REVIEW ARTICLE

Drugs 2005; 65 (7): 927-947
0012-6667/05/0007-0927/$39.95/0



# Antidepressants and Sleep
## A Qualitative Review of the Literature

*Sue Wilson* and *Spilios Argyropoulos*

Psychopharmacology Unit, University of Bristol, Bristol, UK

## Contents



## Abstract

Most antidepressants change sleep; in particular, they alter the physiological patterns of sleep stages recorded overnight with EEG and other physiological measures. These effects are greatest and most consistent on rapid eye movement (REM) sleep, and tend to be in the opposite direction to the sleep abnormalities found in major depression, but are usually of greater degree. Reductions in the amount of REM sleep and increases in REM sleep onset latency are seen after taking antidepressants, both in healthy volunteers and in depressed patients. Antidepressants that increase serotonin function by blocking reuptake or by inhibiting metabolism have the greatest effect on REM sleep. The decrease in amount of REM sleep appears to be greatest early in treatment, and gradually diminishes during long-term treatment, except after monoamine oxidase inhibitors when REM sleep is often absent for many months. Sleep initiation and maintenance are also affected by antidepressants, but the effects are much less consistent between drugs. Some antidepressants such as clomipramine and the selective serotonin receptor inhibitors (SSRIs), particularly fluoxetine, are sleep-disturbing early in treatment and some others such as amitriptyline and the newer serotonin 5-$HT_2$-receptor antagonists are sleep promoting. However, these effects

are fairly short-lived and there are very few significant differences between drugs after a few weeks of treatment. In general, the objectively measured sleep of depressed patients improves during 3–4 weeks of effective antidepressant treatment with most agents, as does their subjective impression of their sleep. Sleep improvement earlier in treatment may be an important clinical goal in some patients, perhaps when insomnia is particularly distressing, or to ensure compliance. In these patients, the choice of a safely used and effective antidepressant which improves sleep in short term is indicated. Patients with other sleep disorders such as restless legs syndrome and REM sleep behaviour disorder should be identified before choosing a treatment, as some antidepressants worsen these conditions. Conversely, there is evidence that some antidepressants may be useful in the treatment of sleep disorders such as night terrors.

It is important to be aware of the sleep effects of antidepressants for a number of reasons. The first reason is that sleep disruption is a major symptom in depression, with over 90% of patients with major depression having sleep complaints.[1] Sleep difficulty is often the symptom which causes depressed patients to seek medical help, and relief of sleep disturbance is important to encourage compliance with medication and psychological treatments. Secondly, one of the few robust biological findings in depression is alteration of sleep architecture (the structure and organisation of sleep). Many depressed patients have alterations in rapid eye movement (REM) sleep; they enter REM sleep earlier than control subjects, that is, their REM onset latency (ROL) is reduced, and non-REM sleep appears to be reduced in the first sleep cycle.[2] These two findings suggest that there is a disruption in both the circadian and the homeostatic drives to sleep. Nearly all antidepressants alter sleep in the opposite direction to these depression-related changes, as does electroconvulsive therapy (ECT), which may mean that sleep is an indirect biological marker of their therapeutic effects in the brain. Importantly, there is evidence that patients who have these sleep changes are more likely to respond to pharmacological than to psychological treatments and also do less well with psychological approaches than normal sleepers,[3] which may have some predictive value in deciding treatment modality. Thirdly, measurement of sleep provides a very sensitive index of aminergic effects in the brain in both healthy volunteers and depressed patients (see figure 1), and longitudinal studies of sleep during drug administration could give important insights into the adaptation mechanisms which have been implicated in the therapeutic effects of antidepressants.

Sleep patterns vary widely from person to person; in general, the average adult sleeps for about 7–8 hours a night but some need only 4–5 hours and some 10–12 hours. The amount of sleep should be sufficient for the sleeper to feel rested and refreshed and able to perform the next day's activities adequately. Many people have intermittent difficulties with sleep, either spending a long time trying to get off to sleep or waking during the night or very early morning; when these difficulties become persistent and result in daytime consequences such as fatigue and poor concentration then they are said to have insomnia. Objective information about sleep may be obtained by recording the EEG and other physiological variables such as muscle activity and eye movements during sleep (by polysomnography). When this is done, a pattern of sleep consisting of five different stages emerges. This pattern varies from person to person, but usually consists of four or five fairly regular cycles of quiet sleep alternating with paradoxical, or active, sleep. The quiet sleep is divided further into four stages. Stage 1 ('dozing') is a very light sleep halfway between sleep and waking and stage 2 is slightly deeper, sometimes with occasional small jerks. Stages 3 and 4, also called slow wave sleep, are of deep sleep during which some restorative processes in the body take place, for

 

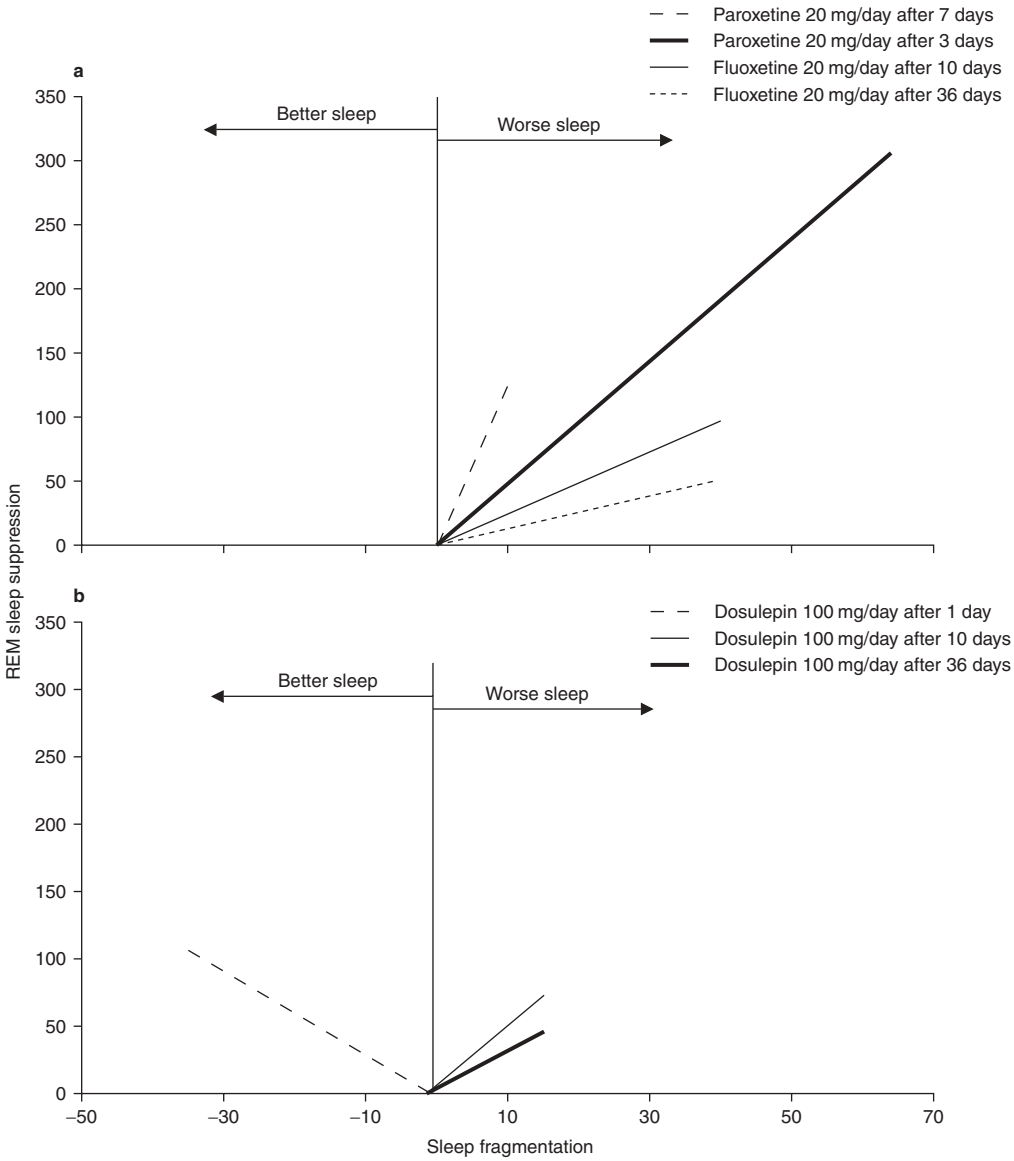


**Fig. 1.** Sleep 'vectors' representing the effects of antidepressants on sleep. Data are extracted from healthy volunteer, placebo-controlled studies in the authors' laboratory. The abscissa (rapid eye movement [REM] sleep suppression factor) is derived from a combination of the amount of REM sleep suppression and the increase in REM sleep onset latency; the ordinate (fragmentation factor) combines wake time after sleep onset and number of awakenings. (**a**) Paroxetine has a greater REM sleep-suppressing effect than fluoxetine, and both REM sleep suppression and fragmentation show reductions after 7 days. Fluoxetine has less REM sleep suppression at 36 days than at 10 days, but fragmentation remains the same. (**b**) Dosulepin improves sleep after a single dose and suppresses REM sleep, but after 10 and 36 days it slightly fragments sleep.[4-6]

instance growth hormone is released, and this slow wave sleep follows a homeostatic pattern, i.e. the longer the time since last sleep the more slow wave sleep occurs. During paradoxical sleep, the EEG appearance is similar to that of waking and there is complete paralysis of the skeletal muscles, and fre-

quent jerky movements of the eyes; this stage of sleep is called REM sleep. Stages 1–4 are referred to as non-REM sleep. Most slow wave sleep takes place in the first half of the night, and periods of REM sleep become progressively longer with each successive cycle of sleep; therefore most REM sleep appears in the second half of the night. The pattern of occurrence of the various stages over the night is normally referred to as 'sleep architecture'. The amounts of time spent in each sleep stage, the number of cycles and the amount of interruption by waking varies widely from person to person, but less so within people. In general there are definite age effects in adulthood, with less slow wave sleep and more time spent awake the older the subject.

This review presents an overview of the sleep effects of antidepressants. The authors have attempted to include all available published controlled studies in healthy volunteers and in depression where actual data are given in the report, but inevitably there will be some omissions.

The MEDLINE database was searched using the search terms 'sleep' AND 'antidepressant', 'sleep' AND '(individual drug)', and NAPS was searched using the term 'antidepressant'. Lists of the references in papers obtained from these searches and from the authors' own database of papers were also utilised.

## 1. Objective Effects on Sleep

### 1.1 Neurotransmitters and Sleep

The effects of antidepressants on sleep are very much associated with their effects on neurotransmitter systems in the brain, particularly their property of increasing synaptic levels of monoamines. The mechanism common to the most widely used antidepressants is that of inhibition of reuptake of serotonin (e.g. selective serotonin receptor inhibitors [SSRIs]), norepinephrine (noradrenaline) [e.g. reboxetine], and both serotonin and norepinephrine (e.g. tricyclics and venlafaxine) into the synapse. Monoamine oxidase (MAO) inhibitors (MAOIs) – both older drugs like phenelzine and newer, reversible drugs like moclobemide – also increase the level of serotonin and norepinephrine (and to a lesser extent dopamine) by preventing breakdown by the enzyme. Other drugs like mianserin and mirtazapine act on the autoreceptors responsible for homeostatic maintenance of monoamine levels, blocking their negative feedback action and so indirectly increasing monoamine levels; they also block serotonin 5-$HT_2$ receptors, for example trazodone and nefazodone.

As well as their main action of increasing monoamine levels, many antidepressants have (usually antagonist) effects at a variety of brain receptors, such as cholinergic, muscarinic, $\alpha_1$- and $\alpha_2$-adrenoceptors, and histamine $H_1$ and 5-HT receptors (see table I).

Sleep studies with very selective drugs like the SSRIs and tryptophan depletion studies in sleep have helped us to understand that increases in serotonin, via uptake blockade or enzyme inhibition, appear to give rise to the effects on REM sleep which is seen after antidepressant treatment.[15,16] Changes in non-REM sleep, and initiation and maintenance of sleep, however, appear to relate to other neurotransmitter actions, and are to some extent dependent on the stage of the illness rather than being simply a measure of antidepressant action (see table II).

### 1.2 Effects on Sleep Architecture

There is extensive literature on the acute effects of antidepressants, though less on their chronic effects. Table II gives a summary of the published data on their effects on REM sleep, and sleep initiation and maintenance. The most consistent effects are on REM sleep, which are similar in magnitude and direction in healthy volunteers and depressed patients.

#### *1.2.1 Selective Serotonin Reuptake Inhibitors*

The two REM sleep effects described with all SSRIs and also with the mixed serotonin/norepinephrine reuptake inhibitor venlafaxine are dose-related and consist of reduction in the overall amount of REM sleep over the night, and delay of the first entry into REM sleep (increased ROL) [see table II].

**Table I.** Properties of antidepressants[7-14]

| Antidepressant | Reuptake blockade[a] | | | Receptor effects | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | NA | SER | DA | ACh | $H_1$ | $\alpha_1$ | $\alpha_2$ | 5-$HT_{1A}$ | 5-$HT_2$ |
| **SSRIs** | | | | | | | | | |
| Fluoxetine | + | ++++ | | | | | | | |
| Citalopram | | +++ | | | | | | | |
| Fluvoxamine | | +++ | | | | | | | |
| Paroxetine | ++ | ++++ | + | ✓ | | | | | |
| Sertraline | + | ++++ | ++ | | | | | | |
| **SNRI** | | | | | | | | | |
| Venlafaxine | ++ | +++ | | | | | | | |
| **NARI** | | | | | | | | | |
| Reboxetine | ++ | + | | | | | | | |
| **TCAs** | | | | | | | | | |
| Clomipramine | ++ | ++++ | | ✓ | ✓ | ✓ | | | |
| Imipramine | ++ | +++ | | ✓ | ✓ | ✓ | | | |
| Desipramine | ++++ | ++ | | ✓ | ✓ | | | | |
| Amitriptyline | ++ | +++ | | ✓ | ✓ | ✓ | | | ✓ |
| Dosulepin | ++ | +++ | | ✓ | ✓ | ✓ | | | |
| Lofepramine | +++ | ++ | | ✓ | | ✓ | | | |
| Trimipramine | | + | | ✓ | ✓ | ✓ | | | ✓ |
| **Other** | | | | | | | | | |
| Mianserin | ++ | | | | ✓ | ✓ | ✓ | | ✓ |
| Mirtazapine | | | | | ✓ | | ✓ | | ✓ |
| Trazodone | | + | | | | ✓ | | ✓ | ✓ |
| Nefazodone | + | + | + | | | ✓ | | ✓ | ✓ |
| Bupropion | +[b] | | + | | | | | | |

a Transporter binding affinity ($K_i$).

b Active metabolite.

**ACh** = acetylcholine; **DA** = dopamine; **$K_i$** = affinity; **NA** = norepinephrine (noradrenaline); **NARI** = norepinephrine reuptake inhibitor; **SER** = serotonin; **SNRI** = selective norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; ✓ indicates $K_i$ < 100 nmol/L; **+** indicates $K_i$ 100–1000 nmol/L; **++** indicates $K_i$ 10–100 nmol/L; **+++** indicates $K_i$ 1–10 nmol/L; **++++** indicates $K_i$ <1 nmol/L.

**Table II.** Sleep effects of antidepressants. Significant findings compared with baseline (depressed patients [Dep]) or placebo (healthy volunteer [HV] studies)[4-6,17-76]

| Drug | Status | Acute (1–2 nights) | | | Subchronic (5–10 nights) | | | Chronic >21 nights | | | Withdrawal |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | decrease in REM sleep | increase in ROL | sleep continuity | decrease in REM sleep | increase in ROL | sleep continuity | decrease in REM sleep | increase in ROL | sleep continuity | rebound of REM sleep |
| SSRI fluoxetine | HV | +/– | ✓/– | ↓ | + | ✓ | ↓ | + | ✓✓ | ↓ | ✓ |
| | Dep | n | n | n | ++ | ✓ | ↓ | + | ✓ | ↓ | n |
| SSRIs (citalopram, | HV | ++ | ✓✓ | ↓ | ++ | ✓✓✓ | ↓ | ++ | ✓✓ | ↓/– | ✓ |
| fluvoxamine, paroxetine, sertraline) | Dep | ++ | ✓✓ | ↓ | ++ | ✓✓✓ | – | ++ | ✓✓ | – | ✓ |
| SNRI (venlafaxine) | HV | ++ | ✓✓ | ↓ | n | n | n | n | n | n | n |
| | Dep | | | | | | | | | | |
| NARI (reboxetine) | HV | n | n | n | n | n | n | n | n | n | n |
| | Dep | – | – | ↓ | + | ✓ | – | + | ✓ | – | n |
| TCAs (e.g. imipramine, clomipramine [CLOM]) | HV | ++ | ✓✓ | ↓ | ++ | ✓✓✓ | ↓ | ++ | n | ↓ | ✓ |
| | Dep | +++ | ✓✓✓ | ↓ | ++ | ✓✓✓ | – | + | ✓✓ | –/(CLOM↓) | n |
| TCAs (e.g. amitriptyline, | HV | – | ✓✓ | ↑ | + | – | – | ++ | ✓ | – | ✓ |
| dosulepin) | Dep | + | ✓✓ | – | ++ | ✓✓ | – | + | ✓✓ | ↑ | ✓ |
| Lofepramine | HV | ++ | ✓ | – | ++ | ✓ | ↓ | n | n | n | n |
| | Dep | n | n | n | n | n | n | n | n | n | n |
| Trimipramine | HV | + | – | ↑ | n | n | ↑ | n | ✓ | n | n |
| | Dep | – | – | ↑ | – | – | ↑ | – | – | ↑ | |
| MAOI (phenelzine) | HV | n | n | n | + | n | n | n | n | n | n |
| | Dep | – | – | n | +++ | ✓✓✓ | n | +++ | ✓✓✓ | n | ✓ |
| Moclobemide | HV | + | – | ↓ | n | n | n | n | n | n | n |
| | Dep | –/↑ | ✓ | – | – | ✓ | ↑ | – | ✓ | – | ✓ |
| Mianserin | HV | + | ✓ | ↑ | + | – | – | n | n | n | |
| | Dep | + | ✓ | ↑ | n | n | n | + | ✓ | ↑ | n |
| Mirtazapine | HV | – | ✓ | ↑ | n | n | n | n | n | n | n |
| | Dep | – | – | ↑ | – | – | ↑ | – | –/✓ | ↑ | n |
| Nefazodone | HV | – | – | – | – | – | ↑ | n | n | n | n |
| | Dep | – | –/↓ | ↑ | – | – | ↑ | – | –/↓ | ↑ | n |
| Trazodone | HV | –/+ | –/✓ | – | + | n | ↑ | n | n | n | ✓ |
| | Dep | – | – | ↑ | + | ✓ | –/↑ | – | ✓ | ↑ | n |
| Bupropion | HV | n | n | n | n | n | n | n | n | n | n |
| | Dep | – | – | – | n | n | n | –/↓ | ✓/– | – | n |

**MAOI** = monoamine oxidase inhibitor; **NARI** = norepinephrine (noradrenaline) reuptake inhibitor; **n** = no results reported; **REM** = rapid eye movement; **ROL** = REM sleep onset latency; **SNRI** = selective norepinephrine reuptake inhibitor; **SSRI** = selective serotonin receptor inhibitor; **TCA** = tricyclic antidepressant; **–** indicates no significant difference; ↑ indicates improved sleep continuity; ↓ indicates worsened sleep continuity; **+** indicates 10–30%; **++** indicates 30–60%; **+++** indicates >60%; ✓ indicates 30–100%; ✓✓ indicates 100–200%; ✓✓✓ indicates >200%.

The single-dose studies often show small effects on ROL, and this is usually due to time of dose administration. SSRIs have relatively long absorption times, with maximum plasma concentrations not achieved until about 4–8 hours after administration.[77] If the drug is given at bedtime, plasma concentrations are probably not high enough early in the night to delay the first REM sleep episode. There is a little evidence that onset of REM sleep effects may be slower after fluoxetine than for the other SSRIs: in one study, maximum increase in ROL after a single 40mg dose was on the third night,[19] and other single-dose studies have not shown the consistent REM sleep effects which appeared after multiple dose administration. This could be attributed to the long time to steady-state of norfluoxetine, the active metabolite. In general, maximal effects on REM sleep can be seen early in treatment with SSRIs, and their magnitude is similar with all SSRIs except fluoxetine, where the changes are generally smaller (table II).

The REM sleep effects described become a little less evident after long-term treatment, this diminution being less obvious with fluoxetine than the other SSRIs (table II). REM sleep amount is markedly reduced early in treatment but gradually returns towards baseline, so studies after 8 weeks or more of treatment rarely show significant reductions in REM sleep. On stopping SSRIs, REM sleep amount showed a rebound increase 4–12 days after fluoxetine withdrawal in the detailed study by Feige et al.[19] and 6 days after citalopram withdrawal in the study by van Bemmel et al.[34] However, ROL appears to be less susceptible to these rebound/withdrawal effects.

REM sleep suppression after SSRIs administration is probably caused by the increased levels of synaptic serotonin and may be mediated through the 5-$HT_{1A}$ receptor. This observation is based on preclinical studies: Monaca et al.[78] showed that in 5-$HT_{1A}$ knockout mice the REM sleep-suppressing effect of citalopram was absent, and in humans, selective 5-$HT_{1A}$-receptor agonist drugs are strongly REM sleep suppressing.[79] Decreasing serotonin availability by rapid tryptophan depletion in patients taking SSRIs has been shown to reverse the SSRI-induced REM sleep suppression.[15]

Changes in sleep initiation and continuity after short-term administration of SSRIs are also similar in healthy volunteers and depressed patients, and consist of increased light (stage 1) sleep, number of arousals from sleep, and time spent awake at night. In general, the magnitude of this arousing effect has been larger in healthy volunteers, but it must be remembered that there is a large baseline difference in these two groups, with depressed patients starting out with very disrupted sleep, and therefore further deterioration is less obvious. These sleep disturbance effects generally diminish over time, with most studies in depressed patients showing no difference from baseline after a few days of treatment. The exception to this is fluoxetine, which continued to disrupt sleep continuity after 8 weeks in a large multicentre study.[24]

Fragmentation of sleep is probably not explained by the stimulation of 5-$HT_{1A}$ receptors responsible for REM sleep effects. Evidence for this is that potent 5-$HT_{1A}$-receptor agonists do not have such marked sleep-fragmenting effects as SSRIs.[80] It may be that stimulation of post-synaptic 5-$HT_2$ receptors is involved, as blocking these receptors with drugs like nefazodone improves sleep[24,31] and chlorophenylpiperazine, a 5-$HT_2$-receptor agonist, is quite sleep-disrupting.[81]

There have been very few reports of changes in overall amount of deep (slow wave) sleep after SSRIs (see section 1.3 on delta sleep ratio [DSR]).

#### *1.2.2 Tricyclic Antidepressants*

REM sleep effects of tricyclic antidepressants (TCAs) in general are similar to those of SSRIs (table II). Clomipramine and imipramine seem to be the most REM sleep-suppressing, although no direct comparisons have been made. Again, there is maximum effect on REM sleep after a few days, with a slight decrease in the chronic phase. The only TCA which does not strongly suppress REM sleep is trimipramine, which differs from the other TCAs in that it is only a weak monoamine reuptake inhibitor. REM sleep rebound after withdrawal has been de-

scribed after most of the TCAs, and may be due to a rebound increase in cholinergic function.

The TCAs differ from each other in their effects on sleep initiation and maintenance. Clomipramine, desipramine and imipramine tend to disrupt sleep on the first night, with increased amounts of waking during sleep.[32,39,40,42-44] After a few days this effect is no longer present in patients, but continues in healthy volunteers, who were good sleepers at baseline. In contrast, amitriptyline and dosulepin improve sleep for short term in healthy volunteers,[28] but not in depressed patients.[46] Most studies show no difference in sleep continuity from baseline after a few days of treatment, but one study[45] showed fewer awakenings after 6 weeks of treatment of depression with amitriptyline. Some TCAs have been shown to increase stage 2 sleep.[28,35]

Trimipramine, as mentioned earlier, does not have the REM sleep effects of other TCAs. However, it is remarkably sleep-promoting, with decreased sleep onset latency, higher sleep efficiency, and longer sleep times reported in short-term studies of healthy volunteers and depressed patients.[39,43,48] The effects may be sustained into long-term treatment in depression[43] and also in insomnia.[82]

What properties of the TCAs might contribute to these differences? REM sleep differences between TCAs are unremarkable except for trimipramine, and possibly its small effect on monoamine uptake may explain its lack of REM sleep effects. As to sleep-promoting effects, TCAs that are $H_1$-receptor antagonists, for instance, might be expected to affect arousal processes, and thus sleep initiation and continuity. There appear to be histaminergic circuits involving the posterior hypothalamus and cortex which are wakefulness-related, and appear to be actively inhibited at sleep onset.[83] There is little evidence of histamine effects on REM sleep or slow wave sleep. The three TCAs that are particularly sleep-promoting are also potent $H_1$-receptor antagonists (table I), but so also are other TCAs which do not improve sleep. Anticholinergic properties of TCAs, too, might affect arousal and sleep continuity as cholinergic neurons have been identified in brainstem projections to higher centres, a part of the general arousal networks. However, the sleep-promoting TCAs are no more or less active at these receptors than the others.

An interesting difference, however, is in their effect at post-synaptic 5-$HT_2$ receptors; amitriptyline is a 5-$HT_2$-receptor antagonist, and antidepressants such as nefazodone and mirtazapine (section 1.2.4), and indeed antipsychotics which are also 5-$HT_2$-receptor antagonists,[84] are known to be sleep-promoting.

#### 1.2.3 Monoamine Oxidase Inhibitors

REM sleep suppression after the older, reversible MAOI phenelzine is profound, with total suppression of REM sleep after about a week of treatment at a dosage of 45–75 mg/day. This has been described in at least two studies of depressed patients.[50,51] It appears to take longer for the REM sleep suppression to appear than for TCAs and SSRIs, being maximal after about a week of treatment, and with maximum rebound effects occurring about 10 days after stopping the drug. These time lags probably reflect the slow and progressive inhibition of the enzyme and the recovery after stopping the drug by synthesis of new enzyme. Only one study, of two healthy volunteers, has been reported,[49] in which there was much less REM sleep suppression but with a similar timescale. An important recent finding is that the REM sleep suppression by phenelzine is reversed by rapid tryptophan depletion, implying that its REM sleep effects are mediated via increased serotonin function.

In general, phenelzine and also tranylcypromine disrupt sleep continuity, with increased waking after sleep onset being described from early in treatment and after 5 weeks.[51]

The reversible MAOI moclobemide, interestingly, does not have these remarkable REM sleep-suppressing effects; in some studies it is a mild REM sleep-suppressor[53] and in one study it[54] increased the amount of REM sleep, but there was a rebound increase in REM sleep on withdrawal. Its inhibition of MAOA is comparable to that of phenelzine, therefore there may be effects of phenelzine, on MAOB or perhaps on serotonin, which moclobemide does not have. Preclinical work has shown

differences *in vitro* on receptor binding after treatment with the two drugs.[85]

#### 1.2.4 Other Antidepressants

Mianserin is a weak inhibitor of norepinephrine reuptake that is thought to exert some of its effects via the blockade of presynaptic $\alpha_2$-adrenoceptors – these are inhibitory and therefore the net result would be an increase in neuronal activity and thus in synaptic norepinephrine.[86] Mianserin modestly suppresses REM sleep (see table II), as do more selective $\alpha_2$-adrenoceptor antagonists, e.g. idazoxan.[87] This action may be via increased norepinephrine in brainstem structures influencing REM sleep. However, unlike more selective $\alpha_2$-adrenoceptor antagonists, it also improves sleep continuity, probably via its action to block $H_1$ receptors (table I).

Mirtazapine also blocks $\alpha_2$-adrenoceptors and therefore increases synaptic norepinephrine, but has the additional property of indirectly stimulating 5-HT neurons, thus also increasing synaptic serotonin.[88] Mirtazapine also modestly increases ROL. It also has a robust and sustained effect in improving sleep continuity in depressed patients; this may be via antihistamine effects as with mianserin, but is probably mediated by its 5-$HT_2$-receptor blocking effects.

Trazodone and nefazodone are weak serotonin reuptake inhibitors; nefazodone also weakly blocks norepinephrine reuptake. Both drugs are 5-$HT_2$-receptor antagonists and also have $\alpha_1$-adrenoceptor blocking effects. Both improve sleep continuity in depressed patients, as for mirtazapine.[31,61,70] Interestingly, although trazodone has a slight suppressing effect on REM sleep, nefazodone does not, and in fact in some studies[62,64] caused an increase in REM sleep and shortening of ROL. It is difficult to explain this; nefazodone is one of the antidepressants which has consistently shown no hint of REM sleep suppression. An increase in REM sleep might be explained by an overall increase in sleep time without REM sleep suppression, but it is less easy to explain shortening of ROL.

Reboxetine is a reuptake inhibitor with much more action to block noradrenergic than serotonergic transport. It is very selective and has little action at other brain receptors. It suppresses REM sleep with the same pattern as TCAs and SSRIs, but less markedly. It seems to have no significant effect on sleep continuity.[76]

Bupropion is an antidepressant whose mode of action has been suggested to be reuptake blockade of dopamine and norepinephrine, and it may also be a dopamine and norepinephrine releasing agent. It too has little action at other brain receptors.[8] Dopamine-increasing drugs do not generally have effects on REM sleep, and bupropion has none in short term. However, two long-term studies in depression have shown opposite actions on REM sleep: in one it suppressed REM sleep in responders[72] and in the other it increased overall in depressed patients.[75] Further studies are required before this is resolved.

Venlafaxine is a selective dual action reuptake inhibitor with greatest action at the serotonin transporter, and about five times less at the norepinephrine transporter.[13] It has little action at neurotransmitter receptors. Venlafaxine has similar effects on sleep to the SSRIs like paroxetine or TCAs like clomipramine.[36,37] A report of another dual transmitter reuptake inhibitor, duloxetine, and sleep in healthy volunteers suggests a similar effect,[89] but milnacipran, in a controlled study in depression, increased ROL without decreasing REM sleep amount.[90] These early reports need to be confirmed.

### 1.3 Delta Sleep Ratio

Although neither SSRIs nor TCAs have any significant effect on slow wave sleep, DSR is a topic which has been explored over the last few years in the quest for an EEG sleep change that would predict clinical response, since EEG changes precede therapeutic effect by weeks.

In healthy subjects, episodes of slow wave activity in non-REM sleep occur discretely, interspersed with the REM sleep episodes in a cyclical pattern, and diminishing over the night according to the homeostatic process of sleep described first by Borbely.[91] In depressed patients, the ratio of the

slow EEG activity in the first sleep cycle to that in the second cycle (called the DSR) is lower than in healthy subjects. In several studies DSR has been reported to be increased after antidepressant treatment,[30,92] and in one of these studies[92] only those patients who responded to treatment showed increase in DSR. However, as described earlier, antidepressants delay the first REM sleep period, allowing the first sleep cycle to be very long, and thus the amount of slow wave activity in the first cycle is high. This increase in DSR is therefore caused by ROL changes, which also occur in healthy subjects. Nefazodone, one of the few antidepressants which do not suppress REM sleep, does not improve DSR.[93]

## 2. Subjective Effects on Sleep

The subjective sleep effects of antidepressants have not been studied as systematically as the polysomnographic effects. For a number of studies in depression the focus is on treatment response, and sleep change is only a secondary outcome measure, with the results being reported summarily. When some subjective sleep measurement is employed, this is mostly in the form of a self-rated sleep diary and/or the three sleep items of the observer-rated Hamilton Rating Scale for Depression (HAM-D), the latter analysed as a subscore of the whole scale. These items cover the aspects of early, middle and late insomnia, each one scored from 0 to 2. The more detailed self-rated sleep questionnaires that have some validity data supporting their use[94] have been very scarcely employed in the study of antidepressants. Of those, the use of the Leeds Sleep Evaluation Questionnaire (LSEQ)[95] has gained currency in recent years. This questionnaire consists of ten 100mm visual analogue scales yielding four factors: getting to sleep, quality of sleep, awakening from sleep, and behaviour following wakefulness. Overall, the scale appears to be reliable and consistent,[96] and the findings from its application in studies of various psychotropic agents in healthy volunteers, depressed patients and patients with insomnia have been reviewed in detail.[97]

The importance of the study of subjective sleep effects of antidepressants is highlighted by the heuristic use of the sedative side effect of some of these drugs to treat sleep problems, whether they are related to depression or not. This clinical practice has a long history and was given a boost in 1983 following the discussion on the abuse and tolerance potential of the benzodiazepines.[98] Polysomnography, of course, is not used routinely in the assessment of treatment of patients with antidepressant compounds, and there is no direct correspondence between objective and subjective sleep measures in what constitutes a good night's sleep (see figure 2).[99,100] A substantial number of patients with sleep complaints do not show any objective findings.[98] From the clinical standpoint, the ability of patients to perceive and report their objective sleep accurately may be less important than their subjective feelings;[101] therefore, these subjective perceptions in relation to the drug they are prescribed should be studied as a relevant aspect of treatment.

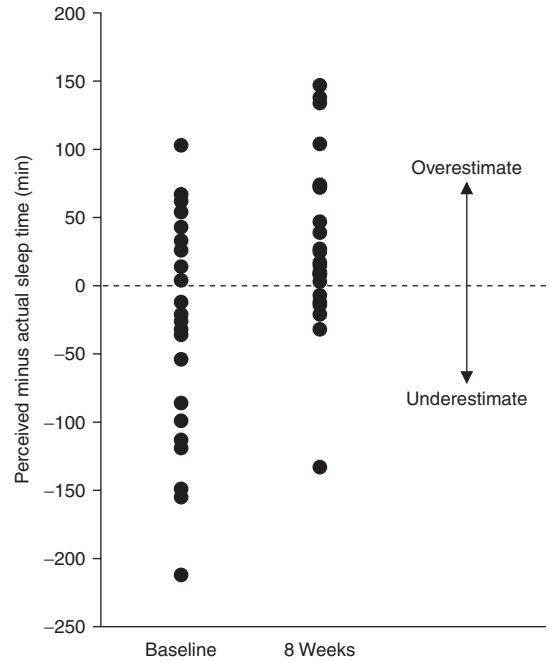


**Fig. 2.** Difference in perception of sleep time before and after antidepressant treatment in depressed patients who responded. After 8 weeks of treatment with paroxetine or nefazodone, underestimation of sleep is much less. [100]

The SSRIs are the group of compounds investigated most extensively with respect to their subjective sleep properties. Reports of healthy volunteer studies with SSRIs tend to be neutral or show some deterioration of sleep in higher doses.[97,102] In depressed patients, however, there is often a difference between objective and subjective measurements with this class of drugs, with objective measures showing that the SSRIs affect sleep negatively, at least in the early stages of treatment, but subjective measures showing improvement. A number of putative explanations have been put forward to account for this discrepancy. Concomitant medication, such as benzodiazepines, is sometimes freely available in studies measuring subjective effects – this does not happen in objective sleep studies.[102] However, this cannot explain why the same discrepancy occurs in studies that employ simultaneous objective and subjective measurements. Apart from the limited correspondence of these two approaches, as mentioned earlier,[100] it has also been suggested that a halo effect of general improvement may bias the subjective reports of sleep quality in particular.[102] Further, the common practice of presenting the baseline and endpoint data might be misleading. There is some tolerance to the sleep disrupting effects of the SSRIs in polysomnography, and improvement of sleep has generally set in by the end of the study. It might be more appropriate to report the data of the first few weeks of a study, when the patient has not seen any improvement in his/her mood yet and the sleep disturbance is at its peak.

### 2.1 Studies in Depression

Paroxetine is the most extensively studied SSRI. A 4-week, double-blind comparison of paroxetine 30 mg/day with amitriptyline 150 mg/day showed equally good improvement in the HAM-D sleep items.[35] Another comparison of paroxetine 20–30 mg/day with amitriptyline 50–100 mg/day in elderly depressed patients confirmed a significant reduction in the individual HAM-D sleep items for both drugs compared with baseline. The same report also highlighted that according to the LSEQ, getting to sleep became easier and quality of sleep improved as a result of both treatments.[103] Another 6-week study with elderly depressed subjects showed that paroxetine 15–30 mg/day was superior in subjective sleep to mianserin 30–60 mg/day. Six of the ten individual items of LSEQ (including ease of getting to sleep, speed of getting to sleep, restfulness of sleep, and reduced awakenings) were significantly improved compared with baseline, while only one item (alertness during the day) improved with mianserin. However, short-acting benzodiazepines were allowed for hypnotic purposes in this study, and unfortunately the HAM-D sleep item data were not reported separately.[104]

Fluoxetine 20 mg/day has been compared with placebo in an 8-week study of depressed patients, which provided analysis of subgroups, including patients with baseline sleep disturbance, with melancholic features, or with reduced ROL. The drug was better than placebo but the difference did not reach statistical significance. The most interesting aspect of this study was that fluoxetine did not appear to worsen subjective sleep, even in melancholic patients.[105] A large (n = 424) 6-week open-label study reported that all 4 LSEQ factors, as well as the HAM-D sleep items, improved significantly with fluoxetine, and that this effect was more pronounced in responders.[106] Unfortunately, this study does not appear to have been published in full. Fluoxetine 20 mg/day was also compared with the tricyclic antidepressant dosulepin 150 mg/day in a 6-week study of 107 depressed patients. Both treatments were equally effective in depression and both were associated with normalisation of sleep, as the patients became less depressed. Despite the non-sedating profile of fluoxetine, the drug displayed subjective sleep normalisation properties that were similar to those of dosulepin. Both drugs had an early positive impact on the ease of getting to sleep, with improvement in the corresponding subscale of LSEQ. Both drugs also improved sleep quality, and there was little evidence of hangover after awakening – somewhat surprising for dosulepin.[107]

In a large (n = 400) comparison of citalopram (two groups 10–30 mg/day and 20–60 mg/day) with imipramine 50–150 mg/day in depressed patients

for 6 weeks, with optional continuation for another 16 weeks, a reduction in HAM-D sleep items was observed in all groups, with no significant differences between them.[108] However, a meta-analysis of the HAM-D sleep items from five controlled studies of citalopram versus TCAs showed that the TCAs had a much more pronounced effect on subjective sleep than citalopram.[109]

Sertraline (mean dosage 72 mg/day) was tested against fluoxetine (mean dosage 28 mg/day) in an 8-week study in depressed patients. Compared with baseline, both groups showed significant improvement in the HAM-D sleep items and in LSEQ, with the exception of factor 3 of the latter (difficulty in awakening and time it took to wake up). However, the raw data are not presented, and benzodiazepines were allowed for hypnotic use or pre-existing anxiety, at the dose taken by the individual before the study.[110] Another 6-week comparison of the same drugs (sertraline 50–100 mg/day vs fluoxetine 20–40 mg/day) reported significant reductions from baseline for both drugs in the HAM-D insomnia items, and this was paralleled by a reduction in the mean daily dose of temazepam used. While significant improvement from baseline was also claimed for LSEQ, no data were presented.[111] No real difference between the two drugs on LSEQ was seen in another 24-week study of over 200 depressed patients (sertraline 50–150 mg/day vs fluoxetine 20–60 mg/day).[112] Again, the data are not presented in detail. Finally, sertraline 50–100 mg/day was compared with another new antidepressant, the selective MAOI moclobemide 300–450 mg/day, in a 12-week study of 172 patients with atypical depression. Both drugs showed an improvement of sleep as measured with LSEQ, compared with their baselines, while sertraline was superior to moclobemide on one factor of the scale (behaviour following waking).[113]

The sleep effects of the older antidepressants for which a specific sleep promoting effect has been claimed have not been investigated extensively. One of these compounds is trazodone. In a small crossover study (n = 11) of depressed patients comparing the effect of a single dose of trazodone (100mg) with placebo, using a variety of subjective outcome measures, including the investigator's own Self-Assessment of Sleep and Awakening Quality Scale (SSA), the drug was significantly better in a measure of sleep quality. It showed a mild but not significant improvement in the total score of SSA and had no effect on awakening.[71] Trazodone was also studied as an adjunct to other antidepressants for depressed patients with insomnia. A dose of 50mg of trazodone or placebo was administered in a crossover study, for 8 nights, to 17 such patients, as an adjunct to treatment with either fluoxetine or bupropion: significant improvement in the Pittsburgh Sleep Quality Index (PSQI) was reported for the trazodone block of the study.[114] A four-way, 6-week study of trazodone 150 mg/day versus mianserin 30–60 mg/day versus dosulepin 75–150 mg/day versus amitriptyline 75–150 mg/day in 227 depressed subjects reported that, with regards to LSEQ, trazodone and dosulepin showed the most pronounced improvement, especially in the ease of getting to sleep and quality of sleep factors, and all four drugs impaired feelings after waking, suggesting a hangover effect. The positive changes observed in LSEQ were numerically slightly bigger than those usually seen with SSRIs.[115] A slightly different result was reported in another comparison of trazodone 150 mg/day with mianserin 30–60 mg/day, over a 6-week study period. As measured by LSEQ again, both treatments produced statistically similar improvement of sleep over time, although the numerical changes were larger with trazodone, and the overall improvement in sleep quality occurred more rapidly in the trazodone group.[116]

Of the new antidepressants introduced in the last 10 years, mirtazapine is considered as being the most sedative. In an open-label study of 17 drug-free patients treated with mirtazapine 15–60 mg/day for 5 weeks, patients' sleep improved substantially, as measured by LSEQ. This improvement referred specifically to the items concerned with the speed and ease of getting off to sleep and the item referring to subjective periods of wakefulness. Patients felt that they were getting off to sleep more quickly and more easily and that they were waking up less during the

night after 4 weeks of treatment.[61] Unfortunately, although data were collected earlier in treatment as well, these are not presented. Mirtazapine (mean dosage 48 mg/day) was also compared with another new antidepressant, venlafaxine (mean dosage 255 mg/day), over an 8-week treatment period of severely depressed patients with melancholic features. On the sleep disturbance items of HAM-D, treatment with mirtazapine resulted in statistically significantly larger changes from baseline than treatment with venlafaxine from first week onwards. This was maintained at all assessment times throughout the study.[117]

Another one of the new compounds for which sleep promoting properties have been claimed, nefazodone 400–500 mg/day, was compared with fluoxetine 20–40 mg/day in an 8-week, double-blind study of 125 depressed patients. Subjective effects on sleep were measured with the sleep items of HAM-D, and through the Inventory for Depressive Symptomatology (IDS)-C (Clinician) and -SR (Self Rated), which have items for early, middle and late insomnia, as well as hypersomnia. Nefazodone was significantly better than fluoxetine from second week onwards on all outcome measures.[24] On the other hand, in an 8-week study of depressed patients, nefazodone 200–600 mg/day was not superior to paroxetine 20–40 mg/day in the HAM-D sleep items (200–600 mg/day).[118] This was further supported by a 24-week study comparing nefazodone 400–600 mg/day with paroxetine 20–40 mg/day, which showed that both drugs improved subjective sleep significantly, as measured with LSEQ and HAM-D sleep items, but there was no difference between them early or late in treatment.[31]

A further 12-week study of nefazodone 300–600 mg/day versus cognitive behavioural analysis system (CBAS) psychotherapy (which did not directly address insomnia issues) or their combination, estimated effects on sleep through extensive diaries completed at regular weekly intervals.[119] The diary entries included bedtime, lights out time, actual wake-up time, planned wake-up time, last time out of bed, latency to sleep onset (minutes), number of awakenings after sleep onset, minutes of wakefulness after sleep onset, and ratings on a 6-point Likert scale of sleep quality and of feeling rested/refreshed upon awakening. Only monotherapy with nefazodone improved early morning awakening and total sleep time. Significant improvements in sleep quality, time awake after sleep onset, and sleep efficiency were present in each of the three treatment groups. These improvements, however, occurred earlier in the course of treatment for participants receiving nefazodone, alone or in combination with psychotherapy. The investigators went on to analyse the data by defining first what would constitute a clinically meaningful early insomnia (the threshold set at a weekly average of sleep latency >30 minutes), time awake after sleep onset (30 minutes again) or early morning awakening (60 minutes). The combination group had a significantly larger proportion of patients who experienced clinically meaningful improvement in sleep onset, sleep maintenance and early morning awakening insomnia compared with the psychotherapy group alone. The nefazodone group alone had a significantly larger proportion of participants who experienced clinically meaningful improvement in early morning awakening insomnia compared with the psychotherapy group, but a significantly smaller proportion of participants who experienced a meaningful improvement in sleep maintenance insomnia compared with the combination group.[119]

### 2.2 Studies in Insomnia Not Related to Depression

In a small (n = 14) open-label study of paroxetine (median dosage 20 mg/day) in patients with primary insomnia, 11 subjects improved substantially and 7 did not meet the diagnostic criteria at the end of the study, according to the PSQI.[120] However, the investigators noted that diary measures that were also collected did not reflect the PSQI index improvement.[121]

Trazodone may also be useful for primary insomnia, having the advantage of low abuse potential and less impairment of performance tasks compared with benzodiazepines.[122] A small study (n = 6) of healthy volunteers using escalating doses of

trazodone (50–200mg) and trimipramine (25–100mg) over 4 consecutive nights showed that the subjects' sleep was normal under both drugs, and the participants were not aware of any changes in their sleep pattern, as judged from their post-sleep detailed sleep log answers.[65] The value of trazodone 50 mg/day as an hypnotic was tested in a 2-week study of 278 patients with primary insomnia, in comparison with zolpidem 10 mg/day and placebo. Questionnaires asking about time required to fall asleep and duration of sleep were used as primary outcome measures, along with a variety of secondary measures. During the first week of treatment, both drugs shortened sleep onset latency and increased sleep duration significantly compared with placebo, but sleep onset latency with zolpidem was also significantly shorter than with trazodone. By week 2, the sleep onset-promoting effect of trazodone had disappeared, and sleep duration did not vary between groups, mainly because of increasing placebo response.[123] It should be noted that the dose of trazodone in this study may have been too low.

Another antidepressant for which sleep promoting properties have been suggested is trimipramine. It has been investigated in primary insomnia, in doses 50–200 mg/day, compared with placebo and lormetazepam, in a 4-week study.[82] The subjective measures used included the PSQI and a number of 1–5 scales of sleep quality, feeling refreshed in the morning, well-being in the evening, and exhaustedness in the evening, as well as psychosomatic symptoms during sleep. Trimipramine decreased the PSQI sum score significantly compared with placebo, and significantly improved sleep quality and feeling rested in the morning and well-being in the evening. The results for lormetazepam, compared with placebo, were in the same direction as with trimipramine, but not as pronounced. The direct comparison of lormetazepam with trimipramine showed a statistically significant superiority of trimipramine for feeling rested in the morning and feeling well in the evening, but not for any other parameters. The investigators concluded that trimipramine may have a role to play in the treatment of insomnia. Of note in this study, the effects on subjectively experienced parameters on sleep were more pronounced than those documented by objective parameters.[82]

Doxepin, another TCA, has been investigated in a 4-week, double-blind, placebo-controlled study of 47 patients with primary insomnia.[124] The dose of the drug used was low (25 or 50mg in the evening). Subjective sleep quality, daytime performance, and energy were assessed daily using visual analogue scales, which were then averaged over 2-week periods in order to minimise the effects of day-to-day variations. The mean value of subjective sleep quality increased with doxepin from 41mm at baseline to 54mm on the 100mm visual analogue scale. This result was statistically significant but can be viewed as clinically modest. Also, the subjects' working ability the following day improved, but their energy was not increased.[124]

A question arising from these studies is whether the statistically significant changes mentioned in these studies are clinically significant. With LSEQ for example, a few millimetres change on the 100mm visual analogue scales appears to be enough to produce statistical significance, but may not be clinically significant. This problem is exemplified in one of the studies referred to earlier in the text, where values for individual LSEQ items are available,[104] as illustrated in table III. The changes in

**Table III.** Leeds Sleep Evaluation Questionnaire (LSEQ) values expressed as mean differences in mm of visual analogue 100mm scales at endpoint of the study (6 weeks) compared with baseline. Negative values indicate worsening.[104] Note that no difference exceeds 10mm, despite the fact that 6 items on paroxetine and 1 on mianserin reached statistical significance. Questions 1–3 are on initiation of sleep, 4–5 on quality, 6–7 on awakening from sleep, and 8–10 on behaviour following waking

| Drug | LSQE values for question number | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Paroxetine 15–30mg | 7.4 | 8.4 | 4.1 | 8.8 | 7.9 | 2.6 | −0.8 | 5.5 | 9.7 | 0.1 |
| Mianserin 30–60mg | 3.4 | 3.6 | 3.2 | 6.3 | 6.6 | −4.4 | −4.1 | −1.1 | 3.6 | −1.3 |

**Table IV.** Mean change from baseline in mm of visual analogue 100mm scale in Leeds Sleep Evaluation Questionnaire factors[106,113]

| Drug | Getting to sleep | Perceived quality of sleep | Ease of awakening from sleep | Behaviour following wakefulness | Reference |
|---|---|---|---|---|---|
| Fluoxetine (responders) | 6.8[a] | 6.8[a] | 6.6[a] | 7.1[a] | 106 |
| Fluoxetine (nonresponders) | 6.0 | 5.9 | 5.7 | 5.6 | 106 |
| Sertraline | 3.19[b] | 1.30[b] | 3.45[b] | 5.98[b] | 113 |
| Moclobemide | 2.33[b] | 0.49 | 2.79[b] | 3.96[b] | 113 |

a Statistical significance between groups.

b Statistical significance within groups (compared with baseline).

absolute terms when LSEQ factors are presented as averages of their individual components are also rather modest.[107] Similarly, in another study[106] where the responders are reported to have had a significantly better improvement in all four LSEQ factors compared with the non-responders, inspection of the data (table IV) shows that the difference in scores between the two groups was about 1%, and therefore of doubtful clinical significance. Table IV illustrates this case further by presenting some more raw data extracted from various studies. It should be noted, in fairness to the studies included in these two tables, that many of the remaining reports cited earlier in the text did not contain enough information for this kind of comparison to be undertaken. However, in the most comprehensive review of the use of LSEQ, only fluvoxamine (in one study)[97] appeared to produce substantial changes in the ease of getting to sleep and sleep quality factors.

However, when data of HAM-D sleep items are observed, the changes sometimes appear to be clinically more relevant, even if most of the reports only give values at a few weeks after the onset of treatment, when the antidepressant effect is established (table V). The use of subjective sleep measurements needs to be reviewed in order to better reflect the changes along the clinical dimension.

## 3. Other Sleep Effects

### 3.1 Sleep-Related Movement Disorder Adverse Effects of Antidepressants

There have been many case reports and small studies of movement disorders during sleep after antidepressant usage, but there are no controlled studies. Ohayon and Roth,[125] in a large survey, found that taking SSRIs was a risk factor for restless legs syndrome. Both mianserin and mirtazapine have been reported to induce or exacerbate restless leg syndrome in small case series and case reports. Periodic limb movements of sleep are often associated with restless legs syndrome but also occur independently, and were increased by venlafaxine[36] and other antidepressants in a few case reports, but bupropion ameliorated these in five patients with periodic limb movement disorder.[126]

Prominent eye movements during stages 2–4 non-REM sleep, either rapid like those in REM sleep or slower like those in stage 1, have been described after TCAs, especially clomipramine,[127,128] and fluoxetine.[129] SSRIs are known to induce or exacerbate bruxism;[130] interestingly this has been ameliorated by buspirone in two

**Table V.** Hamilton Rating Scale for Depression (HAM-D) sleep items, expressed as mean scores (range 0–6)

| Drug | Baseline | Day 3 | Day 10 | Week 4 | Week 6 | Week 8 | Week >20 |
|---|---|---|---|---|---|---|---|
| Sertraline (mean 72mg)[110] | 4.3 | | | | | 1.9 | |
| Fluoxetine (mean 28mg)[110] | 3.8 | | | | | 1.7 | |
| Citalopram (10–30mg)[108] | 4.1 | | | 2.3 | 1.7 | | 1.3 |
| Citalopram (20–60mg)[108] | 3.9 | | | 2.1 | 1.8 | | 1.2 |
| Imipramine (50–150mg)[108] | 4.3 | | | 2.0 | 1.9 | | 0.8 |
| Nefazodone (400–600mg)[31] | 4.5 | 3.9 | 2.3 | 1.8 | 1.2 | 0.9 | 0.3 |
| Paroxetine (20–40mg)[31] | 4.1 | 3.1 | 1.9 | 1.2 | 0.7 | 0.7 | 0.4 |

reports,[131] so may involve 5-$HT_{1A}$-receptor mechanisms.

Recently, mirtazapine was reported to have induced REM sleep behaviour disorder (RBD) in four patients with parkinsonism.[132] Other investigators have observed that atonia during REM sleep is reduced during treatment with serotonergic antidepressants such as SSRIs, clomipramine and venlafaxine, and that these too are a risk factor for RBD.[128,133]

### 3.2 Antidepressants and Dreaming

Although nightmares are reported as an adverse event in clinical trials of SSRIs,[134] numbers were small and the presence of depression may also be a factor. Enhancement of dreaming has been noted during treatment with the SSRIs fluoxetine[135,136] and citalopram,[137] and changes in dream content after sertraline.[138] A controlled study in healthy volunteers showed an increase in emotional intensity of dreams but a decrease in recall with fluvoxamine and paroxetine during 3 weeks' treatment, and an increase in dream report length and bizarreness during withdrawal from fluvoxamine.[139]

The mechanism for these effects is unclear. Certainly there are more awakenings during REM sleep in SSRI-treated subjects, and bouts of REM sleep are moved towards morning wakening by the REM sleep-delaying mechanism, both of which would affect dreaming. However, this does not account for increased emotional intensity.

Excessive dreaming has been described as a withdrawal phenomenon for nearly all antidepressants,[139,140] and may possibly be due to rebound cholinergic effects.

### 3.3 Use of Antidepressants to Treat Other Sleep Disorders

Studies in fibromyalgia[141] and chronic fatigue syndrome[142] have shown subjective sleep improvement after fluoxetine usage. Paroxetine has been reported to be effective in adult night terrors[143] and sleepwalking;[144] of interest to the mechanism of action is that in both these disorders the effects of the SSRI are seen early in treatment – often on the first dose. This means that the mechanism cannot be the same as for lifting mood, which takes 3–4 weeks. We suggest that the most likely explanation is a direct pharmacological action to increase serotonin in brainstem regions suppressing ascending arousal pathways.

The tricyclic antidepressant protriptyline has been used in the past to treat obstructive sleep apnoea syndrome, but with little benefit;[145] however, there are a few small case series where SSRIs have been tried, with minor improvements.[146-148] Imipramine is still occasionally used in the treatment of enuresis in children and adults, with a mechanism that remains unclear, however it is now very much a second-line treatment when other approaches have been tried.[149]

## 4. Practical Implications of the Effects of Antidepressants on Sleep

Antidepressant medications have class- and compound-specific effects on sleep profiles. In the treatment of depression, no single effect of antidepressants on sleep architecture is necessary or sufficient for therapeutic efficacy, but differences in drug effects may help with the choice of specific medications for particular patients. As discussed earlier, most effective antidepressants improve sleep after a few weeks of treatment, but there may be situations where an earlier improvement of sleep, that is, before the mood-lifting effects become apparent, may be desirable. When insomnia is particularly distressing, or in order to increase adherence to treatment, the choice of a safely used and effective antidepressant which improves sleep in short term is indicated. Stimulation of 5-$HT_2$ receptors may contribute to insomnia and changes in sleep architecture seen with SSRIs or venlafaxine. antidepressants with 5-$HT_2$-receptor antagonist properties, such as mirtazapine or nefazodone, improve sleep continuity and may therefore be a good treatment option for depressed patients with marked insomnia. Some patients with depression complain of excessive sleep or daytime somnolence, although the prevalence of these symptoms is not known because there is not sufficient published data distinguishing somnolence

from fatigue in depression. In these patients, sleep-promoting antidepressants should be avoided.

In primary insomnia not related to depression, first-line treatment is usually psychological, with or without short-acting hypnotic drugs which increase GABA function, such as the benzodiazepines and related 'Z' drugs (zaleplon, zolpidem and zopiclone). However, the immediate sleep-improving effects of antidepressant medications which block 5-$HT_2$ receptors such as mirtazapine make these drugs a possible alternative for insomnia, as long as considerations of duration of action are taken into account. Daytime sleepiness with mirtazapine for instance, which has a half-life of 20–40 hours, is prominent during the first week of treatment, but this appears to diminish after a few days.[150] There is very little evidence for efficacy in this indication as yet.

Patients with other sleep disorders such as restless legs syndrome and RBD should be identified before choosing a treatment, as some antidepressants worsen these conditions. Conversely, there is evidence that some antidepressants may be useful in the treatment of sleep disorders such as night terrors.

## 5. Conclusions

SSRI and TCA antidepressants have marked dose-dependent effects on REM sleep in healthy volunteers and depressed patients, with ROL being lengthened and REM sleep amount being reduced. After weeks of treatment, ROL remains long, but the amount of REM sleep recovers, and shows rebound after withdrawal. These changes in amount of REM sleep may reflect receptor adaptation. Other antidepressants have modest or minimal effects on REM sleep. These effects on REM sleep may be related to increased synaptic levels of monoamines brought about by reuptake blockade, and are likely to be mediated by 5-$HT_{1A}$ receptors in REM sleep-initiating areas.

Objective sleep continuity is worsened during early treatment with SSRIs, MAOIs and the more alerting TCAs, with time awake after sleep onset and stage 1 sleep being increased early in treatment. Effects are more marked in healthy volunteers than in depressed patients, probably because healthy volunteers have better baseline sleep. This worsening in sleep improves after a few days in depressed patients, but studies with fluoxetine and phenelzine show increased waking during sleep later in treatment. In general, the deterioration in sleep continuity is not paralleled by a worsening of subjective ratings of sleep, which improve during treatment of depression.

Reports of improvement in objective sleep continuity after some antidepressants, particularly the 5-$HT_2$-receptor antagonists, early in treatment of depression are paralleled by volunteer studies and can therefore be assumed to be a drug effect. Sustained improvements are difficult to separate from illness effects, since sleep continuity also improves in patients successfully treated with psychological treatments.[151] Healthy volunteer studies of long-term effects are rare, and none has shown significant differences from baseline.

Subjective estimates of sleep in depressed patients on antidepressants differ from the objective ones, especially for the most widely used class, the SSRIs, and may be related to illness state. These drugs may differ among themselves in their ability to promote (or not disrupt) subjective sleep. The use of some antidepressants for their sleep-promoting properties in insomnia unrelated to depression, while widespread in clinical practice, has not been systematically substantiated so far. However, reports on subjective effects of mirtazapine, nefazodone, trazodone, trimipramine and doxepin indicate that there may be some value in this practice, particularly early in treatment.

## Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

## References

1. Thase ME. Antidepressant treatment of the depressed patient with insomnia. J Clin Psychiatry 1999; 60 Suppl. 17: 28-31
2. Lauer CJ, Schreiber W, Holsboer F, et al. In quest of identifiying vulnerability markers for psychiatric disorders by all-night polysomnography. Arch Gen Psychiatry 1995; 52: 145-52

3. Thase ME, Buysse DJ, Frank E, et al. Which depressed patients will respond to interpersonal psychotherapy? The role of abnormal EEG sleep profiles. Am J Psychiatry 1997; 154 (4): 502-9
4. Wilson SJ, Bailey JE, Alford C, et al. Effects of 5 weeks of administration of fluoxetine and dothiepin in normal volunteers on sleep, daytime sedation, psychomotor performance and mood. J Psychopharmacol 2002; 16 (4): 321-31
5. Wilson SJ, Bailey JE, Rich AS, et al. Using sleep to evaluate comparative serotonergic effects of paroxetine and citalopram. Eur Neuropsychopharmacol 2004; 14 (5): 367-72
6. Bell C, Wilson S, Rich A. Effects on sleep architecture of pindolol, paroxetine and their combination in healthy volunteers. Psychopharmacology Berl 2003; 166 (2): 102-10
7. Owens MJ, Morgan WN, Plott SJ, et al. Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. J Pharmacol Exp Ther 1997; 283 (3): 1305-22
8. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology (Berl) 1994; 114 (4): 559-65
9. Richelson E, Nelson A. Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther 1984; 230 (1): 94-102
10. Tatsumi M, Groshan K, Blakely RD, et al. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. Eur J Pharmacol 1997; 340 (2-3): 249-58
11. Bolden-Watson C, Richelson E. Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes. Life Sci 1993; 52 (12): 1023-9
12. Claassen V, Davies JE, Hertting G, et al. Fluvoxamine, a specific 5-hydroxytryptamine uptake inhibitor. Br J Pharmacol 1977; 60 (4): 505-16
13. Millan MJ, Gobert A, Lejeune F, et al. S33005, a novel ligand at both serotonin and norepinephrine transporters. I: receptor binding, electrophysiological, and neurochemical profile in comparison with venlafaxine, reboxetine, citalopram, and clomipramine. J Pharmacol Exp Ther 2001; 298 (2): 565-80
14. Millan MJ, Gobert A, Rivet JM, et al. Mirtazapine enhances frontocortical dopaminergic and corticolimbic adrenergic, but not serotonergic, transmission by blockade of alpha2-adrenergic and serotonin2C receptors: a comparison with citalopram. Eur J Neurosci 2000; 12 (3): 1079-95
15. Moore P, Gillin C, Bhatti T, et al. Rapid tryptophan depletion, sleep electroencephalogram, and mood in men with remitted depression on serotonin reuptake inhibitors. Arch Gen Psychiatry 1998; 55 (6): 534-9
16. Landolt HP, Kelsoe JR, Rapaport MH, et al. Rapid tryptophan depletion reverses phenelzine-induced suppression of REM sleep. J Sleep Res 2003; 12 (1): 13-8
17. Saletu B, Frey R, Krupka M, et al. Sleep laboratory studies on the single-dose effects of serotonin reuptake inhibitors paroxetine and fluoxetine on human sleep and awakening qualities. Sleep 1991; 14 (5): 439-47
18. Vasar V, Appelberg B, Rimon R, et al. The effect of fluoxetine on sleep: a longitudinal double blind polysomnographic study of healthy volunteers. Int Clin Psychopharmacol 1994; 9: 203-6
19. Feige B, Voderholzer U, Riemann D, et al. Fluoxetine and sleep EEG: effects of a single dose, subchronic treatment, and discontinuation in healthy subjects. Neuropsychopharmacology 2002; 26 (2): 246-58
20. Nicholson AN, Pascoe PA. Studies on the modulation of the sleep-wakefulness continuum in man by fluoxetine, a 5HT uptake inhibitor. Neuropharmacology 1988; 27: 597-602
21. Winokur A, DeMartinis III NA, McNally DP, et al. Comparative effects of mirtazapine and fluoxetine on sleep physiology measures in patients with major depression and insomnia. Clin Psychiatry 2003; 64 (10): 1224-9
22. Trivedi MH, Rush AJ, Armitage R, et al. Effects of fluoxetine on the polysomnogram in outpatients with major depression. Neuropsychopharmacology 1999; 20 (5): 447-59
23. Hendrickse WA, Roffwarg HP, Granneman BD, et al. The effects of fluoxetine on the polysomnogram of depressed outpatients: a pilot study. Neuropsychopharmacology 1994; 10: 85-91
24. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998; 44 (1): 3-14
25. Sharpley AL, Williamson DJ, Attenburrow ME, et al. The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. Psychopharmacology (Berl) 1996; 126 (1): 50-4
26. Oswald I, Adam K. Effects of paroxetine on human sleep. Br J Clin Pharmacol 1986; 22 (1): 97-9
27. Schlosser R, Roschke J, Rossbach W, et al. Conventional and spectral power analysis of all-night sleep EEG after subchronic treatment with paroxetine in healthy male volunteers. Eur Neuropsychopharmacol 1998; 8 (4): 273-8
28. Wilson SJ, Bailey JE, Alford C, et al. Sleep and daytime sleepiness the next day following single nighttime dose of fluvoxamine, dothiepin and placebo in normal volunteers. J Psychopharmacology 2000; 14: 378-86
29. Hartmann E, Spinweber C. Fluvoxamine, a serotonin reuptake blocker: effects on sleep. J Sleep Res 1979; 8: 98
30. Jindal RD, Friedman ES, Berman SR, et al. Effects of sertraline on sleep architecture in patients with depression. J Clin Psychopharmacol 2003; 23 (6): 540-8
31. Hicks JA, Argyropoulos SV, Rich AS, et al. Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression. Br J Psychiatry 2002 Jun; 180: 528-35
32. Kupfer DJ, Perel JM, Pollock BG, et al. Fluvoxamine versus desipramine: comparative polysomnographic effects. Biol Psychiatry 1991; 29: 33-40
33. Wilson SJ, Bell C, Coupland N, et al. Sleep changes during long-term treatment of depression with fluvoxamine: a home based study. Psychopharmacology 2000; 149: 360-5
34. van Bemmel AL, van den Hoofdakker RH, Beersma DGM, et al. Changes in sleep polygraphic variables and clinical state in depressed patients during treatment with citalopram. Psychopharmacology 1993; 113: 225-30
35. Staner L, Kerkhofs M, Detroux D, et al. Acute, subchronic and withdrawal sleep EEG changes during treatment with paroxetine and amitriptyline: a double-blind randomized trial in major depression. Sleep 1995; 18 (6): 470-7
36. Salin-Pascual RJ, Galicia-Polo L, Drucker-Colin R. Sleep changes after 4 consecutive days of venlafaxine administration in normal volunteers. J Clin Psychiatry 1997 58 (8): 348-50
37. Luthringer R, Toussaint M, Schaltenbrand N, et al. A double-blind, placebo-controlled evaluation of the effects of orally administered venlafaxine on sleep in inpatients with major depression. Psychopharmacol Bull 1996; 32 (4): 637-46

38. Farina B, Della Marca G, Mennuni G, et al. The effects of reboxetine on human sleep architecture in depression: preliminary results. J Affect Disord 2002; 71 (1-3): 273-5
39. Dunleavy DL, Brezinova V, Oswald I, et al. Changes during weeks in effects of tricyclic drugs on the human sleeping brain. Br J Psychiatry 1972; 120 (559): 663-72
40. Hochli D, Riemann D, Zulley J, et al. Is there a relationship between response to total sleep deprivation and efficacy of clomipramine treatment in depressed patients? Acta Psychiatr Scand 1986; 74 (2): 190-2
41. Jobert M, Jahnig P, Schulz H. Effect of two antidepressants on REM sleep and EMG activity during sleep. Neuropsychobiology 1999; 39 (2): 101-9
42. Shipley JE, Kupfer DJ, Griffin SJ, et al. Comparison of effects of desipramine and amitriptyline on EEG sleep of depressed patients. Psychopharmacology (Berl) 1985; 85 (1): 14-22
43. Ware JC, Brown FW, Moorad Jr PJ, et al. Effects on sleep: a double-blind study comparing trimipramine to imipramine in depressed insomniac patients. Sleep 1989; 12 (6): 537-49
44. Shain BN, Naylor M, Shipley JE, et al. Imipramine effects on sleep in depressed adolescents: a preliminary report. Biol Psychiatry 1990; 28 (5): 459-62
45. Mendlewicz J, Kempenaers C, de Maertelaer V. Sleep EEG and amitryptiline treatment in depressed inpatients. Biol Psychiatry 1991; 30 (7): 691-702
46. Gillin JC, Wyatt RJ, Fram D, et al. The relationship between changes in REM sleep and clinical improvement in depressed patients treated with amitriptyline. Psychopharmacology (Berl) 1978; 59 (3): 267-72
47. Herdman JR, Cowen PJ, Campling GM, et al. Effect of lofepramine on 5-HT function and sleep. J Affect Disord 1993; 29 (1): 63-72
48. Nicholson AN, Pascoe PA, Turner C. Modulation of sleep by trimipramine in man. Eur J Clin Pharmacol 1989; 37 (2): 145-50
49. Akindele MO, Evans JI, Oswald I. Mono-amine oxidase inhibitors, sleep and mood. Electroencephalogr Clin Neurophysiol 1970; 29 (1): 47-56
50. Wyatt RJ, Fram DH, Kupfer DJ, et al. Total prolonged drug-induced REM sleep suppression in anxious-depressed patients. Arch Gen Psychiatry 1971; 24 (2): 145-55
51. Landolt HP, Raimo EB, Schnierow BJ, et al. Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. Arch Gen Psychiatry 2001; 58 (3): 268-76
52. Blois R, Gaillard JM. Effects of moclobemide on sleep in healthy human subjects. Acta Psychiatr Scand Suppl 1990; 360: 73-5
53. Monti JM, Alterwain P, Monti D. The effects of moclobemide on nocturnal sleep of depressed patients. J Affect Disord 1990; 20 (3): 201-8
54. Steiger A, Benkert O, Holsboer F. Effects of long-term treatment with the MAO-A inhibitor moclobemide on sleep EEG and nocturnal hormonal secretion in normal men. Neuropsychobiology 1994; 30 (2-3): 101-5
55. Maeda Y, Hayashi T, Furuta H, et al. Effects of mianserin on human sleep. Neuropsychobiology 1990; 24 (4): 198-204
56. Nicholson AN, Pascoe PA, Stone BM. Modulation of catecholamine transmission and sleep in man. Neuropharmacology 1986; 25 (3): 271-4
57. Tormey WP, Buckley MP, O'Kelly DA, et al. Sleep-endocrine profile of the antidepressant mianserin. Curr Med Res Opin 1980; 6 (7): 456-60
58. Mendlewicz J, Dunbar GC, Hoffman G. Changes in sleep EEG architecture during the treatment of depressed patients with mianserin. Acta Psychiatr Scand Suppl 1985; 320: 26-9
59. Aslan S, Isik E, Cosar B. The effects of mirtazapine on sleep: a placebo controlled, double-blind study in young healthy volunteers. Sleep 2002; 25 (6): 677-9
60. Ruigt GS, Kemp B, Groenhout CM, et al. Effect of the antidepressant Org 3770 on human sleep. Eur J Clin Pharmacol 1990; 38 (6): 551-4
61. Schittecatte M, Dumont F, Machowski R, et al. Effects of mirtazapine on sleep polygraphic variables in major depression. Neuropsychobiology 2002; 46 (4): 197-201
62. Sharpley AL, Walsh AE, Cowen PJ. Nefazodone – a novel antidepressant – may increase REM sleep. Biol Psychiatry 1992; 31 (10): 1070-3
63. Ware JC, Rose FV, McBrayer RH. The acute effects of nefazodone, trazodone and buspirone on sleep and sleep-related penile tumescence in normal subjects. Sleep 1994; 17 (6): 544-50
64. Vogel G, Cohen J, Mullis D, et al. Nefazodone and REM sleep: how do antidepressants decrease REM sleep? Sleep 1998; 21 (1): 70-7
65. Ware JC, Pittard JT. Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. J Clin Psychiatry 1990; 51 Suppl.: 18-22
66. Suzuki H, Yamadera H, Nakamura S, et al. Effects of trazodone and imipramine on the biological rhythm: an analysis of sleep EEG and body core temperature. J Nippon Med Sch 2002; 69 (4): 333-41
67. Yamadera H, Nakamura S, Suzuki H, et al. Effects of trazodone hydrochloride and imipramine on polysomnography in healthy subjects. Psychiatry Clin Neurosci 1998; 52 (4): 439-43
68. van Bemmel AL, Havermans RG, van Diest R. Effects of trazodone on EEG sleep and clinical state in major depression. Psychopharmacology (Berl) 1992; 107 (4): 569-74
69. Scharf MB, Sachais BA. Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomniac patients. J Clin Psychiatry 1990; 51 Suppl.: 13-7
70. Mouret J, Lemoine P, Minuit MP, et al. Effects of trazodone on the sleep of depressed subjects: a polygraphic study. Psychopharmacology (Berl) 1988; 95 Suppl.: S37-43
71. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia in depression: differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. Prog Neuropsychopharmacol Biol Psychiatry 2002; 26 (2): 249-60
72. Ott GE, Rao U, Lin KM, et al. Effect of treatment with bupropion on EEG sleep: relationship to antidepressant response. Int J Neuropsychopharmacol. Epub 2004 Apr 26
73. Ott GE, Rao U, Nuccio I, et al. Effect of bupropion-SR on REM sleep: relationship to antidepressant response. Psychopharmacology (Berl) 2002; 165 (1): 29-36
74. Evans L, Golshan S, Kelsoe J, et al. Effects of rapid tryptophan depletion on sleep electroencephalogram and mood in subjects with partially remitted depression on bupropion. Neuropsychopharmacology 2002; 27 (6): 1016-26
75. Nofzinger EA, Reynolds III CF, Thase ME, et al. REM sleep enhancement by bupropion in depressed men. Am J Psychiatry 1995; 152 (2): 274-6
76. Ferini-Strambi L, Manconi M, Castronovo V, et al. Effects of reboxetine on sleep and nocturnal cardiac autonomic activity in patients with dysthymia. J Psychopharmacol 2004; 18 (3): 417-22

77. DeVane CL. Metabolism and pharmacokinetics of selective serotonin reuptake inhibitors. Cell Moll Neurobiol 1999; 19 (4): 443-66
78. Monaca C, Boutrel B, Hen R, et al. 5-HT 1A/1B receptor-mediated effects of the selective serotonin reuptake inhibitor, citalopram, on sleep: studies in 5-HT 1A and 5-HT 1B knock-out mice. Neuropsychopharmacology 2003; 28 (5): 850-6
79. Gillin JC, Jernajczyk W, Valladares-Neto DC, et al. Inhibition of REM sleep by ipsapirone, a 5HT1A agonist, in normal volunteers. Psychopharmacology (Berl) 1994; 116 (4): 433-6
80. Wilson SJ, Bailey JE, Rich AS. The use of sleep measures to compare a new 5HT1A agonist eptapirone with buspirone in humans. J Psychopharmacol. In Press
81. Lawlor BA, Newhouse PA, Balkin TJ, et al. A preliminary study of the effects of nighttime administration of the serotonin agonist, m-CPP, on sleep architecture and behavior in healthy volunteers. Biol Psychiatry 1991; 29 (3): 281-6
82. Riemann D, Voderholzer U, Cohrs S, et al. Trimipramine in primary insomnia: results of a polysomnographic double-blind controlled study. Pharmacopsychiatry 2002; 35: 165-74
83. Haas H, Panula P. The role of histamine and the tuberomamillary nucleus in the nervous system. Nat Rev Neurosci 2003; 4 (2): 121-30
84. Sharpley AL, Vassallo CM, Cowen PJ. Olanzapine increases slow-wave sleep: evidence for blockade of central 5-HT(2C) receptors in vivo. Biol Psychiatry 2000; 47 (5): 468-70
85. Urichuk LJ, Allison K, Holt A, et al. Comparison of neurochemical effects of the monoamine oxidase inhibitors phenelzine, moclobemide and brofaromine in the rat after short- and long-term administration. J Affect Disord 2000; 58 (2): 135-44
86. de Boer T, Nefkens F, van Helvoirt A, et al. Differences in the modulation of noradrenergic and serotonergic transmission by the alpha-2 adrenoceptor antagonists, mirtazapine, mianserin and idazoxan. J Pharmacol Exp Ther 1996; 277: 852-60
87. Wilson SJ, Glue P, Nutt DJ. The effects of the α-2-adrenoceptor antagonist idazoxan on sleep in normal volunteers. J Psychopharmacol 1991; 5: 105-10
88. Haddjeri N, Blier P, de Montigny C. Noradrenergic modulation of central serotonergic neurotransmission: acute and long term actions of mirtazapine. Int Clin Psychopharmacol 1995; 10 Suppl. 4: 11-7
89. Chalon S, Pereira A, Lainey E, et al. Comparative effects of duloxetine and desipramine on sleep EEG in healthy subjects. Psychopharmacology (Berl) 2005; 177 (4): 357-65
90. Lemoine P, Faivre T. Subjective and polysomnographic effects of milnacipran on sleep in depressed patients. Hum Psychopharmacol 2004; 19 (5): 299-303
91. Borbely AA. A two process model of sleep regulation. Hum Neurobiol 1982; 1 (3): 195-204
92. Ehlers CL, Havstad JW, Kupfer DJ. Estimation of the time course of slow-wave sleep over the night in depressed patients: effects of clomipramine and clinical response. Biol Psychiatry 1996; 39 (3): 171-81
93. Veitch W, Wilson SJ, Argyropoulos S, et al. Slow waves in sleep are altered by paroxetine and nefazodone in depressed patients [abstract]. J Psychopharm 2001; 15 (3 Suppl.): A18
94. Sateia MJ, Doghramji K, Hauri PJ, et al. Evaluation of chronic insomnia: an American Academy of Sleep Medicine review. Sleep 2000; 23: 243-308
95. Parrott AC, Hindmarch I. Factor analysis of a sleep evaluation questionnaire. Psychol Med 1978; 8: 325-9
96. Parrott AC, Hindmarch I. The Leeds Sleep Evaluation Questionnaire in psychopharmacological investigations: a review. Psychopharmacology (Berl) 1980; 71: 173-9
97. Zisapel N, Laudon M. Subjective assessment of the effects of CNS-active drugs on sleep by the Leeds Sleep Evaluation Questionnaire: a review. Hum Psychopharmacol 2003; 18: 1-20
98. Ware JC. Tricyclic antidepressants in the treatment of insomnia. J Clin Psychiatry 1983; 44: 25-8
99. Akerstedt T. Do subjective sleep reports describe objective sleep? Insom 2003; 1: 11-6
100. Argyropoulos SV, Hicks JA, Nash JR, et al. Correlation of subjective and objective sleep measurements at different stages of the treatment of depression. Psychiatry Res 2003; 120: 179-90
101. Mayers AG, van Hooff JC, Baldwin DS. Quantifying subjective assessment of sleep and life-quality in antidepressant-treated depressed patients. Hum Psychopharmacol 2003 18: 21-27
102. Oberndorfer S, Saletu-Zyhlarz G, Saletu B. Effects of selective serotonin reuptake inhibitors on objective and subjective sleep quality. Neuropsychobiology 2000; 42: 69-81
103. Hutchinson DR, Tong S, Moon CA, et al. Paroxetine in the treatment of elderly depressed patients in general practice: a double-blind comparison with amitriptyline. Int Clin Psychopharmacol 1992; 6 Suppl. 4: 43-51
104. Dorman T. Sleep and paroxetine: a comparison with mianserin in elderly depressed patients. Int Clin Psychopharmacol 1992; 6 Suppl. 4: 53-8
105. Satterlee WG, Faries D. The effects of fluoxetine on symptoms of insomnia in depressed patients. Psychopharmacol Bull 1995; 31: 227-37
106. Dossenbach M, Martenyi FS, De Verga E. Sleep quality during fluoxetine therapy in depression. Biol Psychiatry 1997; 42: S243
107. Stephenson DA, Harris B, Davies RH, et al. The impact of antidepressants on sleep and anxiety: a comparative study of fluoxetine and dothiepin using the Leeds Sleep Evaluation Questionnaire. Hum Psychopharmacol 2000; 15: 529-34
108. Rosenberg C, Damsbo N, Fuglum E, et al. Citalopram and imipramine in the treatment of depressive patients in general practice: a Nordic multicentre clinical study. Int Clin Psychopharmacol 1994; 9 Suppl. 1: 41-8
109. Bech P, Cialdella P. Citalopram in depression: meta-analysis of intended and unintended effects. Int Clin Psychopharmacol 1992; 6 Suppl. 5: 45-54
110. Aguglia E, Casacchia M, Cassano GB, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. Int Clin Psychopharmacol 1993; 8: 197-202
111. Bennie EH, Mullin JM, Martindale JJ. A double-blind multicenter trial comparing sertraline and fluoxetine in outpatients with major depression. J Clin Psychiatry 1995; 56: 229-37
112. Sechter D, Troy S, Paternetti S, et al. A double-blind comparison of sertraline and fluoxetine in the treatment of major depressive episode in outpatients. Eur Psychiatry 1999; 14: 41-8
113. Sogaard J, Lane R, Latimer P, et al. A 12-week study comparing moclobemide and sertraline in the treatment of outpatients with atypical depression. J Psychopharmacol 1999; 13: 406-14
114. Nierenberg AA, Adler LA, Peselow E, et al. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994; 151: 1069-72
115. Blacker R, Shanks NJ, Chapman N, et al. The drug treatment of depression in general practice: a comparison of nocte adminis-

 

tration of trazodone with mianserin, dothiepin and amitriptyline. Psychopharmacology (Berl) 1988; 95 Suppl.: S18-24

116. Moon CA, Davey A. The efficacy and residual effects of trazodone (150mg nocte) and mianserin in the treatment of depressed general practice patients. Psychopharmacology (Berl) 1988; 95 Suppl.: S7-13
117. Guelfi JD, Ansseau M, Timmerman L, et al. Mirtazapine versus venlafaxine in hospitalized severely depressed patients with melancholic features. J Clin Psychopharmacol 2001; 21: 425-31
118. Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry 1996; 57 Suppl. 2: 46-52
119. Manber R, Rush AJ, Thase ME, et al. The effects of psychotherapy, nefazodone, and their combination on subjective assessment of disturbed sleep in chronic depression. Sleep 2003; 26: 130-6
120. Buysse DJ, Reynolds III CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989; 28: 193-213
121. Nowell PD, Reynolds III CF, Buysse DJ, et al. Paroxetine in the treatment of primary insomnia: preliminary clinical and electroencephalogram sleep data. J Clin Psychiatry 1999; 60: 89-95
122. Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. Psychopharmacology (Berl) 1999; 144: 220-33
123. Walsh JK, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. Hum Psychopharmacol 1998; 13: 191-8
124. Hajak G, Rodenbeck A, Voderholzer U, et al. Doxepin in the treatment of primary insomnia: a placebo-controlled, double-blind, polysomnographic study. J Clin Psychiatry 2001; 62: 453-63
125. Ohayon MM, Roth T. Prevalence of restless legs syndrome and periodic limb movement disorder in the general population. J Psychosom Res 2002; 53 (1): 547-54
126. Nofzinger EA, Fasiczka A, Berman S, et al. Bupropion SR reduces periodic limb movements associated with arousals from sleep in depressed patients with periodic limb movement disorder. J Clin Psychiatry 2000; 61 (11): 858-62
127. Cadilhac J. Tricyclics and REM sleep. In: Guilleminault C, Dement WC, Passouant P, editors. Narcolepsy. New York: Spectrum Publication, 1976: 605-23
128. Guilleminault C, Raynal D, Takahashi S, et al. Evaluation of short-term and long-term treatment of the narcolepsy syndrome with clomipramine hydrochloride. Acta Neurol Scand 1976; 54: 71-87
129. Schenck CH, Mahowald MW, Kim SW, et al. Prominent eye movements during NREM sleep and REM sleep behavior disorder associated with fluoxetine treatment of depression and obsessive-compulsive disorder. Sleep 1992; 15 (3): 226-35
130. Ellison JM, Stanziani P. SSRI-associated nocturnal bruxism in four patients. J Clin Psychiatry 1993; 54 (11): 432-4
131. Wise M. Citalopram-induced bruxism [letter]. Br J Psychiatry 2001; 178: 182
132. Onofrj M, Luciano AL, Thomas A, et al. Mirtazapine induces REM sleep behavior disorder (RBD) in parkinsonism. Neurology 2003; 60 (1): 113-5
133. Winkelman JW, James L. Serotonergic antidepressants are associated with REM sleep without atonia. Sleep 2004; 27 (2): 317-21
134. Pagel JF, Helfter P. Drug induced nightmares: an etiology based review. Hum Psychopharmacol 2003; 18 (1): 59-67
135. Lepkifker E, Dannon PN, Iancu I, et al. Nightmares related to fluoxetine treatment. Clin Neuropharmacol 1995; 18: 90-4
136. Markowitz JC. Fluoxetine and dreaming. J Clin Psychiatry 1991; 52 (10): 432
137. Koponen H, Lepola U, Leiononen E, et al. Citalopram in the treatment of obsessive-compulsive disorder: an open pilot study. Acta Psychiat Scand 1997; 96: 343-6
138. Kirschner NT. Medication and dreams: changes in dream content after drug treatment. Dreaming 1999; 9: 195-200
139. Pace-Schott EF, Gersh T, Silvestri R, et al. SSRI treatment suppresses dream recall frequency but increases subjective dream intensity in normal subjects. J Sleep Res 2001; 10 (2): 129-42
140. Dilsaver SC, Greden JF. Antidepressant withdrawal phenomena. Biol Psychiatry 1984; 19 (2): 237-56
141. Goldenberg D, Mayskiy M, Mossey C, et al. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996; 39 (11): 1852-9
142. Vercoulen JH, Swanink CM, Zitman FG, et al. Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. Lancet 1996; 347 (9005): 858-61
143. Wilson SJ, Lillywhite AR, Potokar JP, et al. Adult night terrors and paroxetine. Lancet 1997; 350 (9072): 185
144. Bengtson H, Broman J-E, Hetta J. The effect of paroxetine on sleepwalking in 8 adults [abstract]. Sleep Res Online 1999; 2 Suppl. 1: 131
145. Smith IE, Quinnell TG. Pharmacotherapies for obstructive sleep apnoea: where are we now? Drugs 2004; 64 (13): 1385-99
146. Kopelman PG, Elliott MW, Simonds A, et al. Short-term use of fluoxetine in asymptomatic obese subjects with sleep-related hypoventilation. Int J Obes Relat Metab Disord 1992; 16 (10): 825-30
147. Kraiczi H, Hedner J, Dahlof P, et al. Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. Sleep 1999; 22 (1): 61-7
148. Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest 1991; 100 (2): 416-21
149. Evans JH. Evidence based management of nocturnal enuresis. BMJ 2001; 323 (7322): 1167-9
150. Radhakishun FS, van den Bos J, van der Heijden BC, et al. Mirtazapine effects on alertness and sleep in patients as recorded by interactive telecommunication during treatment with different dosing regimens. J Clin Psychopharmacol 2000; 20 (5): 531-7
151. Thase ME, Fasiczka AL, Berman SR, et al. Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. Arch Gen Psychiatry 1998; 55 (2): 138-44

Correspondence and offprints: Dr *Sue Wilson*, Psychopharmacology Unit, University of Bristol, Whitson St, Dorothy Hodgkin Building, Bristol, BS1 3NY, UK.
E-mail: sue.wilson@bristol.ac.uk