Antidepressants for insomnia (Protocol)

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[Intervention Protocol]

Antidepressants for insomnia

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects, safety and tolerability of antidepressants for insomnia in adults.

BACKGROUND

Description of the condition

Insomnia disorder is a subjective condition of unsatisfactory sleep, either in terms of sleep onset, sleep maintenance or early waking (Wilson 2010). It is a disorder that impairs daytime well-being and subjective abilities and functioning, and so can be considered a '24-hour' disorder. It often starts with a clear event such as unusual stress at work or is associated with illness of self or family, or bereavement. Once the triggering circumstances have diminished or have been addressed as far as possible, most people will return to normal sleep if they adhere to good sleep habits. However the condition may go on to be a chronic complaint (i.e. symptoms persisting for more than a month), and the main factor influencing this is anxiety about sleep (Morin 2003). Essential features of insomnia are heightened arousal and learned sleep-preventing associations.

In the past, insomnia was often classified into primary and secondary insomnia, where secondary insomnia referred to insomnia occurring in association with another disorder. However, most recent classification systems have moved away from this division as the distinction is now seen as unhelpful (Perlis 2010). The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) recommends the use of the term 'insomnia disorder' which we use for this review, but we are aware that past research papers will use other terms to describe insomnia.

Studies of the prevalence of insomnia in the general population indicate that one third of adults in Western countries experience difficulty with sleep initiation or maintenance at least once a week (LeBlanc 2009; Sateia 2004) and 6% to 15% are thought to meet the criteria for insomnia disorder in that they report sleep disturbance plus significant daytime dysfunction (LeBlanc 2009; Sivertsen 2009). There is a higher incidence of insomnia in women, and the incidence increases in both men and women as they get older.

Insomnia may be present alongside other disorders such as depression, anxiety disorders and physical problems (Baglioni 2011). Once other disorders are properly treated, insomnia may persist and need to be treated. It is important to treat insomnia because

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the condition causes decreased quality of life (Chevalier 1999; Leger 2001; Philip 2006), is associated with impaired functioning in many areas such as memory and executive function (Altena 2008; Edinger 2008; Nissen 2011), and leads to increased risk of a new episode or relapse of depression, anxiety and possibly cardiovascular disorders (Breslau 1996; Neckelmann 2007; Vgontzas 2009).

Description of the intervention

The goal of treating insomnia disorder is to lessen suffering and improve daytime function. The two main treatments shown to be effective, at least in the short-term, are psychological and pharmacological treatments; although evidence is limited for longer-term effects (Riemann 2009). The type of treatment chosen should be patient-guided, should take into account the particular pattern of the problem, i.e. sleep onset or staying asleep, and should be evidence based (Wilson 2010).

Psychological treatments

Psychological interventions designed for insomnia, usually consisting of a package of educational, behavioural and cognitive therapy, have been robustly shown to improve insomnia. Based on extensive published evidence, including nine systematic reviews or meta-analyses, the National Institutes of Health 'Consensus and State of the Science Statement' (NIH 2005) concluded that a cognitive behavioural therapy (CBT) package is "as effective as prescription medications are for short-term treatment of chronic insomnia. Moreover, there are indications that the beneficial effects of CBT, in contrast to those produced by medications, may last well beyond the termination of active treatment". The recent United Kingdom (UK) consensus on treatment of insomnia (Wilson 2010) also recommended that CBT should be used a first-line treatment depending on patient choice, but pointed out that this therapy may not be available, or the patient may not wish to engage in it, and therefore the choice may be a drug treatment.

Drug treatments for insomnia

Most of the licensed drugs for insomnia are allosteric modulators of the GABA-A receptor, and thus enhance GABA function in the brain. In this category are the benzodiazepines and the Z drugs (zopiclone, eszopiclone, zolpidem and zaleplon) and these are commonly referred to as 'hypnotic' medications. These drugs are all effective in insomnia (Buscemi 2007; NIH 2005), but as well as promoting sleep they are anxiolytic, anticonvulsant and myorelaxant, and can cause ataxia and memory problems when taken other than just before a period in bed. If their effect in the brain persists after waking up in the morning, they are described as having 'hangover' effects. Therefore differences in the duration of action of individual drugs are of particular importance, with short-acting drugs giving rise to less risk of next-day effects such as sedation, and impairment of skills such as driving.

Recently, melatonin was licensed for the treatment of insomnia in people aged over 55, and this drug does not give rise to motor or memory effects (Lemoine 2007; Wade 2007). Recent clinical trials have begun to measure daytime outcomes for hypnotic medications, and beneficial effects have been reported for melatonin in over-55s, as well as zolpidem, zopiclone, eszopiclone and lormetazepam. These measures have not been used in studies of other drugs, so their effects on daytime function are not documented.

Duration of prescribing

It has long been stated that hypnotic medication should not be used long-term for the treatment of insomnia. This was the consensus view of the panel of a 1983 National Institute of Health (NIH 1983) Consensus Conference on the medication treatment of insomnia, which became a guideline for clinical practice in the United States (US). Later the UK Committee on Safety of Medicines, the Royal College of Psychiatrists and the National Institute for Health and Clinical Excellence (NICE) guidance (NICE 2004) also recommended only short-term use. While it was appreciated that benzodiazepine hypnotic agents had a favourable risk-benefit ratio and were first-line agents for insomnia management, all these reports expressed concerns about the risks of dependence, and recommended their use should be limited to periods of two to four weeks. This view was not based on data demonstrating an unfavourable transition in the risk- benefit ratio after two to four weeks of treatment, but appears to have emerged because no substantive placebo-controlled trials of hypnotics had been carried out for longer than a few weeks. Despite the recommendation for duration of treatment with hypnotic drugs being only two to four weeks, many millions of patients worldwide remain on long-term treatment (Balter 1992; Ishigooka 1999; Mellinger 1985; Ohayon 1999). Recently, trials of nightly dosing for up to six months' duration suggest that tolerance and withdrawal do not generally occur with some hypnotics: zolpidem (six months of 'as needed' treatment (Krystal 2008)), eszopiclone (two studies of six-months' duration (Krystal 2003; Walsh 2007)); ramelteon (a six-month study with outcome assessed with polysomnography (PSG) but not self-report (Mayer 2009)); and temazepam (a two-month study (Morin 1999)). Other agents have not been studied for longer durations. The available evidence does not suggest there is an unfavourable risk/benefit transition at three to four weeks for any agent. However the recommendations remain in place, and clinicians are generally unwilling to prescribe for long periods.

Antidepressants

The use of antidepressants to treat insomnia is widespread (Morlock 2006; nhsuk 2011; Wilson 2010), but can be considered to be 'off-label' as none is licensed for insomnia. A consensus

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statement from the British Association of Psychopharmacology (BAP) published in 2010 (Wilson 2010) highlighted that "low-doses (sub-therapeutic of depression) of sedating tricyclics, particularly amitriptyline, dosulepin and doxepin, have been used for decades to treat insomnia. This is particularly common practice in the UK" and that "low doses of amitriptyline (10 mg or 25 mg) have been used for long periods in many patients with chronic illness particularly those with pain syndromes". Antidepressants are also widely prescribed 'off licence' in the USA for insomnia, with trazodone, a triazolopyridine derivative, being the most commonly prescribed (Lai 2011) at sub-therapeutic antidepressant doses.

How the intervention might work

Factors that have influenced the use of antidepressants for insomnia are:

1. Low dose antidepressants, particularly the tricyclic amitriptyline, have been shown to be helpful in the treatment of chronic pain and studies have reported reduction in pain-related sleep disturbance (Saarto 2010);
2. Some sedating antidepressants been shown to improve sleep problems in people with depression (Mayers 2005; Wilson 2005); and
3. There is no prescribing duration limitation on antidepressant use in insomnia, so clinicians may perceive these medications have the potential for longer-term use.

The proposed mechanism of action for low dose amitriptyline is as a histamine H1 receptor agonist, although 5HT2 and cholinergic muscarinic antagonism may also contribute. Trazodone, the second most frequently prescribed medication for insomnia in the USA, is an antagonist at 5HT1a, 5HT2 and alpha1 adrenergic receptors as well as a weak 5HT reuptake inhibitor. Trimipramine blocks alpha1 adrenergic, histamine H1, Dopamine D2, serotonin 5HT2 and cholinergic receptors (Wilson 2010).

A meta-analysis of drugs used in treatment of chronic insomnia in 2006 (Buscemi 2007) described seven studies in which antidepressants (doxepin, trazodone, trimipramine) were used to treat insomnia, at doses used in depression. The review concluded that there is some evidence that antidepressants, particularly doxepin and trazodone, may be effective treatments for chronic insomnia, with similar adverse effects to benzodiazepines, but highlighted the paucity of evidence, as did the BAP Consensus Statement (Wilson 2010).

Other factors that should be considered with the use of antidepressants for insomnia are: toxicity in overdose for amitriptyline and other tricyclics; tolerability and side-effect issues such as morning 'hang-over' effects, and increased restless leg syndrome, periodic limb movements in sleep, and sleep bruxism in selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mianserin and mirtazepine.

Why it is important to do this review

Antidepressants are widely prescribed for insomnia despite not being licensed for this use, and there being a poor evidence base for their effectiveness in insomnia. A significant factor in this wide prescription is likely to be concern regarding the longer-term use of hypnotic medications, and guidelines suggesting that long-term use of hypnotics should be avoided due to potential problems of dependency and addiction. Clinicians seek alternative treatments for insomnia that can be used longer term. There is poor availability of psychological treatments, thus alternative medications such as antidepressants and antihistamine are tried. This review will look in a systematic way at the evidence (or lack of it) behind this practice, including the efficacy, safety and tolerability of antidepressants. Other Cochrane systematic reviews are exploring other aspects of insomnia management (i.e. new generation hypnotics (Rösner 2013), Chinese herbs (Xu 2013), acupuncture (Cheuk 2012), valerian (Heumann 2013), antihistamines (Boin 2013) and CBT (Carvalho 2009)). Together, these reviews will help to highlight what is known about insomnia management and what further research is needed to provide clinicians with the information they require to manage this common and troublesome condition.

OBJECTIVES

To assess the effects, safety and tolerability of antidepressants for insomnia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) including cluster and cross-over RCTs.

Types of participants

We will include adult participants (aged 18 or over with no upper age limit) with a primary diagnosis of insomnia (to include Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), International Classification of Sleep Disorders (ICSD), International Statistical Classification of Diseases and Health Related Problems, 10th revision (ICD-10) (WHO 1992) and other well-recognised classifications).

We will include all participant types (including those with co-morbid depression or anxiety disorder and other co-morbidities).

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Types of interventions

Experimental intervention

We will include any antidepressant as monotherapy including all doses.

Antidepressants will be organised into classes for the purposes of this review, as follows.

- Selective serotonin reuptake inhibitors (SSRIs): zimelidine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram.
- Tricyclic antidepressants: amitriptyline, imipramine, trimipramine, doxepin, desipramine, protriptyline, nortriptyline, clomipramine, dothiepin, lofepramine.
- Heterocyclic antidepressants: mianserin, amoxapine, maprotiline.
- MAOIs: *Irreversible*: phenelzine, tranylcipromine, izocarboxazid; *reversible*: brofaramine, moclobemide, tyrima.
- Other antidepressants: *NARIs*: reboxetine, atomoxetine; *NDRIs:* amineptine, buproprion; *SNRIs:* venlafaxine, milnacipram, duloxetine; *NASSAs:* mirtazapine; *SARIs:* trazodone; *unclassified: a*gomelatine, vilazodone.

Comparator interventions

- Placebo.
- Other medications for insomnia (e.g. benzodiazepines, 'Z' drugs).
- A different antidepressant.
- Waiting list control or treatment as usual.

Key
NARI: noradrenaline reuptake inhibitor
NDRI: norepinephrine-dopamine reuptake inhibitor
SNRI: serotonin-norepinephrine reuptake inhibitor
NASSA: noradrenergic and specific serotonergic antidepressant
SARI: serotonin antagonist and reuptake inhibitor

Types of outcome measures

Primary outcomes

1. Efficacy: any subjective improvement in sleep quality or satisfaction with sleep, total sleep duration (measured in hours or minutes), sleep onset latency (measured as time taken to fall asleep), number of nocturnal awakenings or total nocturnal awakening time (measured in hours or minutes) or sleep efficiency (measured as a ratio of time asleep over time in bed).

A variety of rating scales are likely to be reported, e.g. the Pittsburgh Sleep Quality Index (PSQI) (Buysse 1989); the Sleep Impairment Index (Morin 1993). Percentage improvement may be a way of assessing outcomes across different trials.

2. Safety: number and type of spontaneously reported and measured adverse events, including reports of toxicity.

Secondary outcomes

3. Objective measures of change in sleep (such as electroencephalogram (EEG) data).
4. Tolerability: reported information on tolerability (e.g. problems with daytime drowsiness, dropout rates).
5. Effect on daytime symptoms/functioning: reported information on changes in daytime symptoms/functioning.

Timing of outcome assessments

Some trials may have multiple sleep diary endpoints. We plan to report endpoints consistently reported across studies rather than the protocol-stated primary endpoint, if this is the case.

Search methods for identification of studies

Electronic searches

We will search OVID MEDLINE, EMBASE, PsycINFO and the Cochrane Central Register of Controlled Trials (CENTRAL). No language or date restrictions will be applied. We will translate the MEDLINE search strategy (Appendix 1) into appropriate terms (subject headings) for each database.

Searching other resources

We will review the reference lists of included studies to identify further relevant studies. Ongoing studies will be identified through searching the WHO trials portal, Clinical Trials.gov and the IFPMA Clinical Trials Portal.

We will contact key trialists in the area to ask about ongoing work or unpublished studies they might know of, and will list in our review those we have contacted.

Data collection and analysis

Selection of studies

All studies identified will be assessed independently by two review authors using a previously prepared inclusion criteria form. Disagreements concerning the selection of studies will be resolved by a third author. The review authors will not be blinded to the names of the trial authors, institutions or journal of publication. The process of study identification and its results will be outlined as flow diagrams according to the PRISMA statement (Moher 2009).

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Data extraction and management

Data will be extracted separately by two review authors using a data extraction form. In the case of discrepancy, a third author will be consulted. We will collect information on participants (age, gender, diagnosis criteria, sample size, country, setting, number of participants randomised and followed up), intervention (drug, dosage, length of treatment, any co-interventions, controls, placebo) and outcome measures (subjective improvement in sleep, rating scale, numbers of adverse events, objective measures of change in sleep, reported information on tolerability).

Main planned comparisons

The main planned comparisons are each identified antidepressant versus:

1. placebo;
2. other medications for insomnia (e.g. benzodiazepines, 'Z' drugs);
3. other antidepressants; and
4. waiting list control or treatment as usual.

These comparisons will be made initially on a drug level, but it is likely they will need combining at a class of drug level due to the amount of data available. We will only combine drugs in analyses if they are from the same class. The 'other antidepressants' category (see Types of interventions) will be presented together, but again only drugs of the same class will be combined to produce a pooled effect, e.g. duloxetine and venlafaxine.

Assessment of risk of bias in included studies

The potential for bias in included studies will be reported using a 'Risk of bias' table (Higgins 2011). Two review authors will independently assess the risk of bias for all included studies for: random sequence generation; allocation concealment; blinding of participants, incomplete outcome data and other biases, conforming to the methods recommended by the Cochrane Collaboration (Higgins 2011). To determine the risk of bias of a study, for each criterion we will evaluate the presence of sufficient information and the likelihood of potential bias. Each criterion will be rated as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias' (indicating either lack of information or uncertainty over the potential for bias). The two review authors will discuss and resolve disagreements by consensus. If no consensus is reached, a third review author will make the final decision.

Measures of treatment effect

For dichotomous variables, we will calculate the relative risks and risk difference with 95% confidence intervals (CIs).

We will calculate the standardised mean difference (SMD) with 95% CIs for continuous outcome variables.

Unit of analysis issues

Cross-over trials

In cross-over trials, where sufficient data are present, we plan to include in the analysis data from the first period only to avoid carry-over effects.

Cluster-randomised trials

In cluster-randomised trials, we plan to conduct the analysis at the same level as the allocation using a summary measure from each cluster. However, if this appears to unnecessarily reduce the power of the study due to the number and size of the clusters, we will seek statistical advice to determine if a risk ratio or SMD with confidence intervals can be calculated accounting for the cluster design based on a 'multilevel model' or another appropriate method (Higgins 2011).

Studies with multiple treatment groups

In studies with multiple treatment groups we will include the same group of participants only once in the meta-analysis to avoid multiple comparisons. We plan to combine groups to compare a single pair-wise comparison where possible. If this is not appropriate one pair of interventions will be chosen and the others will be excluded.

Dealing with missing data

Where data are suspected to be missing, we will contact the main author of the primary study. If this is unsuccessful, we will impute absent information for continuous data by carrying the last observation forward (Higgins 2011). A sensitivity analysis will be undertaken excluding high levels of missing data. For dichotomous data, we will perform an intention-to-treat analysis.

Assessment of heterogeneity

Before meta-analysis, we will assess studies for clinical homogeneity with respect to type of therapy, control group and outcomes. For studies judged as clinically homogeneous, we will estimate statistical heterogeneity using the I^2 statistic (Higgins 2011), using the following as an approximate guide to interpretation: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as $I^2 \geq 75\%$), we will explore the data further, including by subgroup analyses, in an attempt to explain the heterogeneity.

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Assessment of reporting biases

Comprehensive searching for trials will help to reduce the risk of reporting biases. Data from all identified and selected trials will be entered into a funnel graph where appropriate (requires more than 10 studies) (trial effect versus variance) in an attempt to investigate the likelihood of overt publication bias (Higgins 2011). Funnel plot asymmetry can be caused by a number of factors so this will be interpreted with caution.

Data synthesis

If studies are sufficiently homogeneous for their pooling to be clinically meaningful, we will perform a meta-analysis using a random-effects model, regardless of the I^2 results. We will perform the analysis using Review Manager 5 software (RevMan 2012) and produce forest plots for all analyses.

Subgroup analysis and investigation of heterogeneity

Where sufficient data are available, we will perform subgroup analysis to look at:

1. Those with a diagnosis of depression or anxiety compared to those without a diagnosis of depression or anxiety, since a treatment effect of antidepressants on the symptoms of depression and anxiety may impact on sleep;
2. Those with a recorded physical co-morbidity (e.g. back pain), as those with physical co-morbidities may have different causes for their sleep problems to those with lone insomnia, and this may impact on the effect of antidepressants in these groups; and
3. Dose as a variable, particularly at low dose as a subgroup, as some antidepressants have been widely used in lower than usual antidepressant range treatment doses for the management of sleep problems (e.g. amitriptyline 10 mg). 'Low dose' antidepressants are defined as lower than the usual dose range for treatment of depression.

Subgroup analyses are hypothesis forming rather than hypothesis testing, and therefore will be interpreted with caution.

Sensitivity analysis

Where sufficient studies exist, we will exclude studies that are at higher risk of bias to assess if study quality affects the results. Planned sensitivity analyses include trials with:

- low numbers of participants (i.e. less than 10 per arm);
- lack of double blinding of participants;
- poor concealment of group allocation; and
- significant levels of missing data.

'Summary of findings' table

We will prepare 'Summary of findings' tables, summarising the key findings of the systematic review in line with the standard methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Included in the tables will be the main outcomes (subjective and objective improvement in sleep and adverse events), the magnitude of effect and the amount and quality of evidence. We will use the GRADE approach to assessing the quality of the body of evidence. If data allow, we will present findings by antidepressant group.

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Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

REFERENCES

Additional references

Altena 2008

Altena E, Van Der Werf YD, Strijers RL, Van Someren EJ. Sleep loss affects vigilance: effects of chronic insomnia and sleep therapy. *Journal of Sleep Research* 2008;**17**(3):335–43.

Baglioni 2011

Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al.Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of Affective Disorders* 2011; **135**:1–19.

Balter 1992

Balter MB, Uhlenhuth EH. New epidemiologic findings about insomnia and its treatment. *Journal of Clinical Psychiatry* 1992;**53 Suppl**:34–9.

Boin 2013

Boin AC, Baceti PA, Chambo RC, Rubira CJ, Carvalho MLM, de Oliveira Carvalho PE. Antihistamines for insomnia. Cochrane Database of Systematic Reviews in press.

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Breslau 1996
Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biological Psychiatry* 1996;**39**(6):411–8.

Buscemi 2007
Buscemi N, Vandermeer B, Friesen C, Bialy L, Tubman M, Ospina M, et al.The efficacy and safety of drug treatments for chronic insomnia in adults: a meta-analysis of RCTs. *Journal of General Internal Medicine* 2007;**22**(9):1335–50.

Buysse 1989
Buysse DJ, Reynolds III CF, Monk TH, Berman SB, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research* 1989;**28**:193–213.

Carvalho 2009
Aversa Lopes E, Silva AB, Macedo CR, Soares B, Saconato H, Atallah ÁN. Cognitive behavioural therapy for insomnia. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006814]

Cheuk 2012
Cheuk DKL, Yeung WF, Chung KF, Wong V. Acupuncture for insomnia. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD005472.pub3]

Chevalier 1999
Chevalier H, Los F, Boichut D, Bianchi M, Nutt DJ, Hajak G, et al.Evaluation of severe insomnia in the general population: results of a European multinational survey. *Journal of Psychopharmacology* 1999;**13**(4 Suppl 1):21–4.

Edinger 2008
Edinger JD, Means MK, Carney CE, Krystal AD. Psychomotor performance deficits and their relation to prior nights' sleep among individuals with primary insomnia. *Sleep* 2008;**31**(5):599–607.

Heumann 2013
Heumann C, Hajak G, Rösner S. Valerian for insomnia. Cochrane Database of Systematic Reviews in press.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1 [updated March 2011]. Available from www.cochrane-handbook.org.

Ishigooka 1999
Ishigooka J, Suzuki M, Isawa S, Muraoka H, Murasaki M, Okawa M. Epidemiological study on sleep habits and insomnia of new outpatients visiting general hospitals in Japan. *Psychiatry and Clinical Neurosciences* 1999;**53**(4): 515–22.

Krystal 2003
Krystal AD, Walsh JK, Laska E, Caron J, Amato DA, Wessel TC, et al.Sustained efficacy of eszopiclone over 6 months of nightly treatment: results of a randomized, double-blind, placebo-controlled study in adults with chronic insomnia. *Sleep* 2003;**26**(7):793–9.

Krystal 2008
Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep* 2008;**31**(1):79–90.

Lai 2011
Lai L, Tan MH, Lai YC. Prevalence and factors associated with off-label antidepressant prescriptions for insomnia. *Drug, Healthcare and Patient Safety* 2011;**3**:27–36.

LeBlanc 2009
LeBlanc M, Merette C, Savard J, Ivers H, Baillargeon L, Morin CM. Incidence and risk factors of insomnia in a population-based sample. *Sleep* 2009;**32**(8):1027–37.

Leger 2001
Leger D, Scheuermaier K, Philip P, Paillard M, Guilleminault C. SF-36: evaluation of quality of life in severe and mild insomniacs compared with good sleepers. *Psychosomatic Medicine* 2001;**63**(1):49–55.

Lemoine 2007
Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *Journal of Sleep Research* 2007;**16**(4): 372–80.

Mayer 2009
Mayer G, Wang-Weigand S, Roth-Schechter B, Lehmann R, Staner C, Partinen M. Efficacy and safety of 6-month nightly ramelteon administration in adults with chronic primary insomnia. *Sleep* 2009;**32**(3):351–60.

Mayers 2005
Mayers AG, Baldwin DS. Antidepressants and their effect on sleep. *Human Psychopharmacology* 2005;**20**(8):533–59.

Mellinger 1985
Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Prevalence and correlates. *Archives of General Psychiatry* 1985;**42**(3):225–32.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7):e1000097.

Morin 1993
Morin CM. *Insomnia: Psychological Assessment and Management*. New York, USA: Guilford Press, 1993.

Morin 1999
Morin CM, Colecchi C, Stone J, Sood R, Brink D. Behavioral and pharmacological therapies for late-life insomnia: a randomized controlled trial. *Journal of the American Medical Association* 1999;**281**(11):991–9.

Morin 2003
Morin CM, Rodrigue S, Ivers H. Role of stress, arousal, and coping skills in primary insomnia. *Psychosomatic Medicine* 2003;**65**(2):259–67.

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Morlock 2006
Morlock RJ, Tan M, Mitchell DY. Patient characteristics and patterns of drug use for sleep complaints in the United States: analysis of National Ambulatory Medical Survey data, 1997-2002. *Clinical Therapeutics* 2006;**28**(7): 1044–53.

Neckelmann 2007
Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. *Sleep* 2007;**30**(7):873–80.

nhsuk 2011
nhsuk. Prescription Cost Analysis England 2010. http://www.ic.nhs.uk/statistics-and-data-collections/primary-care/prescriptions/prescription-cost-analysis-england--2010 2011 (accessed June 2011).

NICE 2004
National Institute for Clinical Excellence (NICE). Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia (Technology Appraisal 77) www.nice.org.uk/TA077guidance (accessed 12 Sep 2013). London: NICE, 2004; Vol. http://www.nice.org.uk/nicemedia/live/11530/32845/32845.pdf.

NIH 1983
National institute of Health Consensus development programme. Drugs and Insomnia: The Use of Medications to Promote Sleep. http://consensus.nih.gov/1983/1983insomniadrugs039html.htm. 1983.

NIH 2005
NIH. National Institutes of Health State of the Science Conference statement on Manifestations and Management of Chronic Insomnia in Adults [http://consensus.nih.gov/2005/insomniastatement.htm]. *Sleep* 2005;**28**(9):1049–57.

Nissen 2011
Nissen C, Kloepfer C, Feige B, Piosczyk H, Spiegelhalder K, Voderholzer U, et al.Sleep-related memory consolidation in primary insomnia. *Journal of Sleep Research* 2011;**20**(1 Pt 2):129–36.

Ohayon 1999
Ohayon MM, Caulet M, Arbus L, Billard M, Coquerel A, Guieu JD, et al.Are prescribed medications effective in the treatment of insomnia complaints?. *Journal of Psychosomatic Research* 1999;**47**(4):359–68.

Perlis 2010
Perlis M, Shaw P, Cano G, Espie C. Chapter 78: Models of Insomnia. In: Kryger M, Roth T, Dement W editor(s). *Principles and Practice of Sleep Medicine*. 5th Edition. St Louis, Missouri: Saunders, 2010:850–65.

Philip 2006
Philip P, Leger D, Taillard J, Quera-Salva MA, Niedhammer I, Mosqueda JG, et al.Insomniac complaints interfere with quality of life but not with absenteeism: respective role of depressive and organic comorbidity. *Sleep Medicine* 2006;**7**(7):585–91.

RevMan 2012
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Riemann 2009
Riemann D, Perlis, ML. The treatments of chronic insomnia: a review of benzodiazepine receptor agonists and psychological and behavioural therapies. *Sleep Medicine Reviews* 2009;**13**:205–14.

Rösner 2013
Rösner S, Soyka M, Hajak G, Wehrle R. New generation hypnotics for insomnia. Cochrane Database of Systematic Reviews in press.

Saarto 2010
Saarto T, Wiffen PJ. Antidepressants for neuropathic pain: a Cochrane review. *Journal of Neurology, Neurosurgery and Psychiatry* 2010;**81**(12):1372–3.

Sateia 2004
Sateia MJ, Nowell PD. Insomnia. *Lancet* 2004;**364**(9449): 1959–73.

Sivertsen 2009
Sivertsen B, Krokstad S, Mykletun A, Overland S. Insomnia symptoms and use of health care services and medications: the HUNT-2 study. *Behavioral Sleep Medicine* 2009;**7**(4): 210–22.

Vgontzas 2009
Vgontzas AN, Liao D, Bixler EO, Chrousos GP, Vela-Bueno A. Insomnia with objective short sleep duration is associated with a high risk for hypertension. *Sleep* 2009;**32**(4):491–7.

Wade 2007
Wade AG, Ford I, Crawford G, McMahon AD, Nir T, Laudon M, et al.Efficacy of prolonged release melatonin in insomnia patients aged 55-80 years: quality of sleep and next-day alertness outcomes. *Current Medical Research and Opinion* 2007;**23**(10):2597–605.

Walsh 2007
Walsh JK, Krystal AD, Amato DA, Rubens R, Caron J, Wessel TC, et al.Nightly treatment of primary insomnia with eszopiclone for six months: effect on sleep, quality of life, and work limitations. *Sleep* 2007;**30**(8):959–68.

WHO 1992
World Health Organisation. *ICD-10 Classifications of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organisation, 1992.

Wilson 2005
Wilson S, Argyropoulos S. Antidepressants and sleep: a qualitative review of the literature. *Drugs* 2005;**65**(7): 927–47.

Wilson 2010
Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN, et al.British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian

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rhythm disorders. *Journal of Psychopharmacology* 2010;**24** (11):1577–601.

Xu 2013

Xu L, Li J, Zhang M, Wang L, Yuan W, Ai CL, Wang G, Zhang L. Chinese herbs for insomnia. *Cochrane Database of Systematic Reviews* 2013, Issue 7. [DOI: 10.1002/14651858.CD007841.pub2]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. OVID MEDLINE search strategy

[Condition]

1. exp "SLEEP INITIATION AND MAINTENANCE DISORDERS"/
2. WAKEFULNESS/de [drug effects]
3. SLEEP/de [drug effects]
4. exp SLEEP STAGES/de [drug effects]
5. insomni*.mp.
6. or/1-5

[Intervention]

7. exp ANTIDEPRESSIVE AGENTS/
8. exp MONOAMINE OXIDASE INHIBITORS/
9. exp NEUROTRANSMITTER UPTAKE INHIBITORS/
10. (antidepress* or anti depress* or MAOI* or RIMA* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or neurotransmitter* or dopamin*) and (uptake or reuptake or re uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic or pharmacotherap* or psychotropic).mp.
11. (Agomelatine or Alaproclate or Amoxapine or Amineptine or Amitriptylin*e or Amitriptylinoxide or Atomoxetine or Befloxatone or Benactyzine or Binospirone or Brofaromine or (Buproprion or Amfebutamone) or Butriptyline or Caroxazone or Cianopramine or Cilobamine or Cimoxatone or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clomipramine) or Clorgyline or or Clovoxamine or (CX157 or Tyrima) or Demexiptiline or Deprenyl or (Desipramine* or Pertofrane) or Desvenlafaxine or Dibenzepin or Diclofensine or Dimetacrin*e or Dosulepin or Dothiepin or Doxepin or Duloxetine or Desvenlafaxine or DVS-233 or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluvoxamine or (Hyperforin or Hypericum or St John*) or Imipramin*e or Iprindole or Iproniazid* or Ipsapirone or Isocarboxazid* or Levomilnacipran or Lofepramine* or ("Lu AA21004" or Vortioxetine) or "Lu AA24530" or (LY2216684 or Edivoxetine) or Maprotiline or Melitracen or Metapramine or Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptylin*e or Noxiptilin*e or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezine or Pirlindole or Pivagabine or Pizotyline or Propizepine or Protriptylin*e or Quinupramine or Reboxetine or Rolipram or Scopolamine or Selegiline or Sertraline or Setiptiline or Teciptiline or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromine* or Trazodone or Trimipramine or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone).mp.
12. or/7-11

[RCT Filter]

13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomi#ed.ti,ab.
16. randomly.ab.
17. placebo.ab.
18. trial.ab.

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19. groups.ab.
20. (control$ adj3 (trial or study)).ab,ti.
21. ((singl$ or doubl$ or tripl$ or trebl$) adj3 (blind$ or mask$ or dummy)).mp.
22. exp "SLEEP INITIATION AND MAINTENANCE DISORDERS"/dt [drug therapy]
23. (animals not (humans and animals)).sh.
24. or/13-22
25. 24 not 23

[Condition + Intervention + RCT Filter]

26. (6 and 12 and 25)

CONTRIBUTIONS OF AUTHORS

All authors helped to develop the research question, provided comments and suggestions on draft versions of the protocol and have approved the current version.

HE and SW wrote the protocol.

AM wrote the search strategy.

DECLARATIONS OF INTEREST

SW has received honoraria for lectures from pharmaceutical companies making antidepressants, although none since 2009. SW has no financial interest in any pharmaceutical company.

ALM: Since medical qualification ALM has worked as Director of Clinical Pharmacology in SmithKlineBeecham and has dormant pension contributions through a third party pension provider. He has received research support from Wyeth, Medtronic and Organon on behalf of his employers at the time and been a speaker and/or accepted hospitality from Eli Lilly, Astra Zeneca, Lundbeck, Pfizer, Medtronic and Servier.

DB: On behalf of his employer DB has held research grants from Bristol-Myers Squibb, Cephalon, Eli Lilly Ltd, GlaxoSmithKline, H. Lundbeck A/S, Pierre Fabre, Pfizer Ltd, Roche and Vernalis Ltd. He has served on advisory boards hosted by Astra Zeneca, Bristol-Myers Squibb, Eli Lilly Ltd, GlaxoSmithKline, Grunenthal, H. Lundbeck A/S, Pierre Fabre, and Pfizer Ltd. He is a past president of Depression Alliance and current Medical Patron of Anxiety UK.

HE and A Mayers have no interests to declare.

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