Sleep disturbance is common in major depressive disorder (MDD), and is often characterized by early-morning waking. Melatonin is a hypnotic and synchronizes circadian rhythms. It may also be an antidepressant. The melatonin agonists, ramelteon and agomelatine, have hypnotic and antidepressant properties, but there is a dearth of trials investigating the use of melatonin in MDD. This randomized, controlled trial aimed to determine whether exogenous melatonin is a sleep promoter and antidepressant. Thirty-three participants with a Diagnostic and Statistical Manual of Mental Disorders (fourth edition) diagnosis of MDD and early-morning waking were selected for a 4-week, randomized, double-blind trial of slow-release melatonin (6 mg; vs. placebo) given at bedtime over 4 weeks. Sleep was measured subjectively using sleep diaries and the Leeds Sleep Evaluation Questionnaire and objectively using wrist actigraphy. Of the 33 participants, 31 completed the trial. General Linear Modelling showed significant improvements in depression and sleep over time, but this was not specific to melatonin. However, there was a trend towards an improvement in mood with melatonin, and no adverse side effects were observed. In conclusion, melatonin may be beneficial for treating MDD, it seems to be safe and well tolerated, but its potential for treating depression in people who do not wish to take antidepressants requires further evaluation. 


Keywords: major depressive disorder, melatonin, mood, randomized controlled trial, sleep

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Introduction

Disturbed sleep is a characteristic feature (Benca et al., 1992; Van Bemmel, 1997) and predictor (Perlis et al., 1997) of depressive disorder. Manipulations of the sleep–wake cycle may improve depressive symptoms (Van Bemmel, 1997).

Melatonin is one of the main zeitgebers (external indicators of time) controlling the sleep–wake cycle in humans. Its secretion is stimulated by darkness and suppressed by light (Arendt, 1995). Changes in circadian rhythm occur in affective disorders (Wirz-Justice, 2006), and disruption of the sleep–wake cycle is possibly mediated through melatonin. In seasonal affective disorder (SAD), melatonin secretion is usually phase delayed (Lewy et al., 1987, 2006) and associated with waking later than usual. Early-morning waking is characteristic of nonseasonal depression, but there is no consensus as to the accompanying disturbance of melatonin secretion (Crasson et al., 2004), in which there may be decreased amplitude (Wetterberg, 1978; Frazet et al., 1986; McIntyre et al., 1989), increased amplitude (Parry et al., 2006), phase advances (Checkley, 1989; Sekula et al., 1997) or phase delays (Crasson et al., 2004) of nocturnal melatonin. It has also been suggested that melatonin dysfunction is not central to depression (Childs et al., 1995), but is rather an epiphenomenon.

The effects of exogenous melatonin as a chronobiotic (i.e. a substance that shifts rhythms) (Arendt and Skene, 2005) and a hypnotic (Zhdanova, 2005a, 2005b) have been documented since the 1970s. The hypnotic effect is probably brought about by inducing sleepiness through thermoregulatory changes (Cagnacci et al., 1997). As chronobiotic melatonin has been used to treat nonpsychiatric disorders such as insomnia (Zhdanova et al., 2001), free running circadian rhythms in blind people (Sack et al., 2000), jet lag (Herxheimer and Petrie, 2005) and sleep disorders associated with shift work (Skene et al., 1996). The use of melatonin in psychiatric disorders was summarized in the study by Serfaty (2006). Meta-analyses of the therapeutic effects of melatonin have generated inconsistent results (Brzczinski et al., 2005;
Buscemi et al., 2006), but overall, evidence suggests that melatonin is an effective chronobiotic and a hypnotic, which benefit a number of people (Arendt, 2006).

In SAD, melatonin exerts a corrective phase advance (Lewy et al., 1998, 2003, 2006; Leppamaki et al., 2003), but its effects on mood are equivocal, with worsening symptoms (Rosenthal et al., 1985), no change in symptoms (Wirz-Justice et al., 1990; Leppamaki et al., 2003; Lewy et al., 2003) or improvements in mood (Lewy et al., 1997, 1998).

In nonseasonal depression, the use of melatonin fell into disrepute after a methodologically unsound trial by Carman et al. (1976) suggested that melatonin was ineffective in the treatment of depression and was associated with psychotic symptoms. In Carman et al.'s (1976) study, patients received massive doses of melatonin, in some cases intravenously, throughout the day. Patients also had multiple diagnoses. Carman et al.'s (1976) negative finding may explain why no further studies using melatonin for treating depression were published for more than two decades. However, in 1997 De Vries and Peeters published a case report suggesting an improvement in depression with 5 mg of melatonin, and an open-label study by Fainstein et al. (1997) suggested that administration of melatonin (3 mg nocte) for 21 days improved sleep quality in nine older people with depression. Döllberg et al. (1998) conducted a randomized controlled trial (RCT) of melatonin (5 mg; or placebo) as an adjunct to fluoxetine (20 mg) in 19 outpatient volunteers with a Diagnostic and Statistical Manual of Mental Disorders (fourth edition) classification of major depression (American and Association, 1994). Melatonin was associated with a significant improvement in sleep, but not mood. Similar findings were reported in six out of eight patients with treatment-resistant depression (Dalton et al., 2000). A more recent report suggests that melatonin may be helpful in depressed postmenopausal women (Bellipanni et al., 2005).

The use of melatonergic agonists, ramelteon and agomelatine, on sleep and mood has also been investigated. Ramelteon is a selective MT1/MT2 receptor agonist, approved by the US Food and Drug Administration (FDA) in 2005, for the treatment of insomnia. It improves sleep latency by 21 min (compared with 12 min with placebo) in older people with insomnia (Roth et al., 2005, 2006). Agomelatine (S-20098) is a melatonin agonist and selective 5-HT2c antagonist. Significant improvements in Hamilton Depression Rating Scale (HDRS) scores have also been reported with agomelatine compared with placebo, and its use as novel antidepressant for major depressive disorder seems promising (Loo et al., 2002, 2003; Olie and Emsley, 2005; Kennedy and Emsley, 2006), with approval recently having been granted by the European Medicines Agency. However, it remains unclear whether these beneficial effects are because of its melatonergic or 5-HT2c properties.

Theoretical and clinical evidence suggests that melatonin (or its agonists) may be beneficial for sleep disturbance, and possibly mood, in nonseasonal depression. However, the studies to date have involved small numbers of participants, with a range of diagnoses and no objective measures of sleep used. Variable doses of melatonin have been given and little consideration given to the timing of its administration, which may be crucial (Reppert and Weaver, 1995). We are reporting the largest double-blind, randomized, placebo-controlled trial of melatonin given to people with major depressive disorder. Our primary aim was to determine whether, in addition to treatment-as-usual, 4 weeks of exogenous oral slow-release melatonin (6 mg) given at bedtime resulted in a significant improvement in sleep (sleep length measured by wrist actigraphy) when compared with placebo. Our subsidiary outcome measures were other parameters of sleep and measures of depression [HDRS and Beck Depression Inventory (BDI)].

**Methods**

The study was conducted in North London over 3 years and 3 months. Approval was obtained from the Royal Free Hospital and Medical School Ethics Committee. The participants, 18–65 years of age, were recruited through general practices linked to the North Central Thames Primary Care Research Network (NoCTeN) using direct general practitioner (GP) referrals, databases searches and approaches to patients in GP waiting rooms. Patients were initially asked whether they felt depressed and woke more than 1 h earlier than usual 3 days a week. If this were the case, information about the trial was then provided and those that were agreeable were screened within 3 days. If they had a score of 17 or more on the BDI (Beck et al., 1961) they were given a more in-depth interview using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) to ensure that they met the following entry criteria:

Inclusion criteria: Diagnostic and Statistical Manual of Mental Disorders (fourth edition; American and Association, 1994) classification for major depression (unipolar or bipolar), a score of 17 or more on the BDI and self-reported sleep of 1 h less than normal at least 3 days per week.

Exclusion criteria: another axis 1 diagnosis, delusions or hallucinations, active suicidal ideation, receipt of electroconvulsive therapy within the last 6 months, taking hypnotic medication, a recent change in dose or type of psychotropic medication (e.g. antidepressants, neuroleptics) within the last 4 weeks of being referred for...
assessment, and disclosure of alcohol abuse on the Schedule for Affective Disorders and Schizophrenia interview. All eligible participants were then given 24 h to think about the study before consenting to take part.

Design
The study was a 4-week, double-blind, placebo-controlled trial of melatonin or placebo in addition to treatment-as-usual received from the patient’s GP. Change in medication, by the GP, was discouraged during the trial, but any changes deemed necessary were recorded, as it was not felt ethical to restrict the use of antidepressants. Participants were randomly allocated to one of two groups using random numbers generated by an independent clinical trials co-ordinator. After a week’s baseline data collection, melatonin or placebo tablets were given for 4 weeks at the participant’s usual bedtime. This was followed by a 1-week washout period. Slow-release melatonin (6 mg) (synthetic origin) was provided by Genzyme Pharmaceuticals Ltd. (Haverhill Operations, Haverhill, Suffolk, UK). Melatonin and placebo were identical with respect to preparation and packaging. Both the pharmacist dispensing the trial medication and the researchers were blind to the treatment received. The tablets were distinguishable only by batch number held by the manufacturer. The code for treatment allocation was only revealed once the trial was completed. At the end of the trial, patients continued with usual GP care.

Outcome measures

Measures of sleep
Three measures were used: (i) Objective measures of sleep were obtained by using wrist actigraphy monitors. This is an established method based on wrist movements and uses a number of parameters derived on an algorithm described by Cole et al. (1992) that can distinguish sleep from wakefulness with 88% reliability. Participants pressed a button on the actigraph indicating when they went to bed and when they got up, from which the length of time in bed was calculated. The sleep onset time enables calculation of the length of time taken to fall asleep (sleep latency). It is also possible to calculate the total sleep time (TST), the cumulative length of time the person is awake after falling asleep (wake after sleep onset; WSO), the number of times the person moves in bed (movement index), the number of awakenings and the percentage of time asleep (sleep efficiency; SE). The actigraph epoch length, which provides a cut-off time for significant movement, was set at 30 s. (ii) Subjective measures of sleep were collected using the Leeds Sleep Evaluation Questionnaire (LSEQ; Parrot and Hindmarsh, 1978). This self-completed measure used a visual analogue scale to assess four aspects of sleep: getting to sleep (GTS), quality of sleep, awakening from sleep and behaviour following wakefulness. (iii) Detailed diary information was also completed by participants to ascertain whether they had taken the melatonin, what time did they go to bed, what time did they fall asleep, the number of awakenings, what time did they wake up and what time did they get up. In addition, participants were asked to comment about their sleep.

Measures of depression
Two measures were used: (i) The Beck Depression Inventory (BDI; Beck et al., 1961), a widely used self-report instrument consisting of 21 questions rated on a 4-point Likert scale (0–3); and (ii) the 21-item HDRS (Hamilton, 1960). The HDRS is a 21-item observer-rated instrument that is completed following a thorough clinical interview, and as such is considered potentially more objective. Each item presents a symptom of depression and is rated according to its severity as experienced by the patient.

Other measures
Biases could have been introduced because of a number of factors affecting sleep. These include the time of the year (people sleep slightly longer in winter) and whether data were collected during the week or at weekends. As participants were randomized equally over the year, seasonal effects were minimal. However, data were coded for whether they were collected during the week, or on 1 or 2 weekend days. Measures of compliance with melatonin/placebo were also made by pill counts (in addition to self-reported compliance on the diary sheets). Measures of blindness of patients and rater were obtained using a visual analogue scale. The patients were asked to record any adverse events on their sleep diary charts.

The objective measures of sleep, using wrist actigraphy, were collected during the last 3 days of the baseline data collection week (week 0), the first and fourth week of the melatonin/placebo phase (weeks 1 and 4) and at the end of the washout phase (week 5). Subjective measures of sleep using the LSEQ were collected at the end of each week, and sleep diary entries were made daily by the participants. The BDI was completed at the end of each week.

All medications prescribed were recorded. This included type and dose of antidepressant. As a result of the variety of different antidepressants available, doses were also standardized against imipramine (Bollini et al., 1999).

Statistical analysis
Prestudy power
Power calculations were performed using Epi Info 6 (WHO) to estimate the numbers required, to test our main hypothesis and to detect a significant difference in sleep length at 80% power with a 95% confidence level. It has been suggested that normal sleep time is 6.5 h (American Sleep Disorders Association, 1990) and that it is significantly diminished in depressive disorder, with
TST being roughly 5½ h [standard deviation (SD) of 1 h] (Gillin et al., 1979). We therefore hypothesized that depressed people would sleep an hour less than nondepressed individuals and that melatonin would normalize TST. Thus, using the above data and a similar SD of 1 h for both groups, at 80% power at a $P$ value less than 0.05 significance, 17 people would be required in each group (total of 34).

Studies of depression in primary care populations suggest that there is a SD of 4 points in the HDRS (Mynors-Wallis et al., 1995). A 5-point change in mean HDRS score is usually taken as clinically significant. This corresponds to an effect size of 1.2 SDs. Thus, 11 participants (total of 22) would be required in each arm to show an advantage of melatonin over placebo and to show a significant change in mood in the treatment of depression.

**Missing data**

Actigraph data were collected during the last 3 days of four periods: the baseline period, the first and fourth week of melatonin and the washout period. As data points were normally distributed, data were averaged for each period. In cases in which baseline data were missing, average values for each group (melatonin or placebo) were entered. In cases in which sets of data were missing for the subsequent time period, the last observation carried forward (LOCF) was used.

**Analysis**

Data were analysed using the Statistical Package for Social Sciences (version 10.1.3; SPSS Inc., Chicago, Illinois, USA). Data collected from actigraphs were converted into an analysable form and then analysed using the software supplied by Neurim Pharmaceuticals Ltd. (Tel Aviv, Israel).

Categorical or skewed baseline data were examined using the $\chi^2$ test. In instances in which data were normally distributed, baseline differences were examined using unpaired $t$-tests. General Linear Modelling (GLM) was used to measure differences over time and differences between melatonin and placebo. In instances in which Mauchly’s test for sphericity showed a significant effect, Greenhouse–Geisser statistics were used. We also used the Generalized Estimating Equation (GEE) (Zeger and Liang, 1986) for BDI applying an exchangeable correlation matrix for continuous BDI outcome and adjusting for baseline BDI and time.

Average data sets for each of the periods under study were entered into the analysis. Data were then analysed by ‘group’ (melatonin or placebo) to examine whether this affected the outcome. Both, a completer’s analysis and an intention-to-treat analysis, were performed, and both gave consistent results. However, for convenience, only the data for the intention-to-treat analysis, using LOCF, is presented, but a more detailed analysis, available in the study by Serfaty (2006), was also performed for completers only, and this generated similar results. Subsidiary analysis of sleep was performed to determine the accuracy of self-report data by correlating this with objective actigraph data.

**Results**

A total of 203 people were approached for the study: 80 participants were referred directly by their GPs, 68 were recruited through screening questionnaires in GP surgeries and 33 through a database search of people with a earlier history of depression, and a further 22 contacted the research team after having seen an information sheet or heard about the study by word-of-mouth from a friend or relative.

Of the 170 participants who did not then participate in the study, 84 did not have disturbance of sleep or diagnostic criteria for depression, 44 did not wish to participate, 31 could not be contacted/did not respond to calls and 11 did not have sufficient command over English.

Of the 33 patients recruited to the study, 16 were referred by their GP, 13 were identified from GP databases and four self-referred. For a summary of participant flow, see Fig. 1.

**Dropouts**

Of the 33 initially recruited, two participants dropped out immediately because they felt better.

Missing data analysis: this was performed on 31 sets of self-report data and 29 sets of actigraph data. Mean baseline scores for actigraph recordings were substituted for the two participants for whom data were missing at baseline, and in instances in which follow-up data were missing, the LOCF was used. Baseline self-report questionnaires were completed by 31 participants and baseline actigraph data were available for 29 participants, because two participants had forgotten to wear the device and in two cases the actigraph did not function. At completion, full data sets were available from self-report data for 27 participants and full sets of actigraph data were available for 21 participants, for the same reasons as above. Data for the intention-to-treat analysis were available for 31 participants.

**Baseline data**

There were no significant differences between groups for participants’ age, and the number of people taking prescribed antidepressants (see below) or used hypnotic medication as required (Table 1).
Biases may be introduced because of a number of factors affecting sleep. These include time of year (people sleep slightly longer in winter) and whether sleep data are collected in the week or at weekends. As participants were randomized over the year, seasonal effects were likely to be minimal. Analysis to examine whether data in either group (melatonin or placebo) was more likely to be recorded in the week or at weekends, did not reveal any significant differences (Table 1).

There were no baseline differences in measures of depression (Table 2). Baseline measures of sleep using wrist actigraphy found that individuals who were allocated to the placebo group woke sooner after sleep onset (d.f. = 27, t = 2.26, P = 0.03) and had significantly better sleep efficiency (SE) (d.f. = 27, t = 2.38, P = 0.025) (Table 2).

**Antidepressant prescribing**

Of those individuals who were prescribed antidepressants, 12 were in the melatonin group (five were prescribed fluoxetine, three paroxetine, one citalopram, two venlafaxine and one amitryptyline) and 10 were allocated to the placebo group (three were prescribed fluoxetine, four citalopram, one paroxetine, one nefazodone and one venlafaxine). Antidepressants were standardized into equivalent doses of imipramine (Bollini et al., 1999). At baseline, there were no differences in the
dose of the antidepressant prescribed between the placebo and melatonin group. Only five people in both the melatonin group and the placebo group, respectively, were prescribed a therapeutic dose of 100 mg or more of imipramine. Only four people in each group had been diagnosed at least 12 weeks before entry into the trial and were taking an antidepressant for at least 12 weeks. There were no changes in dose or antidepressant prescription from 2 weeks before entry to the study to the endpoint (final washout).

**Sleep and depression outcomes**

Sleep diary data using GLM revealed a shortened time taken to get to sleep ($F = 5.2$, d.f. = 4, $P = 0.03$), but this was not specific to melatonin, as there was no time by group (melatonin or placebo) interaction.

The LSEQ found a significant improvement in sleep for the group as a whole (Table 2). GLM showed significant improvements with time for GTS ($F = 6.6$, d.f. = 3, $P < 0.001$) and quality of sleep ($F = 4.8$, d.f. = 3, $P < 0.002$), but did not show a time by group (melatonin or placebo) interaction.

**Table 2** Results for main measures of patients allocated to melatonin or placebo groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Washout</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melatonin</td>
<td>Placebo</td>
<td>Melatonin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Depression measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>25.2 (11.4)</td>
<td>26.2 (7.9)</td>
<td>23.4 (11.1)</td>
<td>23.0 (8.4)</td>
</tr>
<tr>
<td>HDRS</td>
<td>18.8 (6.1)</td>
<td>18.8 (3.6)</td>
<td>16.0 (5.3)</td>
<td>16.4 (4.9)</td>
</tr>
<tr>
<td>Sleep diary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to sleep</td>
<td>69.0 (44.6)</td>
<td>68.5 (75.0)</td>
<td>67.5 (50.0)</td>
<td>59.0 (51.4)</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>3.1 (2.0)</td>
<td>2.3 (1.3)</td>
<td>2.3 (1.5)</td>
<td>2.1 (1.0)</td>
</tr>
<tr>
<td>LSEQ</td>
<td>3.7 (2.2)</td>
<td>3.7 (2.0)</td>
<td>5.1 (2.2)</td>
<td>5.5 (1.7)</td>
</tr>
<tr>
<td>GTS</td>
<td>3.4 (2.0)</td>
<td>3.6 (2.0)</td>
<td>4.6 (2.0)</td>
<td>5.2 (2.0)</td>
</tr>
<tr>
<td>QOS</td>
<td>4.2 (2.1)</td>
<td>4.3 (1.9)</td>
<td>4.1 (1.8)</td>
<td>5.0 (1.8)</td>
</tr>
<tr>
<td>AFS</td>
<td>4.7 (1.6)</td>
<td>3.9 (1.5)</td>
<td>4.7 (2.1)</td>
<td>4.6 (1.6)</td>
</tr>
<tr>
<td>BWF</td>
<td>499.1 (679)</td>
<td>473.7 (99.3)</td>
<td>518.5 (79.7)</td>
<td>511.9 (91.8)</td>
</tr>
<tr>
<td>Sleep latency</td>
<td>39.8 (31.2)</td>
<td>21.9 (17.1)</td>
<td>26.9 (25.9)</td>
<td>23.4 (23.2)</td>
</tr>
<tr>
<td>Wake after sleep onset</td>
<td>76.0 (37.4)</td>
<td>47.6 (8.3)*</td>
<td>74.7 (37.1)</td>
<td>53.8 (34.7)</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>370.7 (49.8)</td>
<td>91.7 (107.8)</td>
<td>399.0 (62.7)</td>
<td>422.5 (89.1)</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>29.7 (12.3)</td>
<td>24.1 (8.7)</td>
<td>30.4 (13.1)</td>
<td>26.4 (12.7)</td>
</tr>
<tr>
<td>Movement index</td>
<td>847.4 (481.0)</td>
<td>617.1 (305.6)</td>
<td>891.9 (509.3)</td>
<td>84.6 (399.1)</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>74.7 (8.8)</td>
<td>82.1 (7.5)*</td>
<td>77.5 (10.4)</td>
<td>82.8 (8.9)</td>
</tr>
</tbody>
</table>

Values are expressed as ‘mean (SD)’.

AFS, awakening from sleep; BDI, Beck Depression Inventory; BWF, behaviour following wakefulness; GTS, getting to sleep; HDRS, Hamilton Depression Rating Scale; LSEQ, Leeds Sleep Evaluation Questionnaire; QOS, quality of sleep.

* $P < 0.05$ for unpaired t-test of between-group comparisons. General Linear Modelling stated in text.
Melatonin

were awake for longer (WSO) after getting to sleep. In the melatonin group, and in the placebo group participants

tive measures of sleep: SE was more impaired in the randomization, there were baseline differences in objective
t melatonin. An improvement in mood with time was also observed (Fig. 2), but this was not specific to melatonin.

Adverse effects

Of those taking melatonin, poor sleep was reported by two patients, vivid dreams by one, day time sleepiness by another and a fuzzy feeling the next day by another patient. Vivid dreams were also reported during the washout period of melatonin by one patient (who was also on venlafaxine 75 mg). Of those taking placebo, poor sleep was reported by two patients, daytime sleepiness by one, vivid dreams by one (also on paroxetine 20 mg) and headaches by another.

Discussion

This is the largest RCT investigating the use of melatonin for sleep and mood disturbance in depression. It was designed and presented in accordance with the revised CONSORT guidelines for reporting parallel group randomized trials (Moher et al., 2001). With time, there was a significant improvement in subjective but not objective measures of sleep, but this was not specific to melatonin. An improvement in mood with time was also observed (Fig. 2), but this was not specific to melatonin. Melatonin was not associated with reports of significantly more adverse events.

Although the two groups were similar with respect to demographic factors and severity of depression, despite randomization, there were baseline differences in objective measures of sleep: SE was more impaired in the melatonin group, and in the placebo group participants were awake for longer (WSO) after getting to sleep.

Validit of the measures of sleep

Electroencephalogram polysomnography is a valid and reliable way of measuring sleep disturbance, but is not practical in a naturalistic setting. Wrist actigraphy showed impaired SE (78.3%) in our depressed sample, which is similar to the degree of sleep impairment reported in insomniacs (Sadeh et al., 1989), and worse than the 86% SE reported in healthy individuals (Stanley, 1997). We found that self-report data correlated poorly with those obtained from wrist actigraphy, but all earlier studies investigating the use of melatonin in nonseasonal depression have relied on self-report data (Carman et al., 1976; De Vries and Peeters, 1997; Fainstein et al., 1997; Dolberg et al., 1998; Dalton et al., 2000), which raises concerns about the authors’ conclusions. The validity and reliability of self-report sleep/activity logs, which may not always be filled out accurately (Stanley, 1997), is also highly questionable. There are inherent problems with applying established sleep questionnaires to depressed patients. The LSEQ (Parrot and Hindmarsh, 1978) asks about sleep over the last week, but reports may be influenced by the persons’ ability to recall and by their current mood state; both these factors are influenced by depression. Alternative methods such as independent ratings of sleep by others, for example by a partner, relative or healthcare professionals, may be no better (Serfaty et al., 2002). Objective measures of sleep are therefore necessary.

Possible reasons for no significant effect of melatonin on sleep

Subjective and objective measures of sleep suggested an improvement in GTS over time for both melatonin and placebo, but no between-group differences. There are a number of possible explanations for this. First, there are very large interindividual differences in sleep, which makes detection of between-group differences difficult. Second, early-morning waking was a selection criterion for the study. It is widely accepted that melatonin is a mild hypnotic, which may benefit people with initial insomnia, but may not be useful for early-morning waking. Third, different antidepressants may have different effects on sleep architecture. However, all but one patient was prescribed either an selective serotonin reuptake inhibitor or venlafaxine, which have the least effect on sleep architecture. Furthermore, there was no difference in class or dose between the groups. Fourth, SE, worse in the melatonin group, may have spontaneously remitted; however, this, if anything, would have the effect of showing an improvement in sleep with melatonin. Fifth, though no method of analysis is perfect, both completers analysis and LOCF generated similar results (Serfaty, 2006). Although preferred, LOCF may make unwarranted assumptions about missing data and this can result in underestimating or overestimating treatment effects (Streiner, 2002). Twenty-one actigraph data sets were available (objective measure) at the end of the study. It is worth noting that data were not available because of actigraph malfunction, which is independent of patient

Figure 2

Total Beck Depression Inventory (BDI) score of melatonin versus placebo (mean and ranges for standard error shown).
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factors; data were therefore missing completely at random, which should minimize bias.

Other than our trial, there are no RCTs that have used objective measures of sleep to compare melatonin with placebo in nonseasonal depression. Assuming the reliability of our measures, there are two main possible reasons why we may not have detected a significant difference. First, an effect of melatonin may exist, but our study was underpowered. Second, the effects of melatonin may be small.

Power considerations
The first possibility that the study was underpowered warrants serious consideration. All published studies examining the beneficial effects of melatonin on mood and sleep in nonseasonal depression has methodological problems: small numbers, no placebo control, failure to randomize, no objective measures and publication bias may account for the widespread differing effects of melatonin on sleep and mood described earlier. The sample size in this study was calculated on the basis of the limited data published with regard to the therapeutic effects of melatonin, but in retrospect it is likely that the therapeutic effects of melatonin have been overestimated and that effects similar to those reported with melatonin agonists would be more realistic. Although not evaluated in psychiatric patients (Becker, 2006), a large study (n = 829) by Roth et al. (2005, 2006), funded by Takeda Pharmaceuticals, found that ramelteon, a melatonin agonist, improves sleep by 9 min over placebo in older people with insomnia, and FDA approval has now been granted for its use. In our population, a nonsignificant increase in SE of 3.4% and sleep length of 4.1 min was observed in the melatonin group, which is of a similar order of magnitude to Roth et al.’s (2005, 2006) study. Post-hoc analysis on our data, using means for melatonin/placebo and pooled means for the whole sample population at week 4 of melatonin/placebo compared with baseline, suggests that melatonin may have an effect on sleep. At 80% power at the 5% significance level, using intention-to-treat data, a total of 90 people (45 in each group) would be required to detect this level of improvement in SE.

Possible treatment effects of melatonin
The second possibility, that melatonin’s effect on sleep is lesser than reported earlier, also needs to be addressed. Considerable individual variation in the response to exogenous melatonin exists, depending on the phase of circadian melatonin levels: the ‘phase response curve’. Appropriately timed melatonin may show a corrective phase advance in melatonin secretion in SAD (Lewy et al., 2003), and possibly mood disorder (Leppamaki et al., 2003). Although all our patients had early-morning wakening, which suggests a phase advance type of rhythm disorder, this cannot be certain. The rationale behind providing slow-release melatonin at bedtime was to mimic the natural circadian rhythm by prolonging serum melatonin into the early hours of the morning, thus prolonging sleep. Doses of 3–10 mg of melatonin have consistently been used for people with nonseasonal depression (De Vries and Peeters, 1997; Fainstein et al., 1997; Dolberg et al., 1998; Dalton et al., 2000); however, recent data suggest that this dose may be too large, with serum levels of melatonin being carried over into the next day. Indeed, for this reason, doses as low as 0.1 mg are now recommended for older people with sleep disturbance (Zhdanova et al., 2001) and for treating SAD (Lewy et al., 1998, 2003). The dose in nonseasonal depression remains to be established, and future trials investigating the potential beneficial effects of melatonin in depression should consider using different timing and dosing regimens.

Concomitant use of medication, which may affect sleep, needs to be considered, but there was no difference in prescribed psychotropic medication between the melatonin and placebo groups. Hypnotic medication was prescribed for sleep problems in one patient, but she had been on a stable dose for some months. It is therefore unlikely that hypnotic medication introduced a significant bias.

Melatonin and mood
Of the two earlier RCTs, neither has shown a beneficial effect of melatonin on mood (Carman et al., 1976; Dolberg et al., 1998). GEE modelling suggests that there may be a weak effect of melatonin on mood when using the BDI, but not the HDRS. This finding is of interest, particularly given that a similar compound, the melatonin agonist, agomelatine, seems to have beneficial effects (Loo et al., 2002; Kennedy and Emsley, 2006; Olic and Kasper, 2007) and to offer promising opportunities for treating depression (Lam, 2007).

Prescribed antidepressants
We did not observe any significant differences in mood with melatonin, although there was some suggestion that this may be a type II error. Earlier RCTs of melatonin in depressed people had atypical patient groups (Carman et al., 1976) and nonresponders to fluoxetine (Dolberg et al., 1998), and therefore caution is required in concluding that melatonin may not be of any benefit. Over 70% (22 of 31) of people recruited to our trial were prescribed antidepressants, and this may explain our findings in several ways. First, concomitant antidepressant use may result in an improvement in mood in both the placebo group and the melatonin group, which will reduce between-group differences. However, the number of participants who were prescribed a therapeutic dose of antidepressant was small. Second, melatonin may have a therapeutic effect, but a disproportionate number of people in the placebo group might already be taking an antidepressant. This would reduce the apparent
therapeutic effect of melatonin. However, there were no between-group differences in the prescribed dose of the antidepressant. Third, patients who have failed to respond to antidepressants may represent a treatment-resistant group and therefore may not respond to melatonin. However, few people would satisfy conventional definitions of treatment resistance; only a quarter of the participants could have been prescribed a therapeutic dose of an antidepressant for at least 12 weeks (Quitkin et al., 1993). Furthermore, compliance with antidepressants is known to be poor, as between a quarter and half of the patients do not take their antidepressants as prescribed (Demyttenaere et al., 2001; Pinto-Meza et al., 2008). Interestingly, judged by pill counts, compliance with our intervention was good, which is consistent with the expressed views of patients who chose to participate in a trial of ‘natural treatment’.

Melatonin may act synergistically by augmenting the antidepressant effect, for example, by increasing brain serotonin (Cottizas et al., 1971), and thus have a beneficial effect for those taking subtherapeutic doses of antidepressants. Neither we nor Dolberg et al. (1998) found a beneficial effect of melatonin combined with antidepressants; however, these findings may be explained by a type II error, and the possibility of melatonin for augmentation remains to be evaluated.

Dosing and length of treatment with melatonin
Most studies have investigated the use of melatonin for treating sleep and mood in depressed people over a 3–4 weeks period (Dolberg et al., 1998; Lewy et al., 1998; Dalton et al., 2000). Antidepressants may require up to 12 weeks administration to achieve a therapeutic effect, and an improvement in mood has been associated with a longer treatment period of up to 6 months with melatonin (Bellipanni et al., 2005). Although a longer treatment period may be required, our study findings (Table 2, Fig. 2) were consistent with those for the melatonin agonists (Lam, 2007) ramelteon (Roth et al., 2005, 2006) and agomelatine (Pjrek et al., 2007), suggesting that any beneficial effects occur early in the treatment.

Comparison with melatonin agonists
Approval for the use of agomelatine as a novel antidepressant has been granted by the European Commission and the FDA in the United States. Three RCTs have been carried out examining the effects of agomelatine on mood in humans (Loo et al., 2002; Kennedy and Emsley, 2006; Olie and Kasper, 2007). Given the size of the treatment effect of agomelatine, a sample size of between 200 and 700 participants would be required to show significant advantage of agomelatine over placebo. Trials of antidepressants on FDA and European Medicines Agency databases often include 100 participants per group. We conducted a post-hoc analysis on BDI scores to determine the numbers needed to detect a significant effect of melatonin on mood. At 80% power and at the 5% level of significance, at least 75 participants would be required in each group to detect a 2-point difference in means (estimated SD 2.34). This calculation was adjusted for an estimated inflation factor of 3.4. This factor was determined from our baseline sample (n = 22), which generated an average cluster size of 4.6 and intraclass correlation coefficient of 0.65.

Though caution is necessary when extrapolating to humans, animal models suggest that agomelatine has 5-HT2c antagonist action (cf. melatonin). The beneficial effects mediating change are still undetermined (Hanoun et al., 2004) and melatonin may behave differently from melatonin agonists.

Adaptations of methodology for further studies
As the negative findings in this study were probably related to small sample size, further trials should consist of at least 180 people to show a beneficial effect of melatonin over placebo on sleep and mood. In retrospect, lower doses, approximately 0.5 mg, of melatonin and variable dosing regimens should be considered. The use of a variety of objective and subjective measures of sleep and mood (including the BDI) with repeated recordings is essential. We were also presented with the difficulty of interpreting our findings because of the use of concomitant antidepressants in a subset of patients. Future trials should consider only recruiting patients, where pharmacological treatments have been clearly defined. First, a trial may consider recruiting only participants who are antidepressant-free (a comparison trial of melatonin against placebo). An alternative approach is to recruit only patients receiving antidepressants, providing they satisfy predefined criteria for treatment resistance. This approach would determine whether melatonin might be used to augment antidepressant treatment (augmentation trial).

Conclusion
This pragmatic study in primary care is the largest double-blind placebo-controlled trial to investigate the effects of melatonin as a hypnotic and mood enhancer in major depression. Although this study, which used rigorous methodology, did not show a significant improvement in sleep and mood with melatonin, findings suggest that this may be because of the small sample size and that melatonin’s effects were similar to other recommended treatments (agomelatine, ramelteon and selective serotonin reuptake inhibitors). Given its safety and tolerability, melatonin may have potential for people who do not wish to take antidepressants, but this remains to be further evaluated.

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