**SLEEPain Protocol**

**INTRODUCTION**

**Prevalence of low back pain**

Low back pain (LBP) is a widespread, costly and difficult to manage problem. The lifetime prevalence of LBP is reported to be as high as 84% 1. Low back pain is the fifth most frequent reason for GP visits in the United States, accounting for approximately 2% of all visits 2. LBP causes more disability globally than any other condition 3, and is the leading cause of activity limitation and work absence throughout much of the world3. During 2010, LBP was ranked the sixth leading contributor to overall disease burden, estimated to be 83.0M disability adjusted life years (DALYs). DALYs due to LBP, are the second greatest contributor to overall disease burden in Australia4. Back pain is associated with significant costs, largely due to management being generally ineffective 5, and that it is poorly understood4. It is often assoicated with comorbidites, such as depression and insomnia5. A study examining co morbidites assocaited with chronic low back pain found that sleep disturbances were 3 times more likley in patients with low back pain compared with pain free controls 6. Recently a study found that 50-60% of patients with either acute or chronic low back pain report problems with their sleep7.

**Back pain associated with sleep problems**

The relationship between pain and sleep is bi-directional. In a large longitudinal study conducted in the UK, with over 2000 participants, Morphy et al found that insomnia predisposed people to chronic pain and pain predisposed people to insomnia 8. Although the reasons for these relationships are poorly understood, it has been suggested that adverse effects of poor sleep on pain may be due to reduced rapid eye movement (REM) and subsequent reduced pain thresholds that persist over time9. There appears to be a strong relationship between sleep quality and acute low back pain. In a recent study of 1246 participants with acute low back pain, the effect of poor sleep on their pain was large; for every 1-point decrease in sleep quality, on a 3 point scale, pain intensity increased by 2 points, on a numeric rating scale (NRS). The authors of this study suggested that the size of this effect was greater than most current treatments for low back pain7. However it is unknown whether managing sleep in the acute stage of pain will prevent chronicity.

**Sleep is a modifiable associate to persistent pain**

Given the association between sleep quality and pain, poor sleep quality might be a potential target for pain management. Sleep intervention options include drug therapy and cognitive behaviour therapy-Insomnia (CBH-I). CBT-I is considered the gold standard non-pharmacological treatment 10111213 and has been shown to improve sleep and reduce pain in people with chronic low back pain14. Zopiclone is a hypnotic drug which can provide relief from the symptoms of insomnia15. The most recent NICE guidelines on Z drugs, including Zopiclone, recommend that future research, in the area, should concentrate on the impact of managing sleep, any improvement in sleep quality, on daytime functioning and health-related quality of life15. In this pilot study we intend to investigate the feasibility of managing sleep in patients with acute LBP to prevent persistence and indirectly have a positive effect on their health related quality of life. Pain and disability studies in the acute LBP population do not assess sleep specifically as an indicator of persistent pain but more as a part of an overall assessment. Pre- and postoperative sleep disruptions result in altered pain control and increased likelihood for greater intensity of postoperative pain16. This could also be true for those whose pain is not post-operative, suggesting that disturbed could lead to persistent pain. This is the first study to test the feasibility of controlling sleep in people with acute low back pain to provide preliminary data necessary to design a large (multicentre) randomised placebo controlled study.

**OBJECTIVES**

**Primary Objective**

As a feasibility study, the primary objective is to determine the most efficient and effective design for a large (multicentre) randomised placebo controlled study by;

* Piloting the methodological process
  + Establishing our recruitment setting, rate and population
  + Establishing our procedure, including the randomisation and blinding processes
  + Trialling the use of electronic questionnaires, diary and text message reminders
* Piloting outcome measures to define primary and secondary outcomes
* Piloting outcomes designed to determine the extent of next day effects
* Piloting two different objective measures of sleep, an acti-watch which is worn on the non-dominant arm and a DynaPort MoveMonitor, which is worn around the waist.
* Completing an inquiry into participants’ experience of the trial procedures, interventions and outcomes
* Refining the intervention protocol for future large-scale, multi centre, RCT
  + Establishing attrition rates during the intervention and follow-up periods
  + Exploring the relationship between outcomes changes and sleep quality

**Secondary Objectives**

A secondary aim of this pilot study is to consider an estimate of the effect from the 95% confidence intervals.

**METHODS**

This will be a pilot double blind randomised controlled trial.

**Setting**

Participants will be recruited from primary care centres including GP and physiotherapy clinics in Sydney metropolitan area.

**Sample size**

As a feasibility study at least 32 participants will be recruited. This follows a method advocated by Cocks et Torgerson 17. Their article published in the Journal of Epidemiology suggests a confidence interval(CI) approach to calculating a sample size. They argue that “using a sample size such that it gives a one-sided 80% confidence interval which excludes the minimum important clinical effect size for the main study enhances a pilot study’s utility.” Using this approach, we would calculate the pilot sample size required to produce an upper limit of a one-sided 80% CI which excludes 0.3, which would minimally clinically important effect based on a 10-point numeric rating scale (NRS) for pain intensity. Thirty-two (16 in each group) participants, (approximately 9% of main sample size) would be required to produce a one-sided 80% confidence limit, which would exclude this estimate. If there is a positive intervention effect in the pilot study, then we would conclude that the main trial is worthwhile providing adequate recruitment and follow-up rate was observed in the pilot study.

**Target Population**

Participants will be included if they;

1. Have had an episode of low back within the last 4 weeks
2. Moderate Insomnia defined according to the international classification of sleep disorders II as;
   1. A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically un-restorative or poor in quality.
   2. The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep.
   3. At least one of the following forms of daytime impairment related to the night-time sleep difficulty is reported by the patient: fatigue or malaise; attention, concentration, or memory impairment; social or vocational dysfunction or poor school performance; mood disturbance or irritability; daytime sleepiness; motivation, energy, or initiative reduction; proneness for errors or accidents at work or while driving; tension, headaches, or gastrointestinal symptoms in response to sleep loss; concerns or worries about sleep 18.

The insomnia can predate the LBP but not by more than 2 weeks.

1. Insomnia Severity Index19 score of between 7-21
2. 18-75 years old
3. Both male and females will be included
4. Sufficient understanding of written and verbal English language.

Participants will be excluded if;

1. Diagnosed with any psychiatric disorder or any sleep disorder including primary hypersomnia, narcolepsy, circadian rhythm disorder, parasomnia or dyssomnia.
2. History of an episode of insomnia lasting for greater than 6 months
3. Diagnosed with Sleep Aponea, using Berlin Questionnaire. The Berlin Questionnaire is comprised of 10 questions. It identifies risk factors for sleep apnea, namely snoring behaviour, wake-time sleepiness or fatigue, and the presence of obesity or hypertension. The Berlin questionnaire is one of the few questionnaires that have been validated in primary care patients 20.
4. Have a history of substance abuse or substance dependence subjects with alcohol abuse. Participants will be excluded if they consume more than 14 units (women) or 21 units (men) of alcohol a week
5. Any allergy to Zopiclone or taking any medication that would interact with Zopiclone
6. Consumed more than the nicotine-equivalent of 15 cigarettes a day.
7. Serious hepatic disorder
8. Severe myasthenia gravis
9. Acute narrow angle glaucoma
10. Consumed more than 5 caffeine-containing beverages a day/ caffeine consumption of >500 mg/day
11. Pregnancy or expected pregnancy, or breastfeeding
12. Major surgery or blood donation in the past 12 weeks
13. Have worked night shift or flew >2 time zone in the past month or will have to do so during course of the study; working night shifts and unable or unwilling to discontinue this work pattern
14. They reported other areas of injury or significant pain
15. Presented with any condition that would prevent normal management of low back pain

**Procedure**

A primary care practitioner will provide a potential participant with an information sheet containing details of the study and contact study researchers with their contact details. Study researchers will contact the potential participant within 24 hours to screen for study eligibility.

Eligible participants will then be asked to fill out baseline questionnaires online and a hard copy of Pain Detect Questionnaire Participants will be asked to complete all questionnaires at baseline, 2 weeks and 6 weeks. Participants create their personal research account at registration in the trial online platform and login to their personal account at each session. Participants are anonymised via the assignment of a user ID number. In order to reduce potential biases, participants complete online assessment measures on their own at the computer, with the support of the researcher when requested. Participants will be asked to complete the modified sleep diary daily, for the first 14 days. A text message reminder will be sent to participants at 8.00pm every night and 8.30am every morning during this time.

Participants will be asked to attend an appointment at Woolcock Institute of Medical Research, Neuroscience Research Australia (NeuRA) or to meet with a researcher at their local GP clinic. At this time written informed consent will be obtained. The participant will be given the actiwatch and the DynaPort MoveMonitor. Each participant will also receive 2 Webster packs, each with 7 capsules, with either Zopiclone or placebo. Participants will be reviewed by a physician prior to collecting the prescription. Both the participant and the researcher will be blinded to the contents of the envelope. All participants will be asked to complete a modified version of the Pittsburgh sleep diary for the first 14 days which coincides with when both groups will be taking the capsule. The diary will include one question on pain intensity. Participants will be followed up to 2 weeks and 6 weeks. Participants will be asked to attend a follow up appointment at the Woolcock Institute of Medical Research, NeuRA or their GP clinic at 2 weeks to return the Actiwatch.

**Treatment allocation and Randomisation**

The placebo will be produced by the compounding pharmacist at Hunter Connect Compounding Pharmacy, Wynyard. Zopiclone will be encapsulated in a gelatin capsule in order to identically match the placebo. The placebo will be composed of Avicel in a gelatine capsule. Both the Zopiclone and placebo will be packaged in Webster packaging. There will be no differences in taste or appearance of Zopiclone and the placebo capsules. Participants are randomised immediately prior to the intervention. A randomisation schedule will be created using computer-generated random number table, to allocate participants to one of the two groups: ‘Placebo with Usual Care’ or ‘Zopiclone with Usual Care’. The schedule will be generated by a statistician who is not involved in any other aspect of the study, and all researchers will be blinded to randomisation list. The randomisation list will be supplied to the compounding pharmacist who will allocate the Webster packs accordingly. Sealed sequentially numbered opaque envelopes will be used to ensure allocation concealment. A member of staff, not involved in the trial will inspect the envelopes prior to concealment.

**Blinding**

Both the researcher and the participant will be blinded to group allocation.

**Baseline and outcome measures**

Follow-ups will be carried out at week 2 and week 6. As a feasibility study the primary outcome measure is not defined. Among the proposed outcomes, the participants will be asked to complete a modified Pittsburgh Sleep Diary daily for the first 14 days. Participants will also complete a self-reported pain intensity numeric rating scale (NRS) at 6 weeks following the reported onset of symptoms. Other outcome measures will assess disability, distress and sleep. Participants will be asked to complete the Örebro Musculoskeletal Pain Screen Questionnaire (ÖMPSQ) and The Patient Global Back Recovery Scale (GBRS). Depression and anxiety will be measured using the DASS21. Sleep will be measured using a sleep diary and Insomnia Severity Index and objectively using the Actiwatch. These measures were selected because they are widely employed to assess persistence in low back pain and sleep respectively. Next day effects will be assessed using the Flinders Fatigue Scale Questionnaire, and the Epsworth Sleepiness Scale. The participants will also be asked to complete a participant satisfaction and devices utility questionnaire. To satisfy the inclusion criteria participants will also be asked complete a questionnaire on sleep apnoea, the Berlin Questionnaire.

*Sleep Diary*

All participants will be asked to complete a modified Pittsburgh Sleep Diary (PghSD) over the 14 nights of the study. The PghSD is an instrument with separate components to be completed at bedtime and wake-time. Bedtime components relate to the events of the day preceding the sleep, wake-time components to the sleep period just completed. The diary will be modified to include 2 x 11-point Visual Analogue Scales (VAS) assessing pain intensity and perception of feeling refreshed 21.

*Numeric Rating Scale (NRS)*

This is a valid and reliable measure of pain that is widely used. It is anchored by 0 representing no pain and 10 worst possible pain. Participants are asked to choose a number that best describes their current and average pain in the past day 22.

*Örebro Musculoskeletal Pain Screening Questionnaire (ÖMPSQ)*

The ÖMPSQ was developed to assist health care providers in assessing yellow flags as a complement to the standard medical examination. This instrument has 25 items. The ÖMPSQ has moderate predictive ability in identifying patients with spinal pain at risk of developing chronic pain, disability or taking long-term sick leave 23.

*The Patient Global Back Recovery Scale (GBRS)*

The GBRS is a single-item measure of global recovery with which patients self-classify the degree of their recovery. It is a standard global rating of change scale that aligns with current recommendations, in which the wording specifies recovery from LBP. The instruction to the patient is, “Please rate the extent of your recovery from back pain on the scale below.” The scale is anchored by the written descriptors “very much worse” and “completely recovered” that are congruent with the question. The scale size is 11 points, which is recommended as the best compromise between patient preference, adequate discriminative ability, and test-retest reliability24.

*Pain Detect*

It is a simple, 12-item, patient-based, easy-to-use screening questionnaire that can determine the prevalence of neuropathic pain. As neuropathic pain correlates with more intense pain, we would like to investigate if there is a difference in those with neuropathic pain25.

*DASS21*

The DASS-21 is a 21-item self-report scale that purports to measure levels of depression, stress, and anxiety in the population. Each seven-item scale has four response options ranging from 0 (did not apply to me at all) to 3 (applied to me much, or most of the time). The DASS-21 total scale score has excellent internal consistency and its score interpretations have sound construct validity 26.

*Insomnia Severity Index (Insomnia Index)*

The insomnia Index is a 7-item scale with each item rated on a 5-point Likert scale. It assesses insomnia severity, sleep satisfaction, sleep interference with day-time functioning, noticeability of sleep impairment and distress caused by insomnia over the last 2 weeks. Summation of the 7-itmes provides a score ranging from 0 to 28, where 0-7 indicates no significant insomnia, 8-14 indicates sub-threshold insomnia, 15-21 indicates moderate insomnia and 22-28 indicates severe insomnia. The cut off score of >14 has been reported to be the most accurate point to detect patients with primary insomnia 21.

*Actiwatch*

This is a small wrist-mounted device worn on the non-dominant wrist. It detects and logs movement intensity and duration by means of a small piezo-electric accelerometer. Using sleep analysis software, it is capable of evaluating sleep-wake patterns and common sleep quality variables; i.e. sleep onset latency, sleep efficiency and sleep fragmentation. It has been validated against polysomnography, the ‘gold standard’ for sleep studies in healthy participants and those with sleep disorders. The Actiwatch will be set to average activity count data during recording at 10-sec epochs. Each participant will be requested to wear the Actiwatch for 14 consecutive nights. After the 14 night period participants will return the watch to Neuroscience Research Australia in person or by courier, where data will be downloaded for analysis using the USB Actiwatch-reader and the Actiwatch Sleep v7.27 analysis software. Before analysis, actigraphic data will be automatically converted to 30-sec epochs by the software and all sleep episodes will be visually inspected (scale :1000) to screen for malfunctioning of the devices and non-wear time 27.

*The DynaPort MoveMonitor*

The DynaPort MoveMoitor is a small and light case containing a tri-axial accelerometer, a rechargeable battery, an USB connection, and raw data storage on a MicroSD card. The used accelerometer has a DC response to the Earth’s gravitational field, and uses a seismic or a proof mass suspended by a spring structure in a case. This sensor responds to both slow and fast changes in acceleration, it can also detect body position. It will be used to measure movement during the night. It is attached to an elastic belt and worn on the waist to sit at the level of the sacrum. It is to be worn each night for the first 14 nights of the study.

*The Flinders Fatigue Scale (FFS)*

The FSS is a self-report questionnaire, designed to measure the level of a person’s fatigue in a variety of situations (e.g., “I am easily fatigued,” “Exercise brings on my fatigue”). It is a relatively brief measure, containing only 9 items that provide a global measure of fatigue 28.

*Epsworth Sleepiness Scale*

The Epworth Sleepiness Scale (ESS) is an effective instrument used to measure average daytime sleepiness. The ESS is a self-administered 8-item questionnaire that has been widely used as a simple, reliable, and valid method for assessing daytime sleepiness in adults. The ESS differentiates between average sleepiness and excessive daytime sleepiness that requires intervention. The client self-rates on how likely it is that he/she would doze in eight different situations. Scoring of the answers is 0-3, with 0 being “would never doze” and 3 being “high chance of dozing”. A sum of 10 or more from the eight individual scores reflects above normal daytime sleepiness and need for further evaluation 29.

*The Glasgow Sleep Effort Scale*

The Glasgow Sleep Effort Scale (GSES) is a 7 item tool, designed to measure sleep effort. It is considered a useful and novel measure of clinical assessment and change, which should aid identification of insomnia patients suited to psychological therapies by screening out psychophysiological insomnia. It also allows us to explore performance anxiety about sleep, a need for control over sleep, and/or trying too hard to sleep 30. The GSES has demonstrated moderate to high scale reliability as well as strong sensitivity and specificity 31.

*Participant Satisfaction Questionnaire*

This questionnaire consists of 6 questions to assess participant satisfaction with outcome and trial procedures. It will be administered at the 6-week follow up point only. It will also include questions on devices’ utility. Participants will be requested to provide any free text comments, regarding the current research and their likelihood of participating in research in the future 27.

Follow up reminders will be given by phone and email.

**Interventions**

Managing sleep to decrease pain compares a sleep intervention Zopiclone and placebo additional to the guideline based management of acute low back pain.

Placebo and Usual Care

Placebo will consist of Avicel in gelatine capsules.

Usual care is described below as recommended by Williams et al in accordance with international guidelines and a systematic review of guidelines 32. It includes 5 main elements;

1. Use a diagnostic triage as a basis for management decisions and perform a more extensive examination if the medical history indicates possible serious disease or nerve root compromise.

2. Do not routinely order radiological or ancillary investigations.

3. Educate the patient; provide assurance of a favourable prognosis and encouragement to remain active and avoid bed rest.

4. Regular acetaminophen (paracetamol) is the first choice of analgesics. When this provides insufficient analgesia, regular nonsteroidal anti-inflammatory drugs (NSAIDs) maybe tried. (Some guidelines recommend medicines containing opioids when NSAIDs provide insufficient analgesia.)

5. Review the patient’s progress.

Zopiclone

Of the different insomnia therapies available, only benzodiazepine-receptor agonists and cognitive–behavioural therapy (CBT) are recognised as having adequate evidence in terms of efficacy and safety 33333435. Non benzodiazepine receptor agonists include Z medications, Zolpidem, Zaleplon, and Zopiclone. They are effective and safe hypnotic medications with minimal adverse effects and mild chance of abuse, dependence, and tolerance and no withdrawal or rebound insomnia over long-term use 36 37 38 39. It will be prescribed as a standard dose of 7.5mg to be taken shortly before bedtime for maximum of 14 nights.

**Ethics and Safety**

Informed consent will be obtained from all patients by the study researcher, who will not be in a doctor-patient relationship with the patient. Study participants will have the opportunity to withdraw from the study at any time. Ethics approval will be sought from the University of NSW Human Research Ethics Committee. A psychiatrist or a psychologist will be made available at the Woolcock Institute of Medical Research to review participants should they report any distress as a result of being involved in the trial.

**Data and treatment integrity**

Trial data integrity will be monitored by regularly scrutinising data files for omissions and errors. All data will be double entered and the source of any inconsistencies will be explored and resolved.

**Adverse event reporting**

Adverse events will be recorded throughout the study and rated by the investigator with regard to intensity and likelihood of being drug-related. Zopiclone appears to be well tolerated. Many studies performed on a self-reporting basis show the absence of serious adverse events 40. The most commonly reported adverse event is bitter taste 40. Overall disturbances are rare and mild in intensity. No respiratory changes have been documented during Zopiclone administration in patients with insomnia 40.

**Data analysis**

All data will be coded and entered into the Statistical Package for the Social Sciences (SPSS) database for analysis following data cleaning and checking for errors. Monthly recruitment rates and ratio of number screened: number enrolled will be tabulated. Outcome measures will be analysed using Standardised Response Means (SRM). The assessment of patient satisfaction will be tabulated, as will adherence levels and recorded difficulties experienced with the protocol including the use of the sleep monitoring equipment or adverse events as a result of taking Zopiclone. Statistical analysis will be carried out on an intent-to-treat basis. Group comparisons will be made using ANOVA. The overall survival/ resolution of symptoms rate will be calculated by nonparametric Kaplan-Meier method. The median days to recovery will be calculated. Treatment effects will be represented by point estimates and confidence intervals of all outcome variables at all follow-up points. The following criteria would suggest that a main trial is not feasible; unable to recruit sufficient willing participants, feedback from participants that they were unable/unwilling to complete the outcomes measures or adhere to the outcomes measures, high level of adverse events associated with Zopiclone and /or an estimate of no effect from the 95% confidence intervals.

**CONCLUSION**

This trial aims to conclude whether or not it is feasible to do a large scale trial, how many participants would be necessary to effectively power that study, is the method of randomisation used appropriate and what should be the primary outcome measure.

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