Accepted Manuscript

British Journal of General Practice

Nortriptyline for pain in knee osteoarthritis in general practice: a double blind randomised controlled trial

Hudson, Ben; Williman, Jonathan; Stamp, Lisa; Alchin, John; Hooper, Gary; Mangin, Dee; Lennox Thompson, Bronwyn; Toop, Les

DOI: https://doi.org/10.3399/BJGP.2020.0797

To access the most recent version of this article, please click the DOI URL in the line above.

Received 25 August 2020
Revised 04 January 2021
Accepted 10 January 2021

Nortriptyline for pain in knee osteoarthritis in general practice: a double blind randomised controlled trial

Authors

Dr Ben Hudson MBBS, MRCGP, FRNZCGP[1,*]

Senior Lecturer

Email: ben.hudson@otago.ac.nz

Dr Jonathan A Williman BSc(Hons), PhD, MBiostat[2]

Research Fellow

Email: jonathan.williman@otago.ac.nz

Professor Lisa K Stamp MBChB, FRACP, PhD, DipMus[3,6]

Professor

Email: Lisa.stamp@cdhb.health.nz

Dr John S Alchin MBBS, FAFOEM, Dip Obs, DipIndustrialHealth, DipAvMed[4]

Consultant

Email: John.alchin@cdhb.health.nz

Professor Gary J Hooper MBChB, MD, FRACS, FRNZOA[5,6]

Professor

Email: gary.hooper@otago.ac.nz

Professor Dee Mangin MBChB, FRNZCGP, DPH[1]

Professor

Email: dee.mangin@otago.ac.nz

Dr Bronwyn F Lenox Thompson MSc, PhD, DipOccTh[5]

Clinical Senior Lecturer

Email: bronwyn.thompson@otago.ac.nz

Professor Les Toop MBChB, MD, MRCGP, FRNZCGP[1]

Professor

Email: les.toop@otago.ac.nz

[1] Department of General Practice, University of Otago, Christchurch, P O Box 4345, Christchurch 8140, New Zealand

[2] Biostatistics and Computational Biology Unit, University of Otago, Christchurch, P O Box 4345, Christchurch 8140, New Zealand

[3] Department of Medicine, University of Otago, Christchurch, P O Box 4345, Christchurch 8140, New Zealand

[4] Pain Management Centre, Canterbury District Health Board, Christchurch, New Zealand

[5] Department of Orthopaedic Surgery & Musculoskeletal Medicine, University of Otago, Christchurch, P O Box 4345, Christchurch 8140, New Zealand

[6] Canterbury District Health Board, Christchurch, New Zealand

*Corresponding author. Department of General Practice, University of Otago, Christchurch, P O Box 4345, Christchurch 8140, New Zealand

Abstract

Background

Osteoarthritis (OA) of the knee is a common cause of chronic pain. The currently available analgesics have limited efficacy and may be poorly tolerated.

Aim

To investigate the analgesic efficacy of nortriptyline in people with knee OA.

Design and setting

A two-arm parallel-group 1:1 double blind randomised placebo-controlled trial. Participants were recruited from orthopaedic outpatient clinics, primary care, and by public advertising.

Method

Adults with knee OA and with pain rated as ≥20 points on the 50 point Western Ontario and McMaster University (WOMAC) pain sub-scale were randomised to receive either nortriptyline or identical placebo for 14 weeks. Primary outcome was knee pain at 14 weeks measured using the WOMAC pain sub-scale. Secondary outcomes included function, stiffness, non-steroidal anti-inflammatory drug, opioid and/or paracetamol use, participant global assessment, and adverse effects at 14 weeks.

Results

Of the 205 randomised participants, 201 (98%) completed follow-up at 14 weeks. The baseline-adjusted mean WOMAC pain subscale score at week 14 was 6.15 points lower (95% CI -0.26 to 12.6, p = 0.06) in the nortriptyline vs. the placebo arm. Differences in secondary outcomes generally favoured the nortriptyline arm, but were small and unlikely to be clinically relevant. Dry mouth (87%

vs. 51%, p < 0.001), constipation (69% vs. 30%, p < 0.001), and sweating (31% vs. 21%, p = 0.033) were all more commonly reported by participants taking nortriptyline.

Conclusion

This study suggests nortriptyline does not significantly reduce pain in people with knee OA. Adverse effect profile was as expected.

Key words

General practice

Osteoarthritis, Knee

Analgesia

Antidepressive Agents, Tricyclic

Randomized Controlled Trial [Publication Type]

How this fits in

Patients with knee OA frequently require analgesics, but the analgesics commonly used are not ideal being either insufficiently effective or having serious side effects. We hypothesised that tricyclic antidepressants (TCAs), which are used as analgesics in other chronically painful conditions, may be helpful for patients with OA. In this randomised double-blind placebo-controlled trial we found that nortriptyline did not significantly reduce pain or improve physical function, stiffness or participants'

global assessment of the impact of their OA. Nortriptyline is unlikely to be a useful treatment for patients with knee OA.

Introduction

Osteoarthritis (OA) is the commonest joint disease and is a major cause of pain and disability, reduced quality of life, and large healthcare costs. (1-4) The burden of disease is predicted to rise. (5, 6)

OA management is focused on advice, exercise, weight loss (if obese), analgesia and maintenance of function. (7) The analgesics currently recommended for OA are not ideal: paracetamol is minimally effective (8) and has been linked with increased risk of mortality, cardiovascular disease, gastrointestinal bleeding and renal adverse events. (9) Oral non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing pain, (10) but are associated with renal, gastrointestinal and cardiovascular toxicity. (11) Opioids may also be used despite poor evidence of efficacy, significant side effect burden, and risk of dependency. (12-14) Patients may be offered intra-articular corticosteroid injections, but their analgesic efficacy and safety are uncertain. (15) Knee OA may be treated with joint replacement, but access to this intervention is limited by resource constraints in many countries, (16) and by patient co-morbidity. For younger people, delayed joint replacement may be desirable due to increased lifetime risk of prosthetic failure. (17) Hence there is a need for more effective and better tolerated pain management for people with OA.

Central sensitisation may play an important role in the chronic pain of OA, (18, 19) and some centrally-acting agents have been shown to reduce OA pain. (20, 21) Tricyclic antidepressants (TCAs) are used in other chronic pain conditions, (22, 23) but their analgesic effect in OA has not previously been evaluated. The aim of this study was to assess the efficacy and safety of the TCA nortriptyline for analgesia in knee OA when used in addition to participants' usual analgesia.

Method

Trial design

We conducted a two-arm parallel-group 1:1 randomised double-blind placebo-controlled trial to investigate whether nortriptyline 25mg to 100mg per day provides clinically significant pain relief in patients with OA of the knee. A full protocol has previously been published (24) and results are presented in accordance with the CONSORT guidelines and extension for harms. (25, 26)

Participant recruitment and eligibility

We invited people with knee OA who had been declined specialist orthopaedic assessment for knee replacement (by a referral triaging orthopaedic surgeon who read the referral letters and examined accompanying pre-referral X-rays) and returned to their general practitioner (GP) for ongoing care, or who had been seen by an orthopaedic surgeon but were declined surgical intervention. We also used a range of local marketing and recruitment initiatives targeting older people with knee OA.

For inclusion in the study, participants must have met all of the following criteria:

I. primary knee OA defined according to the American College of Rheumatology clinical criteria for the classification of idiopathic OA of the knee, (27)
II. knee pain of at least 20 points on the Western Ontario and McMaster Universities (WOMAC) numerical rating scale (range 0 to 50 points), (28) and
III. stable analgesic regime for at least the prior two months.

Exclusion criteria included previous joint replacement of the study knee, intra-articular steroid injection within the previous 3 months, secondary OA, concurrent use of any antidepressant, and any established contraindications to TCAs. (24)

Randomisation and blinding

An un-stratified 1:1 allocation computer-generated randomisation list with blocks of varying size (one to four) was prepared by the study statistician. (29) Participants and all investigators and research staff enrolling participants, dispensing medication, and/or assessing outcomes, were blinded to the treatment allocation.

Trial regimen and procedures

Treatment occurred over 14 weeks and was divided into an 8 week dose-adjustment phase and a 6 week steady-dose phase. Participants were instructed to commence taking one capsule (containing either nortriptyline 25mg or placebo) daily for two weeks at which time they were contacted by a research nurse who advised participants to increase or decrease their dose by one capsule per day according to the participant's level of knee pain and adverse effects. Further dose adjustments occurred at four, six and eight weeks, up to a maximum dose of four capsules daily (100mg nortriptyline daily in the treatment group). At week eight, participants were instructed to maintain their current dose until week 14 when the final assessment was undertaken. Throughout the study, participants were free to use and adjust their usual analgesic medication as prescribed by their GP, but were requested not to use any other antidepressants or receive intra-articular steroid injections.

Outcome measures

Primary outcome

The primary outcome was self-reported pain in the study knee over the past 48 hours, captured using the WOMAC 3.1 pain subscale numerical rating scale (NRS).

Secondary outcomes

Secondary outcomes included physical function and stiffness (using WOMAC subscales), global assessment using a visual analogue scale (VAS), response to treatment (according to the Outcome Measures in Rheumatology Osteoarthritis Research Society International [OMERACT-OARSI] responder criteria (30)), quality of life using the RAND 36-Item Health Survey 1.0 (RAND 36), (31) and use of NSAIDs and other analgesics. WOMAC and VAS scores were standardised to a range of 0 (best possible outcome) to 100 (worst possible outcome). RAND 36 physical and mental component summary scores were calculated according simple item sums. (32) Adverse events were captured in free text fields and coded using the Common Terminology Criteria for Adverse Events version 5 (CTCAE). (33) The occurrence and severity of expected antidepressant adverse events at any time during the study were captured for all participants at week 14 using the Antidepressant Side-Effect Checklist (ASEC). (34)

Data collection

Information collected at baseline included demographics, clinical characteristics, baseline measures of outcome variables (WOMAC 3.1 OA index, global assessment by VAS, RAND 36), and analgesic use during the previous two weeks.

All primary and secondary outcome measures were self-reported by participants during face-to-face interviews conducted 14 weeks after commencing study medication. Use of analgesics during the final two weeks of the study was recorded by participants in daily diaries. Daily doses were calculated for each analgesic and pre-specified rules were used to derive equivalent doses of NSAIDs and opioids (appendix). Adverse events were captured at weeks 2, 4, 6, 8 and 14. The occurrence and severity of antidepressant adverse events at any time during the study was captured for all participants at week 14.

Sample size calculation

The study was powered to detect the minimum clinically important difference for reduction in pain at 14 weeks measured using the WOMAC NRS (10% of the scale maximum), (35) with 90% power at a 2-sided significance level of 0.05. We calculated a sample size of 200 which conservatively assumed a pooled standard deviation of 20 points, no correlation between baseline and follow-up scores, and up to 15% attrition. (36)

Statistical analysis

The statistical analysis plan and analysis code were prepared by the study statistician (JW) and agreed upon by the principal investigator (BH) following blinded review of the data but before the randomisation code was broken. Analysis was conducted using R version 3.5.1. (37) The primary analysis followed an intention-to-treat approach and missing data were imputed using multivariate normal multiple imputation. (38) A p value of <0.05 was considered statistically significant.

The mean absolute treatment effect in the primary outcome was estimated using linear regression modelling with baseline WOMAC pain scores included as a covariate. Similar analyses were conducted for the secondary outcomes: physical function, stiffness, global assessment, and quality of life subscales. Absolute and relative differences in the proportion of participants who responded to treatment (according to the OMERACT-OARSI responder criteria (30)) were calculated with 95% confidence intervals using generalised linear regression models.

Heterogeneity of treatment effects (subgroup) analysis followed the framework presented by Kent *et al*. (39) Additional sensitivity analyses were performed adjusting for age, BMI, gender, years with OA, use of assistive devices, presence of any chronic comorbidities, and mental health.

Generalised mixed effects hurdle models were used to estimate differences in (a) the daily likelihood of a participant using an analgesic, and (b) the average number of 'standardised' analgesic tablets taken daily by those who took any. A logistic model was used for part (a) and a truncated generalised Poisson model for part (b). Both models included time of observation, treatment group, and time by treatment as fixed effects, and subject as a random effect.

Results

Participant flow and characteristics

A total of 205 participants were enrolled between November 2015 and October 2017. The final follow-up interview was conducted in February 2018. Outcome data were not collected for four participants: two participants withdrew from the study after randomisation and two were lost to follow-up (Figure). Baseline VAS data were not collected for the first 24 participants (12 participants in both study arms) due to an error in the preparation of these participants' record sheets. Participant demographic and clinical characteristics are presented in Table 1. Participants' baseline characteristics were generally similar in the in the placebo and nortriptyline arms. However, the nortriptyline arm included a greater proportion of obese individuals (74% vs 48%).

Figure

Table 1

Efficacy

Primary outcome

On average, participants given nortriptyline had a WOMAC pain subscale score at week 14 that was 6.15 points lower (95% CI -0.26 to 12.6, p = 0.060) than those receiving placebo. Results were effectively unchanged in sensitivity analysis adjusting for baseline covariates or excluding participants with protocol violations (Table 2).

Secondary outcomes

Participants in the nortriptyline arm achieved a greater improvement in the bodily pain subscale of the RAND 36 survey (baseline adjusted difference 2.75 [95% CI 0.42, 5.08, p = 0.02]). However, no statistically significant differences were observed in the other items of the RAND 36 survey, the WOMAC subscales for physical function or stiffness, the VAS, or the proportion of responders (Table 2). There was no evidence of heterogeneity in treatment effects according to predicted WOMAC pain score at week 14 (p = 0.82), nor predicted responder status (p = 0.67), so further subgroup analyses were not undertaken.

Table 2

Analgesic use

Participants in the nortriptyline group had a greater proportion of days when they did not take any NSAIDs (74% versus 69%, adjusted OR 3.91, 95% CI 2.49 to 6.16) or paracetamol (63% versus 58%, adjusted OR 1.55, 95% CI 1.03 to 2.37). If they did take NSAIDs they took fewer tablets on average (adjusted RR = 0.85, 95% CI 0.80 to 0.90) (Table 3).

Table 3

Safety

There were seven serious adverse events (SAEs): six requiring hospitalisation (three on placebo, three on nortriptyline) and one life-threatening (on nortriptyline) (Table 4). Two SAEs (one hospitalisation for myocardial infarction and one hospitalisation for atrial fibrillation) were considered to be related to study medication. Dry mouth (87% nortriptyline vs. 51% placebo, $p < 0.001$), constipation (59% vs. 30%, $p < 0.001$), and sweating (31% vs. 21%, $p= 0.033$) were all more commonly reported by those taking nortriptyline (Table 4).

Table 4

Test of blinding

When participants were asked what treatment they thought they received, the proportion who correctly guessed was similar amongst those who guessed that they were taking nortriptyline and those who guessed that they were taking placebo: 63% (95% CI 53% to 71%) vs. 70% (95% CI 59% to 80%), $p = 0.06$.

Discussion

Summary

In people with knee OA, the addition of nortriptyline to usual analgesic treatment did not meaningfully improve pain, function, stiffness or participant's global assessment of OA. Participants randomised to nortriptyline were more likely to have days when they did not take paracetamol or

NSAIDs, and when they did take NSAIDs they took fewer doses. However, these differences in analgesic use were small and unlikely to be clinically important.

Dry mouth, constipation and sweating were more likely in participants taking nortriptyline. Serious adverse events occurred in four participants taking nortriptyline and three taking placebo.

Strengths and limitations

We believe this is the first published double-blind randomised controlled trial of the analgesic effect of a tricyclic antidepressant in OA. There are a number of strengths to our study design: primary and secondary outcome measures were recorded at 14 weeks, a follow-up period consistent with OARSI OA study recommendations; (40) our primary outcome was measured using the WOMAC scale a valid, reliable and responsive measure of pain and disability in OA; (41, 42) and our study was adequately powered to detect the minimum clinically important difference in pain.

Another strength of this study was the pragmatic study design in which study medication was taken in addition to usual treatment. We believe this is an appropriate design in that it tested the effect of nortriptyline in the context that it would be used in clinical practice. However, as the design placed no limitation on participants' use of other analgesics, it is possible that it may have masked an analgesic effect of nortriptyline that would have been apparent had we restricted use of other analgesics.

Study participants were recruited from a number of sources. The majority were those with knee OA who had been declined assessment for knee replacement and returned to their general

practitioner's care. Others were recruited through a range of community-based advertising approaches. Recruitment of individuals referred for and declined specialist assessment may have meant that the range of disease severity in participants was greater than is typically encountered in primary care. This may limit extrapolation of our findings to the full range of patients with knee OA encountered in primary care.

Another strength of our study design is that it required participants' study medication doses to be individually titrated according to their levels of pain and medication adverse effects. This is important since nortriptyline metabolism, and hence dosing, have high inter-individual variability: the effective and tolerated daily dose ranges from <25 mg to >100 mg, so individualised dosing is essential. (43, 44) Furthermore, this process of dose-adjustment closely resembles usual clinical practice when initiating a TCA.

A further strength of our study was that we were able to demonstrate reasonably effective blinding of participants. This is of particular importance in trials of TCAs as these medicines have a well-recognised set of adverse effects which may lead to un-blinding.

Whilst this study was adequately powered to detect a clinically important effect of nortriptyline on pain, our sample size was too small to allow sub-group analyses of participants who may have been predisposed to derive greater benefit from nortriptyline, for example those with low mood or higher baseline levels of pain.

Participants' baseline characteristics were generally similar in the placebo and nortriptyline arms. The nortriptyline arm, however, included a greater proportion of obese individuals (74% vs 48%).

Individuals with a higher BMI report greater OA pain than those with lower BMI. (45) This may have introduced bias to our findings, though mean BMI was similar in the two study arms, and adjusting for BMI and other key baseline variables did not substantially alter them.

Comparison with existing literature

This is the first trial of a TCA for pain in OA so no directly comparable studies exist. Our null finding is disappointing since achieving adequate, well-tolerated and safe analgesia for patients with OA is challenging, and few trials of analgesic agents demonstrate an effect size equal to the minimum clinically important difference. (12, 20, 35)

The evidence of TCAs' efficacy in other chronic pain conditions is mixed: TCAs are established as first line agents in neuropathic pain, (46) and have been shown to be effective in chronic headache, (23) post-herpetic neuralgia, and in diabetic neuropathy. (22) Their efficacy in fibromyalgia is less clear, (47, 48) and a recent RCT of amitriptyline in chronic back pain did not show a significant improvement in pain. (49) In OA the relative contribution of central and peripheral sensitisation and nociceptive pain varies between individuals. (50) This may mean that some people are more likely to benefit from centrally-acting analgesics than others. The degree of central sensitisation in an individual can be estimated using clinical scoring systems, (51) and future work on centrally-acting analgesics in OA could explore the potential for stratifying participants based on their degree of central sensitisation in order to determine whether centrally-acting agents might usefully be targeted to those patients with higher levels of central sensitisation.

Implications for research and practice

Nortriptyline taken in addition to standard analgesia does not reduce pain in people with knee OA.

Funding

This study was funded with a project grant from the Health Research Council of New Zealand (ref 14/152). The funding source had no role in the design, execution, analysis, interpretation of the data, or the decision to submit results of this study.

Ethical approval

The study was approved by the New Zealand Northern A Health and Disability Ethics Committee (reference: 14/NTA/139).

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We thank our study participants, research nurses Gwyneth Steenson and Rae Noble-Adams, research administrator Alison Parsons, departmental colleagues Ruth Savage and Kim Pasley, the Canterbury District Health Board orthopaedics outpatient clinic administrative team, and Aarti Patel general manager Canterbury Community Pharmacy Group. We also thank the Health Research Council of New Zealand for funding the study.

References

1. Abbott JH, Usiskin IM, Wilson R, et al. The quality-of-life burden of knee osteoarthritis in New Zealand adults: A model-based evaluation. PLOS ONE. 2017;12(10):e0185676.
2. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime Medical Costs of Knee Osteoarthritis Management in the United States: Impact of Extending Indications for Total Knee Arthroplasty. Arthritis Care Res. 2015;67(2):203-15.
3. Jinks C, Ong B, Richardson J. A mixed methods study to investigate needs assessment for knee pain and disability: population and individual perspectives. BMC Musculoskelet Disord. 2007;8(1):59.
4. Arthritis Care. OA Nation the most comprehensive UK report of people with osteoarthritis2004. Available from: www.arthritiscare.org.uk/.
5. Arthritis New Zealand. The economic cost of arthritis in New Zealand in 2010. Report by Access Economics Pty Limited for: Arthritis New Zealand. 13 April 2010.
6. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
7. National Institute for Health and Care Excellence (NICE). Osteoarthritis Care and management in adults. Clinical guideline CG177 2014. Available from: http://www.nice.org.uk/guidance/cg177/evidence/cg177-osteoarthritis-full-guideline3.
8. Leopoldino AO, Machado GC, Ferreira PH, et al. Paracetamol versus placebo for knee and hip osteoarthritis. Cochrane Database Syst Rev. 2019(2).
9. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis. 2016;75(3):552-9.
10. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet. 2017;390(10090):e21-e33.
11. Coxib and Traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials Lancet. 2013;382:769-79.
12. da Costa BR, Nüesch E, Kasteler R, et al. Oral or transdermal opioids for osteoarthritis of the knee or hip. Cochrane Database Syst Rev. 2014(9).
13. Higgins C, Smith BH, Matthews K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. British Journal of Anaesthesia. 2018;120(6):1335-44.
14. Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA. 2018;319(9):872-82.
15. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: A randomized clinical trial. JAMA. 2017;317(19):1967-75.
16. Gwynne-Jones D. Quantifying the demand for hip and knee replacement in Otago, New Zealand. N Z Med J. 2013;126:7-17.
17. Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. Lancet (London, England). 2017;389(10077):1424-30.
18. Mease PJ, Hanna S, Frakes EP, Altman RD. Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. J Rheumatol. 2011;38(8):1546-51.

19. Neogi T, Frey-Law L, Scholz J, et al. Sensitivity and sensitisation in relation to pain severity in knee osteoarthritis: trait or state? Ann Rheum Dis. 2015;74(4):682-8.
20. Wang ZY, Shi SY, Li SJ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain Med. 2015;16(7):1373-85.
21. Sullivan M, Bentley S, Fan M-Y, Gardner G. A Single-Blind Placebo Run-In Study of Venlafaxine XR for Activity-Limiting Osteoarthritis Pain. Pain Med. 2009;10(5):806-12.
22. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007(4).
23. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: systematic review and meta-analysis. BMJ. 2010;341:c5222.
24. Hudson B, Williman JA, Stamp LK, et al. Nortriptyline in knee osteoarthritis (NortIKA Study): Study protocol for a randomised controlled trial Trials. 2015;16(448).
25. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. 2010;340:c332.
26. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med. 2004;141(10):781-8.
27. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: Classification of osteoarthritis of the knee. Arthritis Rheum. 1986;29(8):1039-49.
28. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40.
29. Snow G. blockrand: Randomization for block random clinical trials. R package version 1.3 2013 [Available from: https://CRAN.R-project.org/package=blockrand.
30. Pham T, van der Heijde D, Altman RD, et al. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12(5):389-99.
31. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health economics. 1993;2(3):217-27.
32. Grassi M, Nucera A. Dimensionality and summary measures of the SF-36 v1.6: comparison of scale- and item-based approach across ECRHS II adults population. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(4):469-78.
33. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).
34. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. Br J Psychiatry. 2009;195(3):202-10.
35. Ehrich EW, Davies GM, Watson DJ, et al. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol. 2000;27(11):2635-41.
36. Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage. 2004;28(1):59-71.
37. R Core Team. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria2018. Available from: https://www.R-project.org/.
38. Honaker J, King G, Blackwell M. Amelia II: A Program for Missing Data. Journal of Statistical Software. 2011;45(7):1-47.
39. Kent DM, Rothwell PM, Ioannidis JP, et al. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. Trials. 2010;11:85.
40. Altman R, Brandt K, Hochberg M, et al. Design and conduct of clinical trials in patients with osteoarthritis: Recommendations from a task force of the Osteoarthritis Research Society: Results from a workshop. Osteoarthritis Cartilage. 1996;4(4):217-43.

41. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. Arthritis Care Res. 2001;45(5):453-61.
42. Rogers JC, Irrgang JJ. Measures of adult lower extremity function: The American Academy of Orthopedic Surgeons Lower Limb Questionnaire, The Activities of Daily Living Scale of the Knee Outcome Survey (ADLS), Foot Function Index (FFI), Functional Assessment System (FAS), Harris Hip Score (HHS), Index of Severity for Hip Osteoarthritis (ISH), Index of Severity for Knee Osteoarthritis (ISK), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™). Arthritis Care Res. 2003;49(S5):S67-S84.
43. New Zealand Formulary. Nortriptyline 2019. Available from: https://www.nzf.org.nz/nzf_2260.
44. Wolf CR, Smith G, Smith RL. Pharmacogenetics. BMJ. 2000;320(7240):987-90.
45. Weiss E. Knee osteoarthritis, body mass index and pain: data from the Osteoarthritis Initiative. Rheumatology (Oxford). 2014;53(11):2095-9.
46. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology. 2015;14(2):162-73.
47. Häuser W, Bernardy K, Üçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: A meta-analysis. JAMA. 2009;301(2):198-209.
48. Häuser W, Walitt B, Fitzcharles M-A, Sommer C. Review of pharmacological therapies in fibromyalgia syndrome. Arthritis research & therapy. 2014;16(1):201-.
49. Urquhart DM, Wluka AE, van Tulder M, et al. Efficacy of low-dose amitriptyline for chronic low back pain: A randomized clinical trial. JAMA Intern Med. 2018;178(11):1474-81.
50. Hochman JR, Gagliese L, Davis AM, Hawker GA. Neuropathic pain symptoms in a community knee OA cohort. Osteoarthritis Cartilage. 2011;19(6):647-54.
51. Hochman JR, Davis AM, Elkayam J, et al. Neuropathic pain symptoms on the modified painDETECT correlate with signs of central sensitization in knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1236-42.

Figure: Enrolment and randomisation

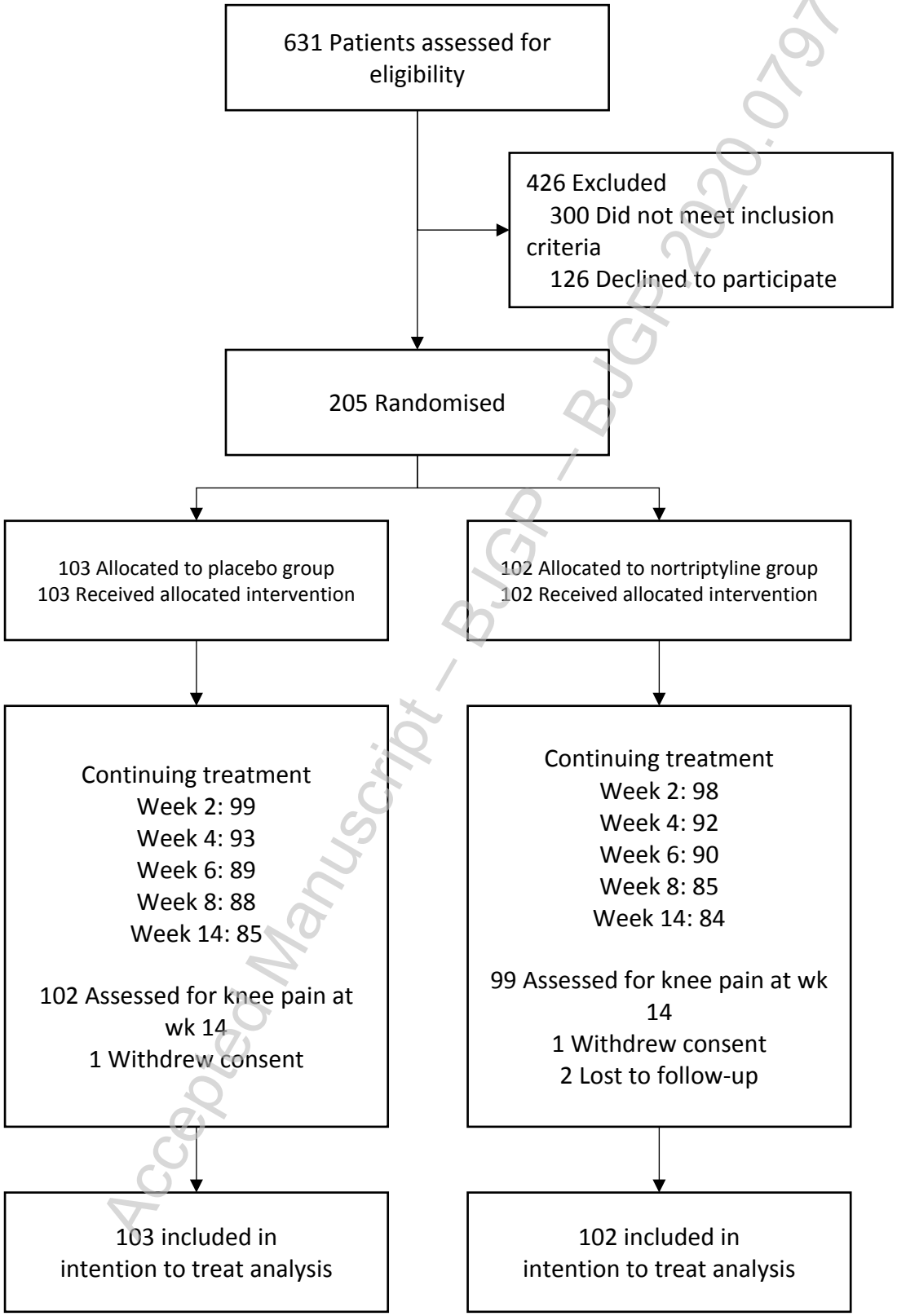

Table 1: Characteristics of study participants at baseline

	Placebo ***N=103***	**Nortriptyline** ***N=102***
Age	64.6 ± 10.3	64.4 ± 7.9
Male	42% (43)	43% (44)
Ethnicity *		
European	84% (87)	94% (96)
Māori	9% (9)	12% (12)
Other	11% (11)	5% (5)
BMI (kg/m^2)	31.3 ± 6.2	33.2 ± 5.7
Healthy (18 to < 25)	6% (6)	7% (7)
Overweight (25 to < 30)	47% (48)	20% (20)
Obese (30 +)	48% (49)	74% (75)
Years with knee OA	6.6 ± 7.1	8.5 ± 7.9
Use of assistive device	38% (39)	40% (41)
Chronic conditions	58% (60)	60% (61)

Data are presented as mean (SD) or (%) n.

*Ethnicity was self-identified. Participants could select more than one ethnicity, so totals may add to more than 100%.

Table 2. Primary and Secondary Continuous Outcomes

	Placebo (n = 103), mean (SD)			Nortriptyline (n = 102), mean (SD)			Baseline adjusted difference
	Baseline	14 weeks	Change	Baseline	14 weeks	Change	at 14 weeks, (95% CI) *p value*
Primary outcome							
WOMAC Pain	61.2 (12.5)	42.5 (24.0)	-18.7 (25.8)	60.2 (13.5)	36.0 (23.2)	-24.3 (22.5)	-6.15 (-12.56, 0.26) *0.06*
Secondary outcomes							
WOMAC Function	59.9 (14.8)	41.9 (24.2)	-18.0 (23.2)	62.8 (15.0)	39.6 (24.4)	-23.2 (21.5)	-4.35 (-10.48, 1.79) *0.16*
WOMAC Stiffness	61.2 (20.1)	47.2 (27.9)	-14.0 (29.5)	65.2 (20.3)	45.4 (27.4)	-19.9 (27.4)	-3.61 (-10.94, 3.72) *0.33*
Global VAS	72.6 (21.1)	53.6 (28.6)	-19.0 (33.0)	74.3 (20.2)	49.3 (30.8)	-25.0 (33.5)	-4.72 (-12.91, 3.46) *0.26*
Quality of Life							
Physical function	31.6 (9.9)	31.0 (10.1)	-0.6 (8.8)	29.9 (10.6)	31.9 (11.5)	2.0 (10.0)	2.02 (-0.39, 4.43) *0.10*
Role physical	39.7 (11.1)	39.7 (12.1)	-0.1 (11.5)	39.9 (11.0)	41.7 (11.9)	1.8 (11.9)	1.97 (-0.95, 4.88) *0.19*
Bodily pain	35.5 (7.5)	38.6 (8.8)	3.1 (9.4)	35.7 (8.1)	41.4 (10.0)	5.8 (8.8)	2.75 (0.42, 5.08) *0.02*
General health	46.1 (8.6)	46.7 (10.1)	0.6 (7.8)	47.4 (8.4)	47.4 (8.7)	0.1 (7.3)	-0.14 (-2.15, 1.88) *0.90*
Energy and vitality	47.1 (10.0)	47.1 (10.8)	0.0 (9.9)	46.2 (8.8)	46.8 (10.9)	0.6 (8.5)	0.29 (-2.15, 2.72) *0.82*
Social function	44.8 (11.4)	43.2 (13.5)	-1.6 (12.8)	44.7 (11.5)	45.0 (12.7)	0.4 (13.2)	1.87 (-1.40, 5.14) *0.26*
Role emotional	47.8 (11.4)	44.7 (12.9)	-3.1 (13.9)	47.3 (11.8)	46.0 (12.9)	-1.3 (11.8)	1.58 (-1.63, 4.79) *0.33*
Emotional well-being	52.1 (8.8)	51.7 (10.0)	-0.4 (8.9)	51.9 (9.1)	51.4 (10.9)	-0.6 (9.7)	-0.22 (-2.66, 2.21) *0.86*

All outcomes have been standardised to a range of 0 to 100. WOMAC and VAS 0 = Best possible outcome. QoL 100 = best possible outcome.

Table 3. Analgesic use by time and treatment group

Mean proportion of days when analgesic was not taken

	Placebo (n = 99)			Nortriptyline (n = 99)			
Analgesic	**Baseline**	**14 weeks**	**Difference**	**Baseline**	**14 weeks**	**Difference**	**Adjusted odds ratio**
Paracetamol	52.5%	57.6%	4.3%	53.0%	62.6%	9.1%	**1.55 (1.03 to 2.37)**
NSAID	66.6%	69.1%	4.1%	61.6%	73.9%	11.5%	**3.91 (2.49 to 6.16)**
Opioid	81.5%	82.8%	0.6%	76.9%	80.8%	4.6%	1.60 (0.86 to 2.99)

Mean standard analgesic tablet count on days when analgesic was taken

	Placebo (n = 99)			Nortriptyline (n = 99)			
Analgesic	**Baseline**	**14 weeks**	**Change**	**Baseline**	**14 weeks**	**Change**	**Adjusted rate ratio**
Paracetamol	4.2	4.2	0.0	3.6	3.5	-0.1	0.97 (0.92 to 1.03)
NSAID	6.4	6.1	-0.3	7.4	6.7	-0.7	**0.85 (0.80 to 0.90)**
Opioid	7.0	6.6	-0.4	5.9	6.8	0.9	0.98 (0.90 to 1.07)

One pill is defined as the equivalent of 500mg paracetamol, 200mg ibuprofen, or 15 mg codeine.

Table 4. Adverse events (SAE, overall and most common)

Event	Placebo (n = 102) *no. of patients (%)*	Nortriptyline (n = 99) *no. of patients (%)*	P Value
Serious adverse events			
Overall	3 (3%)	4 (4%)	0.72
Hospitalisation for lower back pain	1 (1%)	0	
Hospitalisation for atrial fibrillation	0	1 (1%)	
Life-threatening, myocardial infarction	0	1 (1%)	
Hospitalisation for epistaxis	0	1 (1%)	
Hospitalisation for renal calculi	1 (1%)	0	
Hospitalisation for lung infection	1 (1%)	0	
Hospitalisation for hyperglycaemia	0	1 (1%)	
Adverse events			
Antidepressant Side-Effect Checklist at week 14			
Any adverse events	88 (87%)	97 (99%)	p = 0.001
Largest differences			
Dry mouth	52 (51%)	86 (87%)	<0.001
Constipation	31 (30%)	58 (59%)	<0.001
Sweating	21 (21%)	31 (31%)	0.033
Sexual dysfunction	9 (9%)	17 (17%)	0.084
Headache	27 (26%)	14 (14%)	0.009
Diarrhoea	21 (21%)	11 (11%)	0.060

Each event is only recorded once per patient.