-prescription is for treatment of persistent insomnia.

The prescription of benzodiazepine sedative-hypnotics has long been a subject of much debate. On one hand, the BZs are remarkably safer and less prone to problems with abuse or dependence than earlier sedative-hypnotics. The mechanism of action is well-understood and this effect appears to complement, not counteract, the impact of SSRIs and other newer antidepressants on CNS arousal. Interactions between BZs and SSRI, when present, simply result in higher BZ plasma levels, which can readily be dealt with by reduction of BZ dosage. On the other hand, there is a small but definite risk that the patient who begins BZ therapy will become physiologically dependent and never willing to stop therapy. This can occur even within a month of use.[78] A fair proportion of both physicians and their patients have definite reservations about 'getting hooked' on sleeping pills. It is possible that the objective benefits on nightly BZ therapy generally wane during extended treatment, although the patient's subjective (perceived) sense of benefit persists.[79]

The various BZs used for management of persistent or treatment-emergent insomnia are available in generic formulations. The principal factors differentiating between individual compounds are elimination half-lives and duration of action. The BZs can be grouped into 4 categories based on these characteristics: ultra-short (triazolam), short (alprazolam, lorazepam), intermediate (clonazepam), and long (diazepam, nitrazepam). Longer half-lived medications are generally not

used with elders to prevent drug accumulation and hang over.

Abuse potential is linked to both greater lipophylicity of particular BZs and a shorter elimination half-life. Alprazolam and lorazepam tend to be more notorious in this regard. However, all BZs have abuse potential and all potentiate the effects of alcohol. Reports of marked amnestic effects are generally limited to the ultra-short and short-acting BZs, particularly if combined with alcohol. Conversely, 'hang-over' effects are more common with the longer acting BZs.

The effects of BZs on sleep have been studied extensively in healthy volunteers and people with insomnia. Two placebo-controlled studies have shown the benefit of triazolam among patients with depression and insomnia taking TCAs.[81,82] Other controlled studies have documented the concomitant benefit of lormetazepam[83] and chlordiazepoxide[84] in patients being treated with TCAs. Similarly, the efficacy and tolerability of four different BZ agents as adjunctive therapy has been documented in patients being treated with nefazodone.[85]

Perhaps surprisingly, we could not identify any controlled PSG studies of depressed patients taking BZs and concomitant SSRIs. Nevertheless, the results from studies of insomnia should be directly relevant. At therapeutic doses BZs decrease sleep latency and reduce nocturnal awakenings, resulting in an increase in total sleep time. BZs have a modest REM-suppressing effect and typically have no effect on slow wave sleep. Rebound insomnia and increased REM 'pressure' will occur after abrupt discontinuation, even after only a few weeks of therapy. Of course, more pronounced, and even potentially medically dangerous withdrawal syndromes are possible after months of nightly therapy at higher doses.

Studies relying on clinical ratings document that co-administration of a BZ with an antidepressant agent results in more rapid symptomatic improvements than antidepressant monotherapy, especially on ratings of anxiety and insomnia.[86] A recent study of this type compared co-therapy with fluoxetine (20 mg/day) and clonazepam (0.5–1.0 mg) against fluoxetine and placebo.[87] The patients receiving combined therapy experienced significantly greater improvements in depression scores during the first 3 weeks of therapy. However, tapering of clonazepam after 3 weeks resulted in some worsening of depression scores and after 6 weeks of therapy, the fluoxetine plus placebo group had achieved comparable antidepressant response. A more recent study by the same group of researchers shows that continued cotherapy (fluoxetine and clonazepam) though safe even at 18 weeks, loses its advantage over fluoxetine monotherapy at 3 weeks.[88]

The vast majority of patients receiving long-term BZ co-therapy do not require progressive dose escalation. Some patients will develop physiologic tolerance, however, and such patients point to rebound insomnia on nights that the medication was not been taken as powerful evidence of the need for ongoing therapy. Given the likelihood that a successful course of antidepressant therapy will be continued for months or even years, it seems prudent to shift to intermittent BZ doses within the first weeks of therapy if possible (Table 1).

## GABA A receptor agonists

Zolpidem (Ambien®) and zaleplon (Sonata®) are examples of BZ-like drugs that selectively bind to the $\omega_1$ site of the GABA-A receptor. The goal of further lessening the side effects and abuse potential associated with conventional BZs led to the development of these selective compounds. Both the medications are short acting and there are fewer problems with 'hangover' effects. The efficacy of these two medications has been demonstrated in a number of studies.[89,90] Of the two, there is more data available with the use of zolpidem. For example, a large well-controlled, multi-site study has shown the efficacy of zolpidem in insomnia associated with depression that is persistent despite SSRI therapy.[91]

Both of zolpidem and zaleplon are now extensively prescribed by generalists and psychiatrists alike. However, both medications are still patent-protected and, as such, cost is the major limitation when compared to other popular strategies. Moreover, a recent meta-analyses demonstrated evidence of tolerance with the use the zolpidem.[92] The authors also concluded that the available data for zaleplon was insufficient to assess its risk of tolerance.

## Nonprescription ('over the counter') sleep aids

Many patients use 'over the counter' sleep aids because of the convenience (i.e. no doctor's visit or prescription is needed) and freedom of choice (see Table 2). The most commonly chosen brands include potent antihistamines such as diphenhydramine or doxylamine. In the past decade, 'natural' compounds such as valerian, melatonin, 5-hydroxytryptamine, catnip, chamomile, gotu kola, hops, L-trytophan, lavender, passion-flower,

**Table 1** Benzodiazepines commonly used to treat insomnia.

| Benzodiazepine | Usual therapeutic dose | | Time until onset of action (min) | Half life (h) |
|---|---|---|---|---|
| | Adult mg/day | Geriatric mg/day | | |
| Chlorazepate | 3.75-15 | 3.75-7.5 | 30-60 | 6-8 (48-96 for the metabolite) |
| Estazolam | 1-2 | 0.5-1 | 15-30 | 8-24 |
| Oxazepam | 15-30 | 10-15 | 30-60 | 2.8-5.7 |
| Quazepam | 7.5-15 | 7.5 | 20-45 | 15-40 (39-120 for the metabolite) |
| Temazepam | 15-30 | 7.5-15 | 45-60 | 3-25 |
| Triazolam | 0.125-0.25 | 0.125 | 15-30 | 1.5-5 |
| Clonazepam[a]0.5-2 | 0.5-2 | 0.5-2 | 0.25-1 | 20-60 |
| 19-60 | Lorazepam[a] | 1-4 | 0.25-1 | 30-60 |

Adapted with permission from Kupfer DJ and Reynolds CF III, 1997 [80]
[a] Clonazepam and lorazepam are not approved by the FDA for the treatment of insomnia.

skull cap also have gained in popularity.[93] However, there is a paucity of data supporting their use. In a randomized, placebo-controlled double-blind study, depressed patients treated with fluoxetine reported improved sleep with the use of melatonin.[94] That study relied solely on a subjective sleep quality index and did not employ PSG recordings. Similarly, valerian has been credited with improvement in subjective sleep in one study.[95] However, two other studies employing PSG recordings failed to show an improvement in sleep with the use of valerian.[96,97] To the best of our knowledge, there are no studies supporting the use of other 'natural' compounds. Quality control is another potential problem with the 'natural' compounds, as they are classified as dietary supplements in the United States and quality, potency, and bio-availability are not regulated by the Food and Drug Administration (FDA). Lack of FDA oversight also enables manufacturers to make more dramatic claims of benefits. Though tolerance to sedative effects is commonly reported with extended use, there are no reports of withdrawal effects with the discontinuation of these 'over the counter' agents and as such these agents do not seem to be habit-forming. It is ironic that the antihistaminic effects of TCAs such as amitriptyline or doxepin can be reproduced by adding 50 mg of diphenhydramine at bedtime to an ongoing regimen of an SSRI. This combination is costlier than a medication such as amitriptyline, but conserves much of the safety advantage of the newer antidepressants. Some caution is necessary to avoid concomitant use of antihistamine sleep aids and mirtazapine (as a potent histamine$_1$ receptor blockade) and the potential for drug-drug interactions of yet to be identified mechanisms may exist for valerian. Melatonin at supraphysiologic doses also has the theoretic potential to exacerbate depression[98] and suppress secretion of endogenous melatonin.[99]

## Behavioral sleep management

Relatively simple sleep enhancing strategies have been available for years but are seldom utilized by psychiatrists and other physicians. These behavioral management strategies build upon the 'dos and don'ts' of sleep hygiene by educating patients about factors that can disrupt sleep ('stimulus control') and encourage stable sleep-wake schedule ('temporal control'). To summarize briefly, patients are asked to refrain from caffeine and

**Table 2** Over the counter sleep aids.

| | |
|---|---|
| Antihistamines | Diphenhydramine or doxylamine. Available as tablets. They are also present in many over the counter preparations with the suffix 'PM' such as Tylenol® PM |
| Melatonin | Available as a tablet. Dose 1-10 mg |
| Chamomile | A white apple-scented flower. Dried, capsules, aromatic oil used as teas, baths, aroma |
| Hops | Raw flowers/extract used as teas |
| California poppy | A non-narcotic flower. Raw flower/extract used in teas |
| Catnip | Dried leaves used as teas |
| Lemon balm | Raw leaves, oil used as teas, baths, massages |
| Lavender | Oil, lotions used as aroma, teas, massages, baths |
| Passion flower | Dried, capsules, oil used as aroma, teas, bath oil, tablets, capsules |
| Skullcap | Dried leaves, teas, tablets, capsules |
| Valerian root | Raw, tablets, powder used as teas, tablets |
| Gotu kola | Dried herb, tea, dried leaves |

brisk exercise in the evening and to pick a reasonable regular time for 'lights out.' The room is kept cool, dark, and as noise-free as possible. Arousing prompts, such as an illuminated clock face, are turned out of sight and snacking, reading, or watching television in bed is voluntarily suspended. Inability to fall asleep within 15 min triggers a stimulus shift, such as moving to another room and reading under dim light until one is sufficiently drowsy to return to bed. A regular wake time also is set, and should be adhered to regardless of the quality or duration of the night's sleep.

Sleep restriction is a critical aspect of behavioral management. Beyond constraining morning sleep time, napping is discouraged if possible and, if irresistible, limited to a brief 30 min nap at midday (i.e. 'the power nap'). Sleep restriction also may be intensified by slightly curtailing the time spend in bed at night. For example, if the person desires 7 h of sleep and habitually retires at 2300 h, 'lights out' may be delayed to midnight, keeping the wake up time to 0600 h. Bed time may then be shifted backwards in 15 min intervals per week.

Insomnia associated with heightened dysphoric arousal may require more intensive cognitive and behavioral strategies. Progressive deep muscle relaxation and biofeedback are example of more elaborate stimulus control procedures that help the patient shift attentional focus to more calming or neutral inputs. Cognitive interventions are similarly useful to help to recognize disturbing sleep-related thoughts ('If I can't get to sleep within 15 min tomorrow will be a disaster!') and practice less upsetting alternatives ('Although I don't feel as well when I can't sleep, its not the end of the world and I've got a lot of experience functioning despite my insomnia').

Behavioral management strategies typically can be taught within 30–90 min. These strategies have been shown to have more durable benefits than sedative-hypnotics in the treatment of insomnia.[100] The sustained benefit of behavioral management may eventually offset greater acute cost. They do require a greater level of motivation on the part of both patient and provider and the relative underuse largely reflects the comparative ease of writing a prescription. Also, some patients simply cannot master these strategies or despite great effort glean little benefit.

A recent comparative meta-analysis of treatment studies of insomnia shows similar overall benefits for behavioral strategies and pharmacotherapy.[101] Earlier, Morin and colleagues[102] reviewed the evidence regarding the efficacy of non-pharmacological treatments for primary chronic insomnia, and concluded that three therapies (i.e. stimulus control, progressive muscle relaxation and paradoxical intention) met American Psychological Association (APA) criteria for empirically supported treatments. They also noted that three treatments (sleep restriction, biofeedback and multifaceted cognitive-behavioral therapy) met the APA criteria for probably efficacious treatments.

Though most of the empirical evidence supporting behavioral therapy comes from studies of primary insomnia, at least one study demonstrates the benefit of concomitant behavioral and pharmacological treatment in improving insomnia associated with other psychiatric disorders.[103] The work of Morin and his colleagues helped the American Academy of Sleep Medicine (AASM) to frame its practice parameters for the non-pharmacological treatment of chronic insomnia.[104] The AASM has recommended stimulus control as the generally accepted patient care strategy with a high level of clinical certainty. The AASM rated progressive muscle relaxation, paradoxical intention, and biofeedback as therapies with a moderate degree of clinical certainty, and sleep restriction and multicomponent CBT as therapies with uncertain clinical use. The AASM found insufficient evidence to recommend the use of sleep hygiene education, imagery training and cognitive therapy as single therapy. The AASM practice parameters pertain to insomnia in general and their applicability to insomnia associated with depression is uncertain. Further research effort directed at patients with depressive disorders will help optimize treatment for this population. There is also a need for systematic study of concomitant behavioral and pharmacological therapies in the management of insomnia associated with depression.

In summary, sleep disturbances are an integral part of depression. Though a causal relationship between insomnia and depression is unproven, optimum management of insomnia may play an important part in the prevention and treatment of depression. Empirical evidence is available regarding the efficacy of a wide variety of interventions, such as behavioral therapies, pharmacotherapies (including sedating antidepressants, co-prescriptions of antidepressants and hypnotics and over the counter products etc.), in the treatment of insomnia associated with depression. However, due to the paucity of comparative studies of different interventions, treatment algorithm is driven by individual choice of the patients and their clinicians. Continued research is needed to

standardize the treatment of insomnia associated with depression.

## Practice points

- rule out primary sleep disorders such as Sleep apnea, Periodic leg movement syndrome
- consider a newer antidepressant with beneficial effects for sleep (e.g., nefazodone or mirtazapine) as the first line intervention
- when safety and tolerability indicators are favorable, trazodone and some tricyclic antidepressants also might be considered
- for patients who experience treatment-emergent or persistent insomnia while taking SSRIs, bupropion or venlafaxine, either add a hypnotic medication (such as zolpidem, zaleplon, or benzodiazepine), begin behavioral therapy, or switch to a sedating antidepressant
- Reserve antidepressant combinations for patients who have inadequate responses to monotherapy

## Research agenda

To determine if

- the following pharmacotherapies are effective in large polysomnographic studies of patients with insomnia associated with depression?
  - mirtazapine monotherapy
  - combination of trazodone and SSRI or bupropion or venlafaxine
  - combination of benzodiazepines and SSRI, bupropion or venlafaxine
  - combination of 'natural' products and SSRIs, bupropion, venlafaxine
- any of the antidepressant agents is superior to others in comparative studies in these patients?
- the agents such as zolpidem and zaleplon are effective beyond 6 months?
- sequential strategies (e.g. pharmacotherapy followed by behavioral therapy) offer any advantage over monotherapies?
- combined therapy is better than monotherapy (pharmacotherapy or behavioral therapy)?

## References


1. Thase ME, Carpenter L, Kupfer DJ, Frank E. Clinical significance of reversed vegetative subtypes of major depression. *Psychopharmacology Bulletin* 1991; **27**: 17—22.
2. Matza 2, Reviki LS, Davidson DA, Stewart JR, Depression JW. Depression with atypical features in the national comorbidity survey: classification, description and consequences. *Arch Gen Psychiatry* 2003; . In Press.
3. Thase ME, Himmelhoch JM, Mallinger AG, Jarrett DB, Kupfer DJ. Sleep EEG and DST findings in anergic bipolar depression. *Am J Psychiatry* 1989; **146**: 329—333.
4. Rosenthal NE, Sack DA, Gillin JC, Lewy AJ, Goodwin FK, Davenport Y, Mueller PS, Newsome DA, Wehr TA. Seasonal affective disorder. A description of the syndrome and preliminary findings with light therapy. *Arch Gen Psychiatry* 1984; **41**: 72—80.
5. Feinberg M, Carroll BJ. Biological markers for endogenous depression. Effect of age, severity of illness, weight loss, and polarity. *Arch Gen Psychiatry* 1984; **41**: 1080—1085.
6. Frank E, Kupfer DJ, Hamer T, Grochocinski VJ, McEachran AB. Maintenance treatment and psychobiologic correlates of endogenous subtypes. *J. Affect Disord* 1992; **25**: 181—189.
7. Thase ME, Kupfer DJ, Ulrich RF. Electroencephalographic sleep in psychotic depression. A valid subtype? *Arch Gen Psychiatry* 1986; **43**(9): 886—893.
8. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, Gibbons R. Time-related predictors of suicide in major affective disorder. *Am J Psychiatry* 1990; **147**: 1189—1194.
9. Agargun MY, Kara H, Solmaz M. Sleep disturbances and suicidal behavior in patients with major depression. *J Clin Psychiatry* 1997; **58**: 249—251.
10. Reynolds CF, Frank E, Houck PR, Mazumdar S, Dew MA, Cornes C, Buysse DJ, Kupfer DJ. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *Am J Psychiatry* 1997; **154**: 958—962.
11. Buysse DJ, Tu XM, Cherry CR, Begley AE, Kowalski J, Kupfer DJ, Frank E. Pre-treatment REM sleep and subjective sleep quality distinguish depressed psychotherapy remitters and nonremitters. *Biol Psychiatry* 1999; **45**: 205—213.
12. Thase ME, Simons AD. Reynolds CF III: Abnormal electroencephalographic sleep profiles in major depressions: association with response to cognitive behavior therapy. *Arch Gen Psychiatry* 1996; **53**: 99—108.
13. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry* 1996; **39**: 411—418.
14. Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ. Insomnia in young men and subsequent depression. The Johns Hopkins precursors study. *Am J Epidemiol* 1997; **146**: 105—114.

*15. Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: a prospective perspective. *Am J Psychiatry* 2000; **157**: 81—88.


*The most important references are denoted by an asterisk.

16. Perlis ML, Giles DE, Buysse DJ, Tu X, Kupfer DJ. Self-reported sleep disturbance as a prodromal symptom in recurrent depression. *J Affect Disord* 1997; **42**: 209—212.
17. Casper RC, Katz MM, Bowden CL, Davis JM, Koslow SH, Hanin I. The pattern of physical symptom changes in major depressive disorder following treatment with amitriptyline or imipramine. *J Affect Disord* 1994; **31**: 151—164.
18. Buchsbaum MS, Gillin JC, Wu J, Haslett E, Sicotte N, Dupont R, Bunney Jr. WE. Regional cerebral glucose metabolic rate in human sleep assessed by positron emission tomography. *Life Sci* 1989; **45**: 1349—1356.
19. Maquet P, Dive D, Salmon E, Sadzot B, Franco G, Poirrier R, von Frenckell R, Franck G. Cerebral glucose utilization during sleep-wake cycle in man determined by positron emission tomography and and 2 over black square]; [1 and 2 over black square]8F]2-fluoro-2-deoxy-D-glucose method]. *Brain Res* 1990; **513**: 136—439.
20. Horne J. Human slow wave sleep: a review and appraisal of recent findings, with implications for sleep functions, and psychiatric illness. *Experientia* 1992; **48**: 941—954.
21. Kupfer DJ, Thase ME. The use of sleep laboratory in the diagnosis of affective disorders. *Psychiatric Clinics of North America* 1983; **6**: 3—25.
*22. Stickgold R, Hobson JA, Fosse R, Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. *Science* 2001; **294**(5544): 1052—1057.
23. Kramer M. The selective mood regulatory function of dreaming: an update and revision. In: AR Moffitt, M Kramer, RF Hoffman (eds.) *The function of dreaming*. Albany, NY: State University of New York Press 1993; 139—195.
24. Maquet P, Peters JM, Aerts J, Delfiore G, Degueldre C, Luxen A, Franck G. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. *Nature* 1996; **383**: 163—166.
25. Kupfer DJ. Sleep research in depressive illness: clinical implications - a tasting menu. *Biol Psychiatry* 1995; **38**: 391—403.
26. Valerde C, Pastrana LS, Ruiz JA, Solis H, Jurado JL, Sordo CM, Fernandez-Guardiola A, Maisterrena JA. Neuroendocrine and electroencephalographic sleep changes due to acute amphetamine ingestion in human beings. *Neuroendocrinology* 1976; **22**: 57—71.
*27. Benca RM, Obermeyer WH, Thisted RA, Gillin JC. Sleep and psychiatric disorders: a meta-analysis. *Arch Gen Psychiatry* 1992; **4**: 651—668.
28. Pitman RK, Orr SP, Shalev AY, Metzger LJ, Mellman TA. Psychophysiological alterations in post-traumatic stress disorder. *Seminars in Clinical Neuropsychiatry* 1999; **4**: 234—241.
29. King D, Akiskal HS, Lemmi H, Wilson W, Belluomini J, Yerevanian BI. REM density in the differential diagnosis of psychiatric from medical-neurologic disorders: a replication. *Psychiatry Res* 1981; **5**: 267—276.
30. Benca RM. Mood disorders. In: MH Kryger, T Roth, WC Dement (eds.) *Principles and practice of sleep medicine*. London: WB Saunders Company 1994; 899—913.
31. Thase ME, Jindal R, Howland RH. Biological processes in depression. In: I Gottlieb, CL Hammen (eds.) *Handbook of Depression*, 3rd edn. New York, NY: Guilford Press 2002; 192—218.
32. Dahl RE, Lewis DS. Sleep and depression. In: S Gregory, W Luci (eds.) *Sleep disturbance in Children and adolescents with disorders of development: its significance and management*. Mac Keith Press 2001; 161—168.
33. Lauer CJ, Riemann D, Wiegand M, Berger M. From early to late adulthood changes in EEG sleep of depressed patients and healthy volunteers. *Biol Psychiatry* 1991; **29**: 979—993.
*34. Sharpley AL, Cowan PJ. Effects of pharmacological treatments on sleep of depressed patients. *Biol Psychiatry* 1995; **37**: 85—98.
35. Mendlewicz J, Dunbar GC, Hoffman G. Changes in sleep EEG architecture during treatment of depressed patients with mianserin. *Acta Psychiatrica Scand* 1985; **72**(320): 26—29.
36. Nofzinger EA, Reynolds III CF, Thase ME, Frank E, Jennings RJ, Fasiczka AL, Sullivan LR, Kupfer DJ. REM sleep enhancement by bupropion in depressed men. *Am J Psychiatry* 1995; **152**: 274—276.
*37. Rush AJ, Armitage R, Gillin JC, Yonkers KA, Winokur A, Moldofsky H, Vogel GW, Kaplita SB, Fleming JB, Montplaisir J, Erman MK, Albala BJ, McQuade RD. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. *Biol Psychiatry* 1998; **44**: 3—14.
38. Monti JM. Effect of reversible monoamine oxidase-A inhibitor (moclobemide) on sleep of depressed patients. *Br J Psychiatry* 1989; **155**: 61—65.
39. Landolt HP, Raimo EB, Schnierow BJ, Kelsoe JR, Rapaport MH, Gillin JC. Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. *Arch Gen Psychiatry* 2001; **58**: 268—276.
40. Kales A, Caldwell AB, Cadieux RJ, Vela-Bueno A, Ruch LG, Mayes SD. Severe obstructive sleep apnea: II. Associated psychopathological and psychological consequences. *J Chronic Dis* 1985; **38**: 427—434.
41. Millman RP, Fogel BS, McNamara ME et al. Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. *J Clin Psychiatry* 1989; **50**: 348—351.
42. Saletu M, Anderer P, Saletu B, Lindeck-Pozza L, Hauer C, Saletu-Zyhlarz G. EEG mapping in patients with restless legs syndrome as compared with normal controls. *Psychiatry Res* 2002; **115**: 49—61.
43. Pochat MD, Ferber C, Lemoine P. Depressive symptomatology and sleep apnea syndrome. *Encephale* 1993; **19**(6): 601—607.
44. Sanchez AI, Buela-Casal G, Bermudez MP, Casas-Maldonado F. The effects of continuous positive air pressure treatment on anxiety and depression levels in apnea patients. *Psychiatry Clin Neurosci* 2001; **55**: 641—646.
45. Nofzinger EA, Fasiczka A, Berman S, Thase ME. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. *J Clin Psychiatry* 2000; **61**: 858—862.
46. Kryger MH. Management of obstructive sleep apnea. *Chest* 1992; **13**: 481—492.
47. Camacho ME, Morin CM. Effect of temazepam on respiration in elderly insomniacs with mild sleep apnea. *Sleep* 1995; **18**: 644—645.
48. Ware JC, Brown FW, Moorad PJ, Pittard JT, Cobert B. Effects on sleep: a double-blind study comparing trimipramine to imipramine in depressed insomniac patients. *Sleep* 1989; **12**: 537—549.
49. Scharf MB, Hirschowitz J, Zemlan FP, Lichstein M, Woods M. Comparative effects of limbitrol and amitriptyline on sleep efficiency and architecture. *J Clin Psychiatry* 1986; **47**: 587—591.
50. Shipley JE, Kupfer DJ, Griffin SJ, Dealy RS, Coble PA, McEachran AB, Grochocinski VJ, Ulrich R, Perel JM. Comparison of effects of desipramine and amitriptyline on EEG sleep of depressed patients. *Psychopharmacology* 1985; **85**: 14—22.
51. Montero RF, Riemann D, Berger M. Antidepressant and antimanic drugs. In: A Kales (ed.) *Pharmacology of sleep*. Berlin: Springer-Verlag 1995; 465—490.

52. Reynolds CF, Kupfer III DJ. Sleep research in affective disorder: state of the art circa 1987. *Sleep* 1987; (1987): 199—215.
53. Reynolds 3rd CF, Hoch CC, Buysse DJ, George CJ, Houck PR, Mazumdar S, Miller M, Pollock BG, Rifai H, Frank E. Sleep in late-life recurrent depression. Changes during early continuation therapy with nortriptyline. *Neuropsychopharmacology* 1991; **5**: 85—96.
54. Kupfer DJ, Foster FG, Reich L, Thompson KS, Weiss B. EEG sleep changes as predictors in depression. *Am J Psychiatry* 1976; **133**: 622—626.
55. Gillin JC, Wyatt RJ, Fram D, Snyder F. The relationship between changes in REM sleep and clinical improvement in depressed patients treated with amitriptyline. *Psychopharmacology* 1978; **59**: 267—272.
56. Jindal RD, Friedman ES, Berman SR, Fasiczka AL, Howland RH, Thase ME. Effects of sertraline on sleep architecture in patients with depression. *J Clin Psychopharmacol* 2003; **23**: 540—548.
57. Shipley JE, Kupfer DJ, Dealy RS, Griffin SJ, Coble PA, McEachran AB, Grochocinski VJ. Differential effects of amitryptyline and of zimelidine on the sleep electroencephalogram of depressed patients. *Clin Pharmacol. Ther* 1984; **36**(2): 251—259.
58. Kerkhofs M, Rielaert C, de Maertelaer V, Linkowski P, Czarka M, Mendlewicz J. Fluoxetine in major depression: efficacy, safety and effects on sleep polygraphic variables. *Int Clin Psychopharmacol* 1990; **5**: 253—260.
59. Staner L, Kerkhofs M, Detroux D, Leyman S, Linkowski P, Mendlewicz J. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. *Sleep* 1995; **18**: 470—477.
60. Hicks JA, Argyropoulos SV, Rich AS, Nash JR, Bell CJ, Edwards C, Nutt DJ, Wilson SJ. Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression. *Br J Psychiatry* 2002; **180**: 528—535.
61. Nowell PD, Buysse DJ, Dew DA, Reynolds CF, Kupfer DJ. Paroxetine in the treatment of primary insomnia: preliminary clinical and electroencephalogram sleep data. *J Clin Psychiatry* 1999; **60**: 89—95.
62. Knab B, Engel RR. Perception of waking and sleeping: Possible implications for the evaluation of insomnia. *Sleep* 1988; **11**: 265—272.
63. Armitage R, Trivedi M, Hoffmann R, Rush AJ. Relationship between objective and subjective sleep measures in depressed patients and healthy controls. *Depression Anxiety* 1997; **5**: 97—102.
64. Preskorn SH. Comparison of tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. *J Clin Psychiatry* 1995; **56**(6): 12—21.
65. Luthringer R, Toussaint M, Schaltenbrand N, Bailey P, Danjou PH, Hackett D, Guichoux JY, Macher JP. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression. *Psychopharmacol Bull* 1996; **32**: 637—646.
66. Mouret J, Lemoine P, Minuit MP, Benkelfat C, Renardet M. Effects of trazodone on the sleep of depressed subjects—a polygraphic study. *Psychopharmacology* 1988; **95**: 37—43.
67. Scharf MB, Sachais BA. Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomniac patients. *J Clin Psychiatry* 1990; **51**: 13—17.
68. Armitage R, Yonkers K, Cole D, Rush AJ. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. *J Clin Psychopharmacology* 1997; **17**: 161—168.
69. Gillin JC, Rapaport M, Erman MK, Winokur A, Albala BJ. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. *J Clin Psychiatry* 1997; **58**: 185—192. erratum appears in J Clin Psychiatry, 58 275.
70. Thase ME, Rush AJ, Manber R, Kornstein SG, Klein DN, Markowitz JC, Ninan PT, Friedman ES, Dunner DL, Schatzberg AF, Borian FE, Trivedi MH, Keller MB. Differential effects of nefazodone and cognitive behavioral analysis system of psychotherapy on insomnia associated with chronic forms of major depression. *J Clin Psychiatry* 2002; **63**: 493—500.
71. Stahl S. *Essential Pharmacology*. Cambridge: Cambridge University Press 1996.
72. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs* 1999; **57**: 607—631.
73. Winokur A, Gary KA, Rodner S, Rae-Red C, Fernando AT, Szuba MP. Depression, sleep physiology, and antidepressant drugs. *Depression and anxiety* 2001; **14**: 19—28.
74. Winokur A, Sateia MJ, Hayes JB, Bayles-Dazet W, MacDonald MM, Gary KA. Acute effects of mirtazapine on sleep continuity and sleep architecture in depressed patients: a pilot study. *Biol Psychiatry* 2000; **48**: 75—78.
75. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. *Am J Psychiatry* 1994; **151**: 1069—1072.
76. Physician's Desk Reference 2002. Medical Economics Company. Oradell, New Jersey. Edition 56: pp 1105
77. Riedel WJ, Klaassen T, Griez E, Honig A, Menheere PP, van Praag HM. Dissociable hormonal, cognitive and mood responses to neuroendocrine challenge: evidence for receptor-specific serotonergic dysregulation in depressed mood. *Neuropsychopharmacology* 2002; **26**: 358—367.
*78. Furukawa TA, Streiner DL, Young LT. Antidepressant and benzodiazepines for major depression. *Cochrane database syst rev* 2002; : 3.
79 Institute of Medicine, Division of Mental Health and Behavioral Medicine, *Sleeping Pills, Insomnia, and Medical Practice*. Washington, DC: National Academy of Sciences 1979.
80. Kupfer DJ, Reynolds 3rd CF. Management of insomnia. *N Engl J Med* 1997; **336**: 341—346.
81. Cohn JB. Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry* 1983; **44**: 401—406.
82. Dominguez RA, Jacobson AF, Goldstein BJ, Steinbook RM. Comparison of triazolam and placebo in the treatment of insomnia in depressed patients. *Curr Ther Res* 1984; **36**: 856—865.
83. Nolen WA, Haffmans PMJ, Bouvy PF, Duivenvoorden HJ. Hypnotics as concurrent medication in depression. A placebo-controlled, double-blind comparison of flunitrazepam and lormetazepam in patients with major depression, treated with a (tri)cyclic antidepressant. *J Affect Disord* 1993; **28**: 179—188.
84. Schraf MB, Hirschowitz J, Zemlan FP, Lichstein M, Woods M. Comparative effects of limbitrol and amitriptyline on sleep efficiency and architecture. *J Clin Psychiatry* 1986; **47**: 587—591.
85. Rickels K, Schweizer E, Case WG, DeMartinis N, Greenblatt DJ, Mandos LA, Espana FG. Nefazodone in major depression: adjunctive benzodiazepine therapy and tolerability. *J Clin Psychopharmacol* 1998; **18**: 145—153.

86. Sussman 86, Anxiolytic N. Anxiolytic antidepressant augmentation. *J Clin Psychiatry* 1998; **59**: 42—48. discussion 49—50.
87. Smith WT, Londborg PD, Glaudin V, Painter JR. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am J Psychiatry* 1998; **155**: 1339—1345.
88. Smith WT, Londborg PD, Glaudin V, Painter JR. Summit Research Network. Is extended clonazepam cotherapy of fluoxetine effective for outpatients with major depression? *J Affect Disord* 2002; **70**: 251—259.
89. Holm KJ, Goa KL. Zolpidem: an update of its pharmacology, therapeutic efficacy and tolerability in the treatment of insomnia. *Drugs* 2000; **59**: 865—889.
90. Dooley M, Plosker GL. Zaleplon: a review of its use in the treatment of insomnia. *Drugs* 2000; **60**: 413—445.
91. Asnis GM, Chakraburtty A, DuBoff EA, Krystal A, Londborg PD, Rosenberg R, Roth- Schechter B, Scharf MB, Walsh JK. Zolpidem for persistent insomnia in SSRI-treated depressed patients. *J Clin Psychiatry* 1999; **60**: 668—676.
*92. Soldatos CR, Dikeos DG, Whitehead A. Tolerance and rebound insomnia with rapidly eliminated hypnotics: a meta-analysis of sleep laboratory studies. *Int Clin Psychopharmacology* 1999; **14**(5): 287—303.
93. Cauffield JS, Forbes HJ. Dietary supplements used in the treatment of depression, anxiety, and sleep disorders. *Lippincott's Primary Care Practice* 1999; **3**: 290—304.
94. Dolberg OT, Hirschmann S, Grunhaus L. Melatonin for the treatment of sleep disturbances in major depressive disorder. *Am J Psychiatry* 1998; **155**: 1119—1121.
95. Leathwood PD, Chauffard F, Heck E, Munoz-Box R. Aqueous extract of valerian root (Valeriana officinalis L.) improves sleep quality in man. *Pharmacol Biochem Behav* 1982; **17**: 65—71.
96. Leathwood PD, Chauffard F. Quantifying the effects of mild sedatives. *J Psychiatric Research* 1983; **17**: 115—122.
97. Balderer G, Borbely AA. Effect of valerian on human sleep. *Psychopharmacology* 1985; **87**: 406—409.
98. Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry* 1976; **133**: 1181—1186.
99. Leibenluft E, Feldman-naim S, Turner EH, Wehr TA, Rosenthal NE. Effects of exogenous melatonin administration and withdrawal in five patients with rapid-cycling bipolar disorder. *J Clin Psychiatry* 1997; **58**: 383—388.
100. Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late—life insomnia: a randomized controlled trial. *JAMA* 1999; **281**: 991—999.
*101. Smith MT, Perlis ML, Park A, Smith MS, Pennington J, Giles DE, Buysse DJ. Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia. *Am J Psychiatry* 2002; **159**: 5—11.
102. Morin CM, Hauri PJ, Espie CA, Spielman AJ, Buysse DJ, Bootzin RR. Nonpharmacologic treatment of chronic insomnia. *Sleep* 1999; **22**: 1134—1156.
103. Dashevsky BA, Kramer M. Behavioral treatment of chronic insomnia in psychiatrically ill patients. *J Clin Psychiatry* 1998; **59**: 693—699.
*104. Chesson Jr. AL, Anderson WM, Littner M, Davila D, Hartse K, Johnson S, Wise M, Rafecas J. Practice parameters for the nonpharmacologic treatment of chronic insomnia. An American Academy of sleep medicine report. standards of practice committee of the American Academy of sleep medicine. *Sleep* 1999; **22**: 1128—1133.