Supplement 4: Systematic Review Protocol

Abstract

This is a protocol for a Systematic Review of interventions. The objective is to assess whether the quality and regularity of sleep of patients with sleep disturbance related to ocular disease may be improved by administration of a pharmacological agent.

Description of the condition

Sleep is essential for maintaining good health with severe sleep disturbance being associated with depression and cognitive impairment [1]. Sleep disturbance is also recognised to have a significant economic impact [2]. Visually impaired patients often report sleep-wake disruption as a significant problem [3]. Sleep cycles are regulated by an endogenous oscillator in the suprachiasmatic nuclei (SCN). The SCN is recognised as being the circadian pacemaker and generates rhythms with an average period of over 24 hours [4]. In order to maintain synchronisation between sleep cycle and the 24 hour environmental light dark cycle, caused by Earth's rotation, visual cues are required. Light entrainment occurs when light cues are conveyed from photosensitive retinal ganglion cells (pRGC) in the eye to the suprachiasmatic nucleus via the retinohypothalamic tract (RHT): a separate neural pathway from the visual pathway [5]. This resets the circadian pacemaker to realign with the light dark cycle. When pRGCs are damaged or missing, as is the case with many visually impaired patients, the circadian rhythm can become disturbed. In severe cases patients can become 'free-running' where the intrinsic oscillation of the circadian pacemaker is completely unaffected by environmental time cues. A free-running rhythm is characterized by the timing of the circadian cycle consistently becoming delayed by as much as 60 to 70 minutes per day [6]. Patients who become free-running frequently experience periodic insomnia and daytime sleepiness due to their circadian rhythm being out of phase with the environment. It is common for patients with sleep disturbance to attempt to force themselves to keep to the social cycle of staying wake during the day and falling asleep at night but this seldom successful causing physical and psychological side effects, such as depressed mood; extreme fatigue; increased napping and decreased appetite, during the day [7]. There are currently no

recognised treatments for visual disturbance related circadian rhythm disruption in the UK and this is not addressed by any National Institute for Health and Care Excellence NICE guidelines.

Description of the interventions

Both pharmacological and non-pharmacological interventions have been used for treating sleep wake disturbance. Phototherapy has successfully been used to treat free running patients [8,9] but may be inappropriate in visually disturbed patients who lack the physiological ability to transmit visual information to the SCN. Pharmacological interventions have focussed on melatonin supplementation and melatonin agonists in an attempt to resynchronise to the 24-hour light-dark cycle. Daily administration of exogenous melatonin has been shown to cause re-entrainment in blind patients [6,10]. Ramelteon (Rozerem) is a melatonin agonist that has been shown to advance the phase of circadian rhythms in healthy individuals [11]. Tasimelteon (Hetlioz) is a selective agonist for melatonin and has received FDA approval for treatment of sleep-wake disturbance in blind patients (Dhillon et al, 2014), however due to the cost its use is limited.

How the intervention might work

Melatonin, ramelteon and tasimelteon are agonists of the MT_1 and MT_2 receptors within the SCN. MT2 receptors are recognised to support the regulation of circadian rhythm and MT1 receptors are involved in inducing sleep [12]. By exogenous activation of the MT_1 and MT_2 receptors sleep maintenance and initiation can be improved and endogenous circadian rhythms can be shifted[13].

Why it is important to do this review

Circadian rhythms are vital for coordinating bodies through their daily cycles, governing a number of processes such as body temperature, cardiovascular efficiency, melatonin production, and sleep. Short term disruption to circadian rhythms can contribute to cognitive and memory impairment, impulsiveness, and negative effects on empathy[14]. Long term disruption may lead to the development

of cardiovascular problems, type II diabetes, immunosuppression, and cancer[15,16]. There are currently no recognised treatments for visual disturbance related circadian rhythm disruption in the UK.

Objectives

To assess whether the quality and regularity of sleep of patients with sleep disturbance related to ocular disease may be improved by administration of a pharmacological agent.

Methods

Criteria for considering studies for this review

Types of studies

Both published and unpublished randomized controlled trials (RCTs) will be included.

Types of participants

Participants with a recognised ocular disease or anophthalmia will be included.

Inclusion will not be limited by severity of the ocular condition of participants or by the severity of sleep disturbance.

There will be no restriction on patient gender, age or ethnicity.

Types of interventions

Studies will be included that compared the use of a pharmaceutical agent, given at an appropriate clinical dose with the intention of promoting night-time sleep, against:

a placebo

no agent

another agent, administered specifically to promote sleep or;

usual care.

Types of outcome measures

The main outcome will be quantity and quality of sleep. Due to the lack of a commonly accepted 'gold-standard' to objectively represent sleep, studies will be included if they use either a validated or an unvalidated scale for the measurement of sleep.

The frequency and type of adverse events will be a secondary outcome. Adverse events will be considered as any untoward medical occurrence not necessarily having a causal relationship with the treatment.

Any outcomes (validated or unvalidated) that report to assess sleep duration, sleep quality or sleep latency will be included. Questionnaire assessments based on Likert scales, whether validated or not will be included. As will measures involving the compilation of sleep diaries, such as the Pittsburgh Sleep Diary [17].

Studies that report the quantity and quality of sleep as measured by objective equipment will be included. For example, polysomnography (PSG) is considered the most accurate and objective tool for measuring sleep and identifying sleep disorders [18].

Other tools that give an indication of sleep such as actigraphy (a device that is worn on the wrist that measures movement and is analysed to score total sleep time, sleep efficiency and awakenings [19]) will be included.

Primary outcomes

1. Quantity and quality of sleep as measured through reports of participants or by personnel assessments or as measured by PSG, actigraphy, or similar.

Secondary outcomes

1. Adverse events

Search methods for identification of studies

Electronic searches

The following databases will be searched using the search strategy in Appendix A.

The Cochrane Central Register of Controlled Trials (CENTRAL; most recent issue)

MEDLINE via Ovid (from 1946 to the present)

Embase via Ovid (from 1974 to the present)

PsycINFO via Ovid (from 1806 to the present)

CINAHL (EBSCOhost)

Due to the limitations of available resources only English language papers will be included.

Searching other resources

Additional trials will be identified by searching of bibliographies from key reviews identified from the searches.

Grey literature will be searched through 'OpenGrey' (available at http://www.opengrey.eu./).

Relevant ongoing literature will be sought through (www.clinicaltrials.gov, the International Standard Randomized Controlled Trial Number (ISRCTN) registry and the World Health Organization (WHO) International Clinical Trials Registry Platform).

Data collection and analysis

The review author (Colm Andrews (CA) will independently carry out all inclusion/exclusion and data extraction. The primary review author (CA) will perform all data analysis.

Selection of studies

Reference management software (Zotero) will be used to collect and collate search results and to remove duplicates.

Two review authors will independently screen titles and abstracts

The full texts of all potentially relevant studies will be sourced and determined against inclusion and exclusion criteria (see appendix A). And two review authors will identify and record reasons for exclusion of the ineligible studies.

Abstracts will only be included at this stage if they provide sufficient information and relevant results that include sufficient data for each intervention or comparison group.

The number of papers retrieved at each stage will be recorded and reported using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart [20]

Data extraction and management

A data extraction sheet will be used to extract:

Methods - Study design; setting; dates of study;, location, number of centres, withdrawals.

Participants - number of participants randomized to each group; baseline characteristics including age range, gender, condition and severity of condition and visual acuity range.

Interventions - details of intervention and comparison agents (to include dose and timing).

Outcomes - review outcomes as measured and reported by study authors (to include types of assessment tools, methods of data synthesis, units of measure, and length of follow-up).

Outcome data - results of outcome measures.

Risk of bias

Notes: funding sources and potential conflicts of interest of authors

The data extraction sheet shall be piloted on a representative sample of the studies to be reviewed.

Assessment of risk of bias in included studies

Study quality, study limitations and extent of potential bias will be assessed using the Cochrane 'Risk of bias' tool [21].

As masking of participants and assessors to intervention and control agents is feasible; lack of blinding of personnel may introduce risk of bias.

The risk of participants' concomitant medication having an effect on sleep will be considered. Other potential biases in the included studies will be assessed. For each domain, two review authors (CA and SS) will grade risk of bias as low, high or unclear along with a justification for the judgement, before comparing results and reaching consensus, if a consensus cannot be reached the primary review author (CA) will make the casting decision. This will be represented in a 'Risk of bias' table. The domains to be assessed will be: random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and researchers (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); inappropriate washout period; inappropriate timing of treatment; other bias.

Measures of treatment effect

Measures of participant-reported outcomes and objective measures of quantity and quality of sleep may differ for each study, depending on the scales used.

Physical consequences of sleep deprivation and mortality will be reported as dichotomous data (number of participant events per group).

Psychological consequences of sleep deprivation will be reported as dichotomous or continuous data (e.g. number of participant events per group, mean scores per group on a scale measuring anxiety) as appropriate.

Dealing with missing data

In the case of missing data, the principal investigator of the study will be contacted in order to attempt to obtain further information.

Assessment of heterogeneity

Meta-analysis results will be investigated for clinical and statistical heterogeneity, where possible. Chi-square tests for heterogeneity will be used to test for statistical heterogeneity over the trials in the meta-analysis.

Assessment of reporting biases

Reporting bias will be minimised in the following ways:

Publication bias: Both published and unpublished studies will be included. Published results will be compared to published protocol.

Multiple (duplicate) publication bias: In the case of studies with multiple publications, the publication with the most mature data will be used for extracting data on outcomes.

Data synthesis

If a sufficient number of studies with clinically similar patients and methodology are available we will pool their results in meta-analyses using the Cochrane Review Manager software [22].

For time-to-event data, hazard ratios will be pooled using the generic inverse variance facility of RevMan 5.3.

For any dichotomous outcomes, the risk ratio for each study will be calculated and then pooled.

For continuous outcomes, the mean differences between the treatment arms at the end of follow-up will be pooled if all trials measure the outcome on the same scale, otherwise standardised mean differences will be pooled.

The random-effects models with inverse variance weighting will be used for all meta-analyses to accommodate for potential statistical heterogeneity [23].

Subgroup analysis and investigation of heterogeneity

If a sufficient number of eligible studies are available subgroup analysis will be performed based comparing: adults vs children; severity of condition and type of condition.

Pooled synthesis will be performed using RevMan [24].

Sensitivity analysis

Sensitivity analyse will be performed excluding studies at high risk of bias.

Summary of findings

The GRADE approach incorporates assessment of indirectness, study limitations, inconsistency, publication bias and imprecision [25]. The principles of the GRADE system will be used to provide an overall assessment of evidence related to the outcomes.

Declaration of Interest

Colm Andrews: None know

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