Efficacy of Low-Dose Amitriptyline for Chronic Low Back Pain
A Randomized Clinical Trial

ORIGINAL, REVISED AND PUBLISHED STUDY PROTOCOLS

Dr Donna Urquhart, Assoc Prof Anita Wluka, Prof Maurits van Tulder, Assoc Prof Stephane Heritier, Prof Andrew Forbes, Dr Chris Fong, Dr Yuanyuan Wang, Prof Malcolm Sim, Prof Stephen Gibson, Dr Carolyn Arnold, Prof Flavia Cicuttini

Investigator Contact: Dr Donna Urquhart / Prof Flavia Cicuttini

Department of Epidemiology and Preventive Medicine
School of Public Health and Preventive Medicine
Monash University
Alfred Hospital
Commercial Road
Melbourne Vic 3004
Australia
Phone: (03) 9903-0555
Fax: (03) 9903-0567
CONTENTS

Original protocol 3
Revised protocol 15
Summary of changes 27
Published protocol 29
ORIGINAL STUDY PROTOCOL

Date: Version 1 25th November 2011
SUMMARY/SYNOPSIS

Chronic low back pain (LBP) is a major public health problem. Although antidepressants are commonly used to treat pain in this condition, their efficacy is unproven.

Our Cochrane systematic reviews concluded that there is no clear evidence that antidepressants are effective for LBP. However, they identified significant heterogeneity in the study populations, with most trials not distinguishing between those with and without neuropathic LBP.

Neuropathic LBP is common and a significant cause of disability. Although the efficacy of antidepressants for neuropathic LBP is unknown, there is preliminary evidence to suggest that they may be beneficial in this subgroup of LBP.

Aims
In community-based adults with chronic, neuropathic LBP, we aim to determine:
1. If low dose amitriptyline (tricyclic antidepressant) is more effective than placebo in the management of pain
2. If low dose amitriptyline is more effective than placebo in improving function and reducing absence from paid/unpaid work
3. The cost-effectiveness of low-dose amitriptyline compared to placebo

Methods
A double-blind, randomized, placebo-controlled trial with an economic evaluation. We will recruit 150 subjects with chronic, neuropathic LBP. Participants will receive low-dose amitriptyline or an active placebo for 6 months. Pain, function and absence from work will be assessed at baseline, 3 and 6 months using valid instruments. Our economic evaluation will determine and compare all back pain related costs of patients receiving antidepressants and placebo.

Implications
If antidepressants are found to be effective, it will provide high quality evidence for their use and cost-effectiveness, potentially enabling this treatment option to be considered by more individuals with neuropathic low back pain. If we do not find antidepressants to be effective, then our trial will provide strong evidence to significantly reduce the prescription rate and subsidisation of antidepressant therapy.
1. INTRODUCTION

1.1 Title
Is low dose amitriptyline more effective than placebo in the management of chronic, neuropathic low back pain? A double-blind, randomized, placebo-controlled trial with an economic evaluation.

1.2 Rationale
Chronic low back pain is a major, but poorly understood, public health problem. Low dose antidepressants, at a much lower dose than used for the treatment of depression, are commonly used to manage chronic low back pain. This is the case, even though the evidence for their efficacy is unproven.

While our recent Cochrane systematic review concluded that there is no documented benefit from the use of antidepressant therapy, it identified a number of limitations in the available data, including the heterogeneity of populations previously investigated, particularly in relation to whether neuropathic pain was present or not. Moreover, there is evidence that low dose tricyclic antidepressants are effective in the treatment of neuropathic pain, such as diabetic and postherpetic neuralgia.

Chronic, neuropathic low back pain is a common and a significant cause of disability and results in a huge socioeconomic burden. If the use of antidepressants can reduce pain and loss of productivity associated with chronic, neuropathic low back pain, this could significantly reduce the costs associated with this debilitating condition, reducing the need for ongoing treatment and surgery, as well resulting in greater improvements in quality of life. If antidepressants are not cost-effective then their prescription for neuropathic, low back pain should be ceased and not subsidized.

The proposed study represents a potentially cost effective and innovative approach to the management of chronic, neuropathic low back pain and lends itself to a feasible public health intervention if successful. This study supports the objectives of the “Bone and Joint Decade” and addresses a National Health Priority Area.

2. OBJECTIVES

2.1 Primary
To perform a double-blind, randomized, placebo-controlled trial to investigate whether low dose amitriptyline (a tricyclic antidepressant) is more effective than placebo in the management of pain in community-based adults with chronic, neuropathic low back pain.

2.2 Secondary
To investigate whether low dose amitriptyline is more effective than placebo in improving functional status and minimizing absence from paid/unpaid work in chronic, neuropathic low back pain.

3. STUDY DESIGN

3.1 Experimental Design
A pragmatic, double-blind, randomized, placebo-controlled trial with an economic evaluation. The study will be conducted with adherence to the CONSORT guidelines.
3.2 Subject Selection

3.2.1 Definition of Disease State

We will recruit patients with chronic, neuropathic low back pain, defined as:

- Low back pain: defined as pain localised below the scapulae and above the gluteal folds
- Chronic pain: defined as pain that has been present for at least 3 months. Back pain that requires specific interventions are likely to have been clarified by 3 months and self-limiting back pain will have resolved.
- Presence of neuropathic pain: There is currently no reliable gold standard for the diagnosis of neuropathic pain and there are inherent limitations with most diagnostic tests, such as magnetic resonance imaging and neurophysiological tests. Current recommendations for the identification of neuropathic pain include a clinical examination and a screening tool.

3.2.2 Clinical Examination

We will perform a series of clinical tests, involving a neurological examination (including reflexes and muscle power), neural tension test, and sensory tests. The neural tension test will involve a straight leg raising test, which has a pooled sensitivity estimated to be 91%, and the sensory examination will follow the short-form protocol developed by the German Research Network on Neuropathic Pain, which includes a range of well established tests, such as thermal, mechanical and vibration threshold testing. These will be performed by the study physician.

3.2.3 Screening Tool: painDETECT questionnaire

We will administer the painDETECT questionnaire, a simple, patient-based, easy-to-use screening questionnaire, which has been shown to be reliable and valid for the identification of neuropathic pain components in heterogeneous cohorts of low back pain patients. The questionnaire has been validated in about 8,000 patients with low back pain, and reaches about 80% sensitivity and specificity. The results of the clinical examination and questionnaire will be recorded at baseline.

3.2.4 Source and Number

We will recruit patients from hospital departments and outpatient clinics and general practitioner and allied health clinics located in Melbourne.

3.2.5 Entrance Criteria

Aged 18-70 years. Occupational low back pain is a major economic burden in the working population in Australia. We aim to perform an economic analysis. However, individuals will be included in the trial whether they perform paid or unpaid work.

Exclusion criteria:

- Specific pathological entities, such as infection, metastasis, osteoporosis, fractures.
- Candidates for spinal surgery
- Major co-existing illness which might confound assessment of function or for which antidepressants may be inappropriate
- Other significant musculoskeletal conditions (eg fibromyalgia)
- Patients with any diagnosed depression or any prior or current use of antidepressants
- History of psychosis
- Any contra-indication or allergy to antidepressant medication
- Inability to provide informed consent
3.3 Study Medication

Participants in the intervention arm will receive the tricyclic antidepressant, amitriptyline (Alphapharm, NSW; low dose; 25mg), and those in the control arm will receive an active placebo, benztropine mesylate (Phebra, NSW; 1mg). Amitriptyline and benztropine will be administered in identical capsules to be taken in a single dose at the same time each day (9.00 pm).

3.3.1 Rationale for selecting the tricyclic antidepressant amitriptyline

Low dose amitriptyline is commonly prescribed in Australia for the management of chronic pain. It has been shown to be an effective treatment for various pain conditions, including fibromyalgia, ankylosing spondylitis and headaches, and can act on pain independent of depression. Amitriptyline blocks the reuptake of norepinephrine and serotonin, neurotransmitters known to inhibit the transmission of pain. It is generally well tolerated.

3.3.2 Rationale for selecting the Benztropine mesylate

We have selected benztropine, an active placebo, as it mimics the side effects of amitriptyline, such as dry mouth and constipation, while having no known effect on chronic pain. Given this trial involves blinding, the choice of placebo is critical. If the side effects of the drug are not mimicked by the placebo then there is potential for unblinding. Benzotropine produces more effective blinding than an inert placebo and has been used as an active placebo in previous trials of neuropathic pain.

3.3.3 Side Effects/Adverse events

Low dose amitriptyline is commonly used in general practice to treat pain. Typically lower dosages, ranging from 10 to 50 mg daily, are used for pain modification. Based on previous studies, we would expect adverse events to occur in our trial, but for these to be mild and generally not lead to withdrawal. Adverse events such as dry mouth, mild constipation and fatigue can occur.

Adverse experiences will be documented at each assessment point throughout the study. Any serious adverse experiences, that is an adverse experience which is incapacitating and prevents normal everyday activities and/or requires therapeutic intervention (i.e. use of a prescription drug or hospitalisation), will be reported to the appropriate human research ethics committee and the appropriate procedures conducted.

3.3.4 Length of treatment

The length of the trial will be 6 months. Participants will commence on the medication/placebo to test the therapeutic efficacy of amitriptyline and side-effects of the medication will be monitored throughout the trial. Given the longest trial of antidepressants in chronic low back pain has been 12 weeks, a trial of 6 months enables the efficacy of the treatment to be examined over a longer time period.

3.4 Study Procedure

3.4.1 Recruitment

Participants will be recruited from hospital departments and outpatient clinics and general practitioner and allied health clinics in Melbourne.
Participants will be identified by; (i) clinicians having contact with patients and (ii) hospital staff checking patient hospital and clinic lists. Patients lists will be checked both retrospectively and prospectively to identify relevant patients. The names of potential participants will then be provided to the research team.

Initial contact with participants will be made by either the treating clinician or research personnel involved with the trial;
1. The treating clinician, who has a clinician/patient relationship with the participant, will briefly introduce the trial to the patient and ask them if they would be interested in being contacted by research staff with further information. This will occur in the clinic setting. If participants indicate they are happy to be contacted further, research personnel will contact them to discuss the study by phone.
2. In the case where potential participants have been identified from patient lists, participants will be posted a letter introducing them to the study and asking whether they would be interested in being contacted further. The letter will include a section enabling participants to opt-out of being contacted further. Senior research personnel will then contact participants who chose to receive further information about the study by phone.

3.4.2 Baseline Assessment
Participants who agree to be part of the study and have signed the study consent form will be assessed at baseline by a blinded study physician. A study physician was selected as low dose antidepressants, such as amitriptyline, are commonly prescribed by physicians for the management of pain in Australia. The physician will perform the clinical tests and administer the painDETECT questionnaire (as described in section 3.2.1).

3.4.3 Commencement of the trial
On entry to the trial participants will receive either amitriptyline or the placebo. The randomisation, dispensing and drug accountability (ie storage, returns and disposal) will be undertaken by the Clinical Trials Pharmacy Department of the Alfred Hospital. Participants will receive either amitriptyline or placebo for a 3 month period at their initial baseline assessment. The study physician will discuss the dosage, side-effects and use of other medications with the participant. The participant will also be provided information from the ‘Consumer Medicines’ Advice Information sheet on amitriptyline.

3.4.4 Monitoring
To monitor compliance and side effects, participants will be monitored at 2 weeks, 1-2 months, 3 months, 4-5 months and 6 months using a validated questionnaire, the UKU Side Effects Rating Scale. This questionnaire involves a standardized, physician-administered interview for assessing the severity and impact of side effects on daily function due to psychotropic drugs. The participants’ physician will also be notified of their inclusion in the trial.

3.4.5 Outcome measures
The following primary and secondary outcome measures will be measured by blinded research assistants at baseline and 3 and 6 months. These time periods allow for assessment at baseline, during the trial, and at the conclusion of the study.
Primary outcome measure: Pain intensity, measured on the Descriptor Differential Scale (DDS)\(^5\) and a visual analogue scale of at least 100 mm. The DDS is a valid measure of pain. It has been used in previous trials of antidepressants in low back pain, enabling calculation of study sample size and comparison of results.

Secondary outcome measures:
- Functional status; Roland Morris Disability Questionnaire (RDQ; back pain specific scale)\(^5\)
- Absence from paid/unpaid work; Short Form Health and Labour Questionnaire (SHLQ)\(^5\)

Additional measures:
- Global improvement; 6-point scale, ranging from “much worse” to “completely recovered”
- General Health Status, measured using the EuroQuol Instrument (EuroQol) \(^5\)
- Severity of mood symptoms will be assessed using the Beck Depression Inventory (BDI) \(^5\)
- Psychosocial variables including fear of movement/(re)injury using the 17-item Tampa scale\(^5\)

3.4.6 Other measures
1. Anthropometry: Includes height and weight measured at baseline and 6 months.
2. Analgesics: Participants will be asked to discontinue opioid analgesics. This is an exclusion criteria. However, participants will be allowed to continue non-opioid analgesia and non-steroid anti-inflammatory medication. Data on their usage will be collected.
3. Physical activity: Using International Physical Activity Questionnaire (IPAQ – short version)\(^6\)
4. Compensation status: For each individual, we will record whether their back pain is associated with a compensation claim, and if so, the nature of the claim ie type (ie WorkSafe, Transport Accident Commission), duration, items approved and associated costs.

4. EXPERIMENTAL CONTROL

4.1 Randomisation
Randomization will be performed by an independent body - the Clinical Trials Department of the Alfred Hospital. Allocation concealment will be ensured by the use of identical, active placebo, and the use of a central automated allocation procedure, with security in place to ensure allocation data cannot be accessed or influenced by any person. Block randomization based on clinical site of recruitment will be used to reduce the confounding effects of the site. Randomization will be stratified by age and compensation status since subjects aged 50 years or greater have the capacity to influence the primary outcome of return to work and compensation, which has previously been shown to have adverse effects on self-reported pain and disability, both before and after interventions\(^4\).

4.2 Blinding Procedure
Participants will be blinded to whether they are in the intervention or placebo group. Blinding will involve the use of an active placebo. The active placebo will mimic the side-effects of amitriptyline. The physicians undertaking the baseline assessment and monitoring the side-effects and the research assistants administering the outcomes measures will also be blinded to the group participants are allocated to.

5. STATISTICAL CONSIDERATIONS
Summary statistics comparing randomized arms at baseline will be tabulated. Intention to treat analyses of primary and secondary continuous outcomes will be performed by linear regression
adjusting for the baseline of the outcome variable where relevant. Logistic regression will be performed for binary outcomes. Adjustment for imbalanced baseline factors, including the presence of symptoms other than neuropathic pain (e.g., reduced muscle power and reflexes), will be performed as supplementary analyses. Analyses of treatment efficacy will be done by censoring individuals at the time of any protocol deviation and developing a model for the probability of deviation, followed by weighted analyses using only the uncensored individuals where the weights are the inverse probability of censoring. This produces estimates of treatment effect as if there was full compliance with the protocol in this RCT and is far preferable to per-protocol analyses based on (unweighted) observed compliance. This RCT is well-placed to model non-compliance with frequent monitoring for adverse events and resultant prognostic information.

5.1 Sample size for primary outcome measures

A. Reduction in pain intensity: In a recent study of patients with low back pain, similar to those to be recruited for the current study (pain of moderate intensity (Mean: 9.4 (4.0)), the control group (n=22) had a pain score that reduced to a mean (SD) = 6.2 (2.8) on the Descriptor Differential Scale following treatment, while the pain score of the treatment group (TCA) (n=19) reduced to a mean (SD) score = 4.5 (2.6). With an α=0.05 and n=60 in each arm of the study, we have 90% power to detect a difference of this size (1.7), which reflects clinically significant reductions in pain intensity from moderate to mild or from strong to moderate, which is equivalent to a decrease of 2 units (17%) on the Descriptor Differential Scale (0-12 per descriptor).

B) Improvement in functional status, expressed on a back pain-specific scale: With 60 in each arm of the study, we will have 90% power to detect a clinically relevant difference in disability (improvement of 13-16% in disability or 3-4 points on the 24 point Roland Morris Disability Questionnaire after 26 weeks) (α=0.05, 2 sided significance), which corresponds to a significant improvement in key functional activities, including walking and dressing.

More generally, with 60 per arm we have 90% power to detect a difference of 0.60 standard deviations. With our primarily analyses involving adjustment for the baseline value of the outcome, we will have greater than 90% power according to the size of the baseline-followup correlation. Given our previous experience in such studies we expect a maximum drop out rate of 20% so we will recruit a total of 150 (75 in each arm of the study).

6. ADMINISTRATIVE PROCEDURES

6.1 Amendments to the Protocol

All modifications of the study will be written and filed as amendments to this protocol, maintaining original section identification. Such modification(s) will be approved by the appropriate Ethics Committees (where applicable). Any modifications to the study will be applied for all subsequent patients.

6.2 Early Termination or Extension of the Study

This research project may be terminated early for such reasons as unacceptable side effects, drug shown not to be effective or the drug/treatment being shown to work and not need further testing. In this event the human research ethics committees involved with be notified and the appropriate procedures followed.
6.3 **Drug Accountability, Drug Packaging and Labelling, Storage of Study Drugs**

The randomisation, dispensing (packaging and labelling) and drug accountability (ie storage, returns and disposal) will be undertaken by the Clinical Trials Pharmacy Department of the Alfred Hospital. Please refer to Pharmacy Resources Agreement for further information.

6.4 **Confidentiality/Publication of Study Results**

Study results will be published in aggregate form so that no results pertaining to any individual can be identified.

6.5 **Retention of Records**

All records associated with this study will be kept for at least 15 years as specified in the guidelines (Monash University Faculty of Medicine, Nursing and Health Science – A Guide to Good Research Practice (2011)).

6.6 **Audits**

The investigators and research staff will participate and assist any audit of the project.

7. **ETHICAL PROCEDURES**

7.1 **Guidelines for Good Clinical Research Practice**

This study will be performed in accordance with the Monash University Faculty of Medicine, Nursing and Health Science – A Guide to Good Research Practice (2011) and NHMRC National Statement on Ethical Conduct in Human Research (2007).

7.2 **Precautionary Advice**

Given amitriptyline could have effects which interfere with subjects’ normal activities or procedures e.g. drowsiness affecting ability to drive or use machinery, the research staff/investigators will give precautionary advice to the participants.

7.3 **Participant Information and Consent Form (PI&CF)**

An individual Participant Information and Consent Form has been prepared. Research staff will ensure that the approved consent form is signed by each patient prior to entry into the study.

Each patient’s signed consent form will be retained and for confidentiality purposes will not be removed from the Monash University Department of Epidemiology and Preventive Medicine.

Volunteers/patients will be advised that they are free to refuse to participate in, or to withdraw from the study at any time. The medical care provided will not be affected by agreement or refusal to participate in this study.

7.4 **Ethics Committee**

This protocol will be submitted to the appropriate Human Ethics and Research Committees and their approval obtained.
8. REFERENCES


SUMMARY/SYNOPSIS

Chronic low back pain (LBP) is a major public health problem. Although antidepressants are commonly used to treat pain in this condition, their efficacy is unproven. Of note, our Cochrane systematic reviews concluded that there is no clear evidence that antidepressants are effective for LBP.

Aims
In community-based adults with chronic LBP, we aim to determine:
1. If low dose amitriptyline (tricyclic antidepressant) is more effective than placebo in the management of pain
2. If low dose amitriptyline is more effective than placebo in improving function and reducing absence from paid/unpaid work
3. The cost-effectiveness of low-dose amitriptyline compared to placebo

Methods
A double-blind, randomized, placebo-controlled trial with an economic evaluation. We will recruit 150 subjects with chronic LBP. Participants will receive low-dose amitriptyline or an active placebo for 6 months. Pain, function and absence from work will be assessed at baseline, 3 and 6 months using valid instruments. Our economic evaluation will determine and compare all back pain related costs of patients receiving antidepressants and placebo.

Implications
If antidepressants are found to be effective, it will provide high quality evidence for their use and cost-effectiveness, potentially enabling this treatment option to be considered by more individuals with low back pain. If we do not find antidepressants to be effective, then our trial will provide strong evidence to significantly reduce the prescription rate and subsidisation of antidepressant therapy.
1. INTRODUCTION

1.1 Title
Is low dose amitriptyline more effective than placebo in the management of chronic low back pain? A double-blind, randomized, placebo-controlled trial with an economic evaluation.

1.2 Rationale
Chronic low back pain is a major, but poorly understood, public health problem. Low dose antidepressants, at a much lower dose than used for the treatment of depression, are commonly used to manage chronic low back pain. This is the case, even though the evidence for their efficacy is unproven. While our recent Cochrane systematic review concluded that there is no documented benefit from the use of antidepressant therapy, it identified a number of limitations in the available data.

Chronic low back pain is a common and a significant cause of disability and results in a huge socioeconomic burden. If the use of antidepressants can reduce pain and loss of productivity associated with chronic low back pain, this could significantly reduce the costs associated with this debilitating condition, reducing the need for ongoing treatment and surgery, as well resulting in greater improvements in quality of life. If antidepressants are not cost-effective then their prescription for low back pain should be ceased and not subsidized.

The proposed study represents a potentially cost effective and innovative approach to the management of chronic low back pain and lends itself to a feasible public health intervention if successful. This study supports the objectives of the “Bone and Joint Decade” and addresses a National Health Priority Area.

2. OBJECTIVES

2.1 Primary
To perform a double-blind, randomized, placebo-controlled trial to investigate whether low dose amitriptyline (a tricyclic antidepressant) is more effective than placebo in the management of pain in community-based adults with chronic low back pain.

2.2 Secondary
To investigate whether low dose amitriptyline is more effective than placebo in improving functional status and minimizing absence from paid/unpaid work in chronic low back pain.

3. STUDY DESIGN

3.1 Experimental Design
A pragmatic, double-blind, randomized, placebo-controlled trial with an economic evaluation. The study will be conducted with adherence to the CONSORT guidelines.

3.2 Subject Selection

3.2.1 Definition of Disease State
We will recruit patients with chronic low back pain, defined as:
- Low back pain: defined as pain localised below the scapulae and above the gluteal folds
• Chronic pain: defined as pain that has been present for at least 3 months. Back pain that requires specific interventions are likely to have been clarified by 3 months and self-limiting back pain will have resolved.

3.2.2 Clinical Examination
We will perform a series of clinical tests, involving a neurological examination (including reflexes and muscle power), neural tension test, and sensory tests. The neural tension test will involve a straight leg raising test, which has a pooled sensitivity estimated to be 91%41, and the sensory examination will follow the short-form protocol developed by the German Research Network on Neuropathic Pain, which includes a range of well established tests, such as thermal, mechanical and vibration threshold testing42. These will be performed by the study physician.

3.2.3 Screening Tool: painDETECT questionnaire
We will administer the painDETECT questionnaire, a simple, patient-based, easy-to-use screening questionnaire, which has been shown to be reliable and valid for the identification of neuropathic pain components in heterogeneous cohorts of low back pain patients40. The questionnaire has been validated in about 8,000 patients with low back pain, and reaches about 80% sensitivity and specificity. The results of the clinical examination and questionnaire will be recorded at baseline.

3.2.4 Source and Number
We will recruit patients from hospital departments and outpatient clinics and general practitioner and allied health clinics located in Melbourne.

3.2.5 Entrance Criteria
Aged 18-75 years: Occupational low back pain is a major economic burden in the working population in Australia. We aim to perform an economic analysis. However, individuals will be included in the trial whether they perform paid or unpaid work.

Exclusion criteria:
• Specific pathological entities, such as infection, metastasis, osteoporosis, fractures.
• Candidates for spinal surgery
• Major co-existing illness which might confound assessment of function or for which antidepressants may be inappropriate
• Other significant musculoskeletal conditions (eg fibromyalgia)
• Patients with any diagnosed depression or any prior or current use of antidepressants
• History of psychosis
• Any contra-indication or allergy to antidepressant medication
• Inability to provide informed consent

3.3 Study Medication
Participants in the intervention arm will receive the tricyclic antidepressant, amitriptyline (Alphapharm, NSW; low dose; 25mg), and those in the control arm will receive an active placebo, benztropine mesylate (Phebra, NSW; 1mg). Amitriptyline and benztropine will be administered in identical capsules to be taken in a single dose at the same time each day (9.00 pm).

3.3.1 Rationale for selecting the tricyclic antidepressant amitriptyline
Low dose amitriptyline is commonly prescribed in Australia for the management of chronic pain34. It has been shown to be an effective treatment for various pain conditions, including fibromyalgia35, ankylosing spondylitis36 and headaches37, and can act on pain independent of depression28. It has been reported to be the most effective antidepressant for the treatment of neuropathic pain, such as...
diabetic neuropathy and neuralgia. Amitriptyline blocks the reuptake of norepinephrine and serotonin, neurotransmitters known to inhibit the transmission of pain. It is generally well tolerated.

3.3.2 Rationale for selecting the Benztropine mesylate
We have selected benztropine, an active placebo, as it mimics the side effects of amitriptyline, such as dry mouth and constipation, while having no known effect on chronic pain. Given this trial involves blinding, the choice of placebo is critical. If the side effects of the drug are not mimicked by the placebo then there is potential for unblinding. Benztropine produces more effective blinding than an inert placebo and has been used as an active placebo in previous trials of low back pain.

3.3.3 Side Effects/ Adverse events
Low dose amitriptyline is commonly used in general practice to treat pain. Typically lower dosages, ranging from 10 to 50 mg daily, are used for pain modification. Based on previous studies, we would expect adverse-events to occur in our trial, but for these to be mild and generally not lead to withdrawal. Adverse events such as dry mouth, mild constipation and fatigue can occur.

Adverse experiences will be documented at each assessment point throughout the study. Any serious adverse experiences, that is an adverse experience which is incapacitating and prevents normal everyday activities and/or requires therapeutic intervention (i.e. use of a prescription drug or hospitalisation), will be reported to the appropriate human research ethics committee and the appropriate procedures conducted.

3.3.4 Length of treatment
The length of the trial will be 6 months. Participants will commence on the medication/placebo to test the therapeutic efficacy of amitriptyline and side-effects of the medication will be monitored throughout the trial. Given the longest trial of anti-depressants in chronic low back pain has been 12 weeks, a trial of 6 months enables the efficacy of the treatment to be examined over a longer time period.

3.4 Study Procedure

3.4.1 Recruitment
Participants will be recruited from hospital departments and outpatient clinics and general practitioner and allied health clinics in Melbourne. Study flyers will also be placed on noticeboards at hospitals, clinics, local gyms, pilates centres and community groups. Advertisements will be placed in newspapers, magazines, and university and hospital newsletters and on internet sites. Participants will be identified by; (i) clinicians having contact with patients and (ii) hospital staff checking patient hospital and clinic lists. Patients lists will be checked both retrospectively and prospectively to identify relevant patients. The names of potential participants will then be provided to the research team.

Initial contact with participants will be made using the following methods;
1. The treating clinician, who has a clinician/patient relationship with the participant, will briefly introduce the trial to the patient and ask them if they would be interested in further information regarding the study. If the patient is interested in learning more about the study the treating clinician or research staff will provide the patient with a study flyer with some brief information about the trial. This will occur in the clinic setting. If participants indicate they are happy to be contacted further, research personnel will contact them to discuss the study by phone.
2. In the case where potential participants have been identified from patient lists, participants will be posted a letter introducing them to the study and asking whether they would be interested in being contacted further. The letter will include a section enabling participants to opt-out of being contacted further. Senior research personnel will then contact participants who chose to receive further information about the study by phone.

3. Study flyers will also be placed on hospital and clinic noticeboards. Potential participants who read the flyer and are interested in learning more about the study will be able to contact research personnel.

4. Advertisements will be placed in newspapers, magazines, and university and hospital newsletters and on internet sites. Potential participants who read the advertisement and are interested in learning more about the study will be able to contact research personnel.

3.4.2 Baseline Assessment
Participants who agree to be part of the study and have signed the study consent form will be assessed at baseline by a blinded study physician. A study physician was selected as low dose antidepressants, such as amitriptyline, are commonly prescribed by physicians for the management of pain in Australia. The physician will perform the clinical tests and administer the painDETECT questionnaire (as described in section 3.2.1).

3.4.3 Commencement of the trial
On entry to the trial participants will receive either amitriptyline or the placebo. The randomisation, dispensing and drug accountability (ie storage, returns and disposal) will be undertaken by the Clinical Trials Pharmacy Department of the Alfred Hospital. Participants will receive either amitriptyline or placebo for a 3 month period at their initial baseline assessment. The study physician will discuss the dosage, side-effects and use of other medications with the participant. The participant will also be provided information from the ‘Consumer Medicines’ Advice Information sheet on amitriptyline.

3.4.4 Monitoring
To monitor compliance and side effects, participants will be monitored at 2 weeks, 1-2 months, 3 months, 4-5 months and 6 months using a validated questionnaire, the UKU Side Effects Rating Scale. This questionnaire involves a standardized, physician-administered interview for assessing the severity and impact of side effects on daily function due to psychotropic drugs. The participants’ physician will also be notified of their inclusion in the trial.

3.4.5 Outcome measures
The following primary and secondary outcome measures will be measured by blinded research assistants at baseline and 3 and 6 months. These time periods allow for assessment at baseline, during the trial, and at the conclusion of the study.

Primary outcome measure: Pain intensity, measured on the Descriptor Differential Scale (DDS) and a visual analogue scale of at least 20 mm. The DDS is a valid measure of pain. It has been used in previous trials of antidepressants in low back pain, enabling calculation of study sample size and comparison of results.

Secondary outcome measures:
- Functional status; Roland Morris Disability Questionnaire (RDQ; back pain specific scale)
- Absence from paid/unpaid work; Short Form Health and Labour Questionnaire (SHLQ)

20
Additional measures:
- Global improvement; 6-point scale, ranging from “much worse” to “completely recovered”
- General Health Status, measured using the EuroQuol Instrument (EuroQol) \(^{56}\)
- Severity of mood symptoms will be assessed using the Beck Depression Inventory (BDI) \(^{57}\)
- Psychosocial variables including fear of movement/(re)injury using the 17-item Tampa scale\(^{58}\)

3.4.6 Other measures
1. Anthropometry: Includes height and weight measured at baseline and 6 months.
2. Analgesics: Participants will be asked to discontinue opioid analgesics. This is an exclusion criteria. However, participants will be allowed to continue non-opioid analgesia and non-steroid anti-inflammatory medication. Data on their usage will be collected.
3. Physical activity: Using International Physical Activity Questionnaire (IPAQ – short version)\(^{61}\)
4. Compensation status: For each individual, we will record whether their back pain is associated with a compensation claim, and if so, the nature of the claim ie type (ie WorkSafe, Transport Accident Commission), duration, items approved and associated costs.

4. EXPERIMENTAL CONTROL

4.1 Randomisation
Randomization will be performed by an independent body - the Clinical Trials Department of the Alfred Hospital. Allocation concealment will be ensured by the use of identical, active placebo, and the use of a central automated allocation procedure, with security in place to ensure allocation data cannot be accessed or influenced by any person. Block randomization based on clinical site of recruitment will be used to reduce the confounding effects of the site. Randomization will be stratified by age and compensation status since subjects aged 50 years or greater have the capacity to influence the primary outcome of return to work and compensation, which has previously been shown to have adverse effects on self-reported pain and disability, both before and after interventions\(^{46}\).

4.2 Blinding Procedure
Participants will be blinded to whether they are in the intervention or placebo group. Blinding will involve the use of an active placebo. The active placebo will mimic the side-effects of amitriptyline. The physicians undertaking the baseline assessment and monitoring the side-effects and the research assistants administering the outcomes measures will also be blinded to the group participants are allocated to.

5. STATISTICAL CONSIDERATIONS
Summary statistics comparing randomized arms at baseline will be tabulated. Intention to treat analyses of primary and secondary continuous outcomes will be performed by linear regression adjusting for the baseline of the outcome variable where relevant. Logistic regression will be performed for binary outcomes. Adjustment for imbalanced baseline factors, including the presence of symptoms other than neuropathic pain (eg reduced muscle power and reflexes), will be performed as supplementary analyses. Analyses of treatment efficacy will be done by censoring individuals at the time of any protocol deviation and developing a model for the probability of deviation, followed by weighted analyses using only the uncensored individuals where the weights are the inverse probability of censoring. This produces estimates of treatment effect as if there was full compliance with the protocol in this RCT and is far preferable to per-protocol analyses based on (unweighted) observed compliance\(^{62}\). This RCT is well-placed to model non-compliance with frequent monitoring for adverse events and resultant prognostic information.
5.1 Sample size for primary outcome measures

A. Reduction in pain intensity: In a recent study of patients with low back pain, similar to those to be recruited for the current study (pain of moderate intensity (Mean: 9.4 (4.0)), the control group (n=22) had a pain score that reduced to a mean (SD) = 6.2 (2.8) on the Descriptor Differential Scale following treatment, while the pain score of the treatment group (TCA) (n=19) reduced to a mean (SD) score = 4.5 (2.6) 43. With an α=0.05 and n=60 in each arm of the study, we have 90% power to detect a difference of this size (1.7), which reflects clinically significant reductions in pain intensity from moderate to mild or from strong to moderate, which is equivalent to a decrease of 2 units (17%) on the Descriptor Differential Scale (0-12 per descriptor)63.

B) Improvement in functional status, expressed on a back pain-specific scale: With 60 in each arm of the study, we will have 90% power to detect a clinically relevant difference in disability (improvement of 13-16% in disability or 3-4 points on the 24 point Roland Morris Disability Questionnaire after 26 weeks 64) (α=0.05, 2 sided significance), which corresponds to a significant improvement in key functional activities, including walking and dressing65.

More generally, with 60 per arm we have 90% power to detect a difference of 0.60 standard deviations. With our primarily analyses involving adjustment for the baseline value of the outcome, we will have greater than 90% power according to the size of the baseline-followup correlation. Given our previous experience in such studies we expect a maximum drop out rate of 20% so we will recruit a total of 150 (75 in each arm of the study).

6. ADMINISTRATIVE PROCEDURES

6.1 Amendments to the Protocol
All modifications of the study will be written and filed as amendments to this protocol, maintaining original section identification. Such modification(s) will be approved by the appropriate Ethics Committees (where applicable). Any modifications to the study will be applied for all subsequent patients.

6.2 Early Termination or Extension of the Study
This research project may be terminated early for such reasons as unacceptable side effects, drug shown not to be effective or the drug/treatment being shown to work and not need further testing. In this event the human research ethics committees involved with be notified and the appropriate procedures followed.

6.3 Drug Accountability, Drug Packaging and Labelling, Storage of Study Drugs
The randomisation, dispensing (packaging and labelling) and drug accountability (ie storage, returns and disposal) will be undertaken by the Clinical Trials Pharmacy Department of the Alfred Hospital. Please refer to Pharmacy Resources Agreement for further information.

6.4 Confidentiality/Publication of Study Results
Study results will be published in aggregate form so that no results pertaining to any individual can be identified.

6.5 Retention of Records
All records associated with this study will be kept for at least 15 years as specified in the guidelines (Monash University Faculty of Medicine, Nursing and Health Science – A Guide to Good Research Practice (2011)).
6.6 Audits
The investigators and research staff will participate and assist any audit of the project.

7. ETHICAL PROCEDURES

7.1 Guidelines for Good Clinical Research Practice
This study will be performed in accordance with the Monash University Faculty of Medicine, Nursing and Health Science – A Guide to Good Research Practice (2011) and NHMRC National Statement on Ethical Conduct in Human Research (2007).

7.2 Precautionary Advice
Given amitriptyline could have effects which interfere with subjects’ normal activities or procedures e.g. drowsiness affecting ability to drive or use machinery, the research staff/investigators will give precautionary advice to the participants.

7.3 Participant Information and Consent Form (PI&CF)
An individual Participant Information and Consent Form has been prepared. Research staff will ensure that the approved consent form is signed by each patient prior to entry into the study.

Each patient’s signed consent form will be retained and for confidentiality purposes will not be removed from the Monash University Department of Epidemiology and Preventive Medicine.

Volunteers/patients will be advised that they are free to refuse to participate in, or to withdraw from the study at any time. The medical care provided will not be affected by agreement or refusal to participate in this study.

7.4 Ethics Committee
This protocol will be submitted to the appropriate Human Ethics and Research Committees and their approval obtained.
8. REFERENCES


Summary of Changes

1. Participant: inclusion criteria

<table>
<thead>
<tr>
<th>Original</th>
<th>Update</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 18-70 years</td>
<td>Aged 18-75 years</td>
<td>The upper age limit was increased to 75 years during the trial to assist with recruitment.</td>
</tr>
</tbody>
</table>

2. Participant: inclusion criteria

<table>
<thead>
<tr>
<th>Original</th>
<th>Update</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>We will recruit patients with chronic, neuropathic low back pain, defined as:</td>
<td>We will recruit patients with chronic low back pain, defined as:</td>
<td>The inclusion criteria were changed from chronic, neuropathic low back pain to chronic low back pain prior to commencing recruitment to allow the efficacy of a low-dose antidepressant to be determined in a patient population that is well-defined, and highly prevalent and generalizable.</td>
</tr>
<tr>
<td>• Low back pain: defined as pain localised below the scapulae and above the gluteal folds</td>
<td>• Low back pain: defined as pain localised below the scapulae and above the gluteal folds</td>
<td></td>
</tr>
<tr>
<td>• Chronic pain: defined as pain that has been present for at least 3 months. Back pain that requires specific interventions are likely to have been clarified by 3 months and self-liming back pain will have resolved</td>
<td>• Chronic pain: defined as pain that has been present for at least 3 months. Back pain that requires specific interventions are likely to have been clarified by 3 months and self-liming back pain will have resolved</td>
<td></td>
</tr>
<tr>
<td>• Presence of neuropathic pain: There is currently no reliable gold standard for the diagnosis of neuropathic pain and there are inherent limitations with most diagnostic tests, such as magnetic resonance imaging and neurophysiological tests. Current recommendations for the identification of neuropathic pain include a clinical examination and a screening tool.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Participant: exclusion criteria

| Original | Update | |
|----------|--------| |
| - Specific pathological entities, such as infection, metastasis, osteoporosis, fractures. | - Specific pathological entities, such as infection, metastasis, osteoporosis, fractures. |
| - Candidates for spinal surgery | - Candidates for spinal surgery |
| - Major co-existing illness which might confound assessment of function or for which antidepressants may be inappropriate | - Major co-existing illness which might confound assessment of function or for which antidepressants may be inappropriate |
| - Other significant musculoskeletal conditions (e.g. fibromyalgia) | - Other significant musculoskeletal conditions (e.g. fibromyalgia) |
| - Patients with any diagnosed depression or any prior or current use of antidepressants | - Patients with any diagnosed depression or any prior or current use of antidepressants |
| - History of psychosis | - History of psychosis |
| - Any contra-indication or allergy to antidepressant medication | - Any contra-indication or allergy to antidepressant medication |
| - Inability to provide informed consent | - Inability to provide informed consent |

The protocol was updated throughout the document to reflect this change.
- Patients with any diagnosed depression with or without the use of medication
- Any prior or current use of antidepressants
- Current use of opioids
- Any contra-indication or allergy to amitriptyline
- Pregnancy or planning/trying to become pregnant or breastfeeding
- Inability to provide informed consent

**Reason:** Changes were made to the exclusion criteria to ensure a specific type of low back pain was investigated and that participant safety was optimised.

4. **Recruitment**

**Original:** Participants will be recruited from hospital departments and outpatient clinics and general practitioner and allied health clinics in Melbourne.

**Update:** Participants will be recruited from hospital departments and outpatient clinics and general practitioner and allied health clinics in Melbourne. Study flyers will also be placed on hospital and clinic noticeboards. Advertisements will be placed in newspapers, magazines, and university and hospital newsletters and on internet sites.

**Reason:** We used additional recruitment strategies, such as study flyers and advertising, to optimise recruitment for the trial.

5. **Secondary aim**

**Original:** In community-based adults with chronic, neuropathic LBP, we aim to determine:

(iii) the cost-effectiveness of low-dose amitriptyline compared to placebo.

**Reason:** Due to poor patient compliance with collecting cost-effectiveness data, we did not complete an economic evaluation.

6. **Block randomisation**

**Original:** Block randomization based on clinical site of recruitment will be used to reduce the confounding effects of the site. Randomization will be stratified by age and compensation status since subjects aged 50 years or greater have the capacity to influence the primary outcome of return to work and compensation, which has previously been shown to have adverse effects on self-reported pain and disability, both before and after interventions.46

**Reason:** Given participants were primarily recruited from the general community rather than several clinical sites, block randomisation was not required. Similarly, stratification was not conducted as it was not applicable for the cohort recruited.