Medications for daytime sleepiness in individuals with idiopathic hypersomnia (Protocol)

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Medications for daytime sleepiness in individuals with idiopathic hypersomnia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:
To assess the effects of medications for daytime sleepiness and related symptoms in individuals with idiopathic hypersomnia, and in particular whether medications may:

1. reduce subjective measures of sleepiness;
2. reduce objective measures of sleepiness;
3. reduce symptoms of cognitive dysfunction;
4. improve quality of life; and
5. be associated with adverse events.

BACKGROUND

Description of the condition

Idiopathic hypersomnia is a chronic neurologic sleep disorder that manifests as excessive daytime sleepiness occurring despite normal or prolonged sleep times (i.e. exceeding 11 hours of sleep per 24-hour period), in the absence of other disorders that impair sleep quality, such as sleep apnea. Symptoms and signs of idiopathic hypersomnia also include marked sleep inertia (severe and prolonged difficulties with awakening), long and unrefreshing naps, and high measured sleep efficiency in the sleep laboratory, although some patients meeting diagnostic criteria for idiopathic hypersomnia do not endorse these classic ancillary symptoms (Bassetti 1997; Anderson 2007; ICSD-3 2014). Depressive symptoms and difficulties with concentration and attention are frequently present in patients with idiopathic hypersomnia, and quality of life is reduced (Dauvilliers 2009; Vernet 2009; Vernet 2010; Ozaki 2012). The cause of idiopathic hypersomnia remains unknown at present, although abnormalities of sleep macro- and microstructure have
medications have been used in clinical practice for the treatment of idiopathic hypersomnia. Many of these medications are known or are suspected to be effective in treating excessive daytime sleepiness in other disorders, such as narcolepsy or obstructive sleep apnea, and then are extended for use in idiopathic hypersomnia with or without specific testing in patients with that disorder. Clinical series suggest that this strategy results in satisfactory symptom control in the majority of patients, with a poorer response to treatment in up to one third (Bassetti 1997; Anderson 2007; Ali 2009). Medication classes that have been used in the treatment of idiopathic hypersomnia include amphetamines, non-amphetamine wake-promoting agents (e.g., modafinil, mazindol), histamine H3 antagonists/inverse agonists, GABA-B/gamma hydroxybutyrate agonists, levohydroxyxine, alerting antidepressants such as bupropion, melatonin (for sleep inertia) and GABA-A antagonists (Montplaisir 2001; Morgenthaler 2007; Shinno 2011; Rye 2012; Nittur 2013; Leu-Semenescu 2014; Trotti 2015; Trotti 2016; Leu-Semenescu 2016).

Description of the intervention

Multiple medications have been used in clinical practice for the treatment of idiopathic hypersomnia. Many of these medications are known or are suspected to be effective in treating excessive daytime sleepiness in other disorders, such as narcolepsy or obstructive sleep apnea, and then are extended for use in idiopathic hypersomnia with or without specific testing in patients with that disorder. Clinical series suggest that this strategy results in satisfactory symptom control in the majority of patients, with a poorer response to treatment in up to one third (Bassetti 1997; Anderson 2007; Ali 2009). Medication classes that have been used in the treatment of idiopathic hypersomnia include amphetamines, non-amphetamine wake-promoting agents (e.g., modafinil, mazindol), histamine H3 antagonists/inverse agonists, GABA-B/gamma hydroxybutyrate agonists, levohydroxyxine, alerting antidepressants such as bupropion, melatonin (for sleep inertia) and GABA-A antagonists (Montplaisir 2001; Morgenthaler 2007; Shinno 2011; Rye 2012; Nittur 2013; Leu-Semenescu 2014; Trotti 2015; Trotti 2016; Leu-Semenescu 2016).

How the intervention might work

Amphetamines increase the release and block the reuptake of monoaminergic neurotransmitters (i.e. dopamine, norepinephrine, and serotonin) and their effects on dopaminergic neurotransmission are particularly important for their effects at promoting wakefulness (Banerjee 2004; Gowda 2014). Multiple potential mechanisms of action have been proposed for modafinil, including effects on dopaminergic neurotransmission (Banerjee 2004; Gowda 2014). The alerting potential of mazindol and bupropion may also be related to their actions as dopamine reuptake inhibitors (Heal 2014). Histamine H3 antagonists/inverse agonists promote wakefulness by increasing central nervous system histamine levels (Leu-Semenescu 2014). The mechanism by which agonists of GABA-B/gamma hydroxybutyrate reduce sleepiness is not known, although deep sleep is increased (Gowda 2014). Levotyroxine might improve alertness via hormonal effects or by increasing central nervous system histamine levels (Shinno 2011). Because patients with idiopathic hypersomnia tend to have a circadian phase delay, evening use of melatonin has been proposed as a method of advancing the circadian rhythm and improving sleep inertia (Vernet 2009). GABA-A antagonists have been used in patients with idiopathic hypersomnia based on the finding of a positive allosteric modulator of GABA-A receptors within the cerebrospinal fluid of hypersomnolent patients (Rye 2012) and the known sleep-promoting effects of the GABA-A system (Lu 2006).

Why it is important to do this review

There are currently no medications approved for the treatment of idiopathic hypersomnia by the United States Food and Drug Administration, thus all pharmacologic treatment of patients with idiopathic hypersomnia in the United States is ‘off-label’. The European Medicines Agency has explicitly stated that modafinil should only be used in patients with narcolepsy, not in patients with idiopathic hypersomnia (EMA Modafinil 2010), although modafinil is one of the medications recommended for treatment of idiopathic hypersomnia in expert consensus guidelines (Morgenthaler 2007). As a result of this disagreement and lack of regulatory approval, clinical decision-making regarding treatment of idiopathic hypersomnia can be challenging. Furthermore, the medications used for the treatment of idiopathic hypersomnia carry risk for serious side effects or medication interactions, including but not limited to addiction (amphetamines), respiratory depression or coma (sodium oxybate), superinfection and antibiotic resistance (the GABA-A receptor antagonist clarithromycin), and reduced efficacy of hormonal birth control (modafinil, armodafinil) (Trotti 2013; Krahn 2015). Patients and prescribers must carefully weigh the trade-offs of risk and benefit when choosing a treatment option.

OBJECTIVES

To assess the effects of medications for excessive daytime sleepiness and related symptoms in individuals with idiopathic hypersomnia, and in particular whether medications may:

1. reduce subjective measures of sleepiness;
2. reduce objective measures of sleepiness;
3. reduce objective measures of sleepiness;
3. reduce symptoms of cognitive dysfunction;
4. improve quality of life; and
5. be associated with adverse events.

**M E T H O D S**

**Criteria for considering studies for this review**

**Types of studies**
We will include studies that are parallel or cross-over randomized controlled trials. Double, single, and unblinded trials will be included. In the case of cross-over studies, only the first period will be used.

**Types of participants**
We will consider people with a diagnosis of idiopathic hypersomnia, of any age and either gender. Diagnostic criteria to be used include the ICSD (any edition) and the DSM (any edition; diagnoses of primary hypersomnia, hypersomnolence disorder, or other idiopathic hypersomnia equivalent). Diagnoses of idiopathic hypersomnia based on clinical assessment, in the absence of diagnostic MSLT findings, will be included if there is detail provided about how the diagnosis was made. Studies that include both patients with idiopathic hypersomnia and patients with another disorder (e.g. narcolepsy) will be included if data on the subgroup with idiopathic hypersomnia can be obtained. In such a case, only the data from the subgroup with idiopathic hypersomnia would be used.

**Types of interventions**
Any medication (at any dose), prescription or over-the-counter, hypothesized to help with symptoms of idiopathic hypersomnia or known to help with sleepiness in other conditions, compared to placebo, another medication, or a behavioral intervention. Studies that allow use of other wake-promoting or psychoactive medications during the trial will be included, if access to such medications was equal in all groups.

**Types of outcome measures**

**Primary outcomes**
1. Subjective measure of daytime sleepiness using the Epworth Sleepiness Scale

**Secondary outcomes**
1. Other subjective measures of hypersomnia, including other scales quantifying subjective sleepiness, sleep logs or other patient-completed reports of sleep times, subjective rating scales of sleep drunkenness/sleep inertia
2. Objective measures of sleepiness, including multiple sleep latency test mean sleep latency, maintenance of wakefulness mean sleep latency, psychomotor vigilance testing measures of reaction times, pupillometry, driving simulators or real-life measured driving performance, actigraphy, 24-hour ad-lib polysomnography
3. Subjective reports of cognitive dysfunction or objective measures of cognitive performance, assessed by standardized questionnaire or testing instruments
4. Quality of life scales, measures of ability to function in work, school, or other important activities
5. Adverse events, as measured by:
   i) rate of adverse events
   ii) dropout or withdrawal due to adverse events
   iii) dropout or withdrawal due to lack of efficacy

**Search methods for identification of studies**

**Electronic searches**
We will search the following databases.
- Cochrane Epilepsy Group Specialized Register.
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO).
- MEDLINE (Ovid) 1946-.
- ClinicalTrials.gov.
- WHO International Clinical Trials Registry Platform (ICTRP).

The proposed search strategy for MEDLINE is set out in Appendix 1. This strategy will be modified for use with the other databases.

**Searching other resources**
We will review relevant conference proceedings and systematic reviews, as well as the reference lists in included studies, for other relevant studies.

**Data collection and analysis**

**Selection of studies**
Two authors (LMT and RH) will independently review all titles and abstracts of publications identified by the search. Publications
that clearly do not meet inclusion criteria, as judged independently by both authors, will be excluded at this stage. Full text of remaining publications will be obtained to identify all that meet the inclusion criteria. In the case where one or more of the review authors were investigators on an identified study, the investigators will be excluded from decision-making about that study, which will be performed instead by two review authors not involved in the study. Any disagreements between authors on study inclusion will be resolved by consensus among review authors.

**Data extraction and management**

A data extraction form (Covidence) will be used for data collection. Two authors (LMT and RH) will independently extract the following characteristics of each included trial from published reports. In cases where relevant data are not available in the published report, we will contact the investigators to request additional data. In the case where one or more of the review authors were investigators on an included study, the investigators will not extract data and data will be extracted instead by two review authors not involved in the study.

**Participant factors:**
- age
- sex
- baseline multiple sleep latency test results
- baseline sleep length (by actigraphy, sleep log, 24-hour polysomnography, or other measure)
- baseline subjective sleepiness severity

**Trial design:**
- study design (randomization, blinding, parallel versus cross-over)
- study duration, start date, and end date
- country of first author
- where the study was conducted (both country and care setting, e.g. tertiary referral center for idiopathic hypersomnia versus general sleep clinic)
- multi- or single-center trial
- study inclusion and exclusion criteria
- criteria used to define idiopathic hypersomnia
- idiopathic hypersomnia patients only, or subjects from multiple diagnostic categories included
- number enrolled and number completing in each intervention group
- number and type of wake-promoting and/or psychoactive medications allowed as co-interventions during the trial
- funding source

**Intervention and control:**
- active and control interventions (type, dosing, duration, etc)
- outcomes measured
- adverse events
- any subgroup analyses performed

### Assessment of risk of bias in included studies

Two review authors (CFM and LAB) will assess the risk of bias using the Cochrane ’Risk of bias’ tool, following the approach described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). In the case where one or more of the review authors were investigators on an included study, the investigators will not assess risk of bias, which will instead be assessed by two review authors not involved in the trial. We will assess the risk of bias as: low risk, high risk, or uncertain risk.

We will evaluate the following characteristics:
- sequence generation
- allocation concealment
- blinding of participants and personnel and blinding of outcome assessors
- incomplete outcome data
- selective outcome reporting
- other potential threats to validity

### Measures of treatment effect

We will perform statistical analyses in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.

For continuous data available as means and standard deviations with the same outcome measure (e.g. the Epworth Sleepiness Scale), we will use mean difference (MD) with 95% confidence interval (CI) to measure treatment effect. For continuous data assessing the same outcome using different measures (e.g. two different quality of life scales), we will use standardized mean difference (SMD) with 95% CI.

For dichotomous data, we will use relative risk (RR) with 95% CI.

### Unit of analysis issues

The unit of analysis will be the individual trial participant. In the case of cross-over trials, only data from the first treatment period will be used in meta-analysis.

### Dealing with missing data

For individuals missing data such as drop-out or loss to follow up, we will use an intention-to-treat analysis whenever possible. Studies that include any outcome of interest will be included, even if the primary outcome is not measured. We will discuss potential implications of missing data in the ”Discussion” section.

### Assessment of heterogeneity

For each intervention effect, we will test heterogeneity using the standard Chi² and I² statistics. We will consider a P value of less than 0.10 suggestive of heterogeneity. The interpretation of I² for heterogeneity will follow the Cochrane Handbook as follows:
- 0 to 40%: may not be important heterogeneity;
• 30% to 60%: moderate heterogeneity;
• 50% to -90%: substantial heterogeneity;
• 75% to 100%: considerable heterogeneity.

We will use a random-effects model for meta-analysis. We will assess possible sources of heterogeneity by sensitivity analyses, if sufficient numbers of trials are available.

Assessment of reporting biases
We will assess for publication biases by funnel plot, if at least 10 trials are available. We will compare published protocols (when available) to study reports to assess for incomplete outcome reporting.

Data synthesis
Analyses will be performed using RevMan. Meta-analysis of measures of treatment effect will be performed separately for each medication and medication class (in the case of trials of different medications within the same class, e.g. modafinil and armodafinil).

Subgroup analysis and investigation of heterogeneity
The multiple diagnostic criteria that have been used for the definition of idiopathic hypersomnia may result in substantial heterogeneity. We will perform subgroup analyses by long sleep versus normal sleep duration and by method of diagnosis of idiopathic hypersomnia (e.g. comparing those meeting MSLT criteria versus those with a clinical diagnosis lacking MSLT criteria, ICSD versus DSM criteria, MSLT versus measured total sleep time of > 660 minutes).

Sensitivity analysis
We will perform sensitivity analyses, as recommended in the Cochrane Handbook, to evaluate the effect of including versus excluding those studies at high risk of bias.

Summarising and interpreting results
We will use the GRADE approach to interpret findings (Schunemann 2011). We will use GRADE Profiler Software (GRADEPro 2004), and import data from Review Manager 5 (RevMan 2014), to create 'Summary of findings' tables for each comparison included in the review for the primary outcomes.

The 'Summary of findings' table for each comparison will include information on overall quality of the evidence from the trials and information of importance for healthcare decision-making. The GRADE approach determines the quality of evidence on the basis of an evaluation of eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect and dose-response gradient). We will use these to guide our conclusions and recommendations.

ACKNOWLEDGEMENTS
We gratefully acknowledge Graham Chan for his assistance with drafting the search strategy and the Cochrane Epilepsy Group for administrative and technical assistance.

REFERENCES

Additional references
Ali 2009

Anderson 2007

Banerjee 2004

Bassetti 1997

Dauvilliers 2009

EMA Modafinil 2010

Gowda 2014

GRADEPro 2004 [Computer program]
Medications for daytime sleepiness in individuals with idiopathic hypersomnia (Protocol)

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hypersomnolence: clinical experience with 153 patients. 

**Vernet 2009**
Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. 

**Vernet 2010**

**Šonka 2015**

* Indicates the major publication for the study

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**AP PEND I CES**

**Appendix 1. MEDLINE (Ovid) search strategy**
This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011).

1. exp Hypersomnolence, Idiopathic/
2. hypersom$$.tw.$
3. ("non-rapid eye movement" or NREM) and narcolep$.tw.$
4. 1 or 2 or 3
5. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
6. clinical trials as topic.sh.
7. trial.ti.
8. 5 or 6 or 7
9. exp animals/ not humans.sh.
10. 8 not 9
11. 4 and 10
12. remove duplicates from 11

**CONTR I B U T I O N S O F A U T H O R S**

LMT: drafting the protocol

LAB, CFM, RH: revising the protocol
DECLARATIONS OF INTEREST

Dr. Trotti has performed clinical trials of medications used for daytime sleepiness in idiopathic hypersomnia. Her institution receives funding for ongoing clinical trials of medications for daytime sleepiness (Jazz Pharmaceuticals, Balance Therapeutics).

Dr. Hoque is the site-PI of an ongoing clinical trial of a medication for daytime sleepiness in idiopathic hypersomnia (Balance Therapeutics).

Dr. Becker and Ms. Friederich Murray report no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institutes of Health, USA.
  K23 NS083748 (to LMT)
- National Institute for Health Research (NIHR), UK.

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