PARACETAMOL FOR ACUTE LOW BACK PAIN

MARCO SCHREIJENBERG

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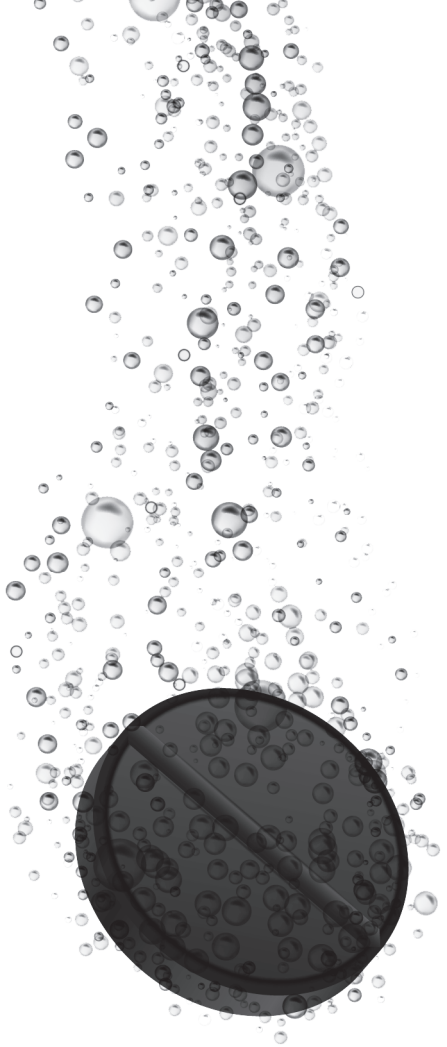

Chapter 1

General Introduction

LOW BACK PAIN: A GLOBAL HEALTH PROBLEM

Low back pain (LBP) is one of the most common musculoskeletal symptoms (1) as well as the leading cause of impaired physical functioning globally (2). In the Western world, 60 to 90% of all people will experience at least one episode of LBP in their life (3) and, at any given point in time, more than half a billion people worldwide experience LBP which limits their normal activities (4, 5). In the Netherlands, the incidence of LBP is 80 per 1000 patient years (6) and the prevalence is 101 per 1000 males and 135.6 per 1000 females (7); altogether, over 2 million people in Netherlands had spinal pain (back- and or neck pain) in the year 2017 (7). Both incidence and prevalence of LBP increase with age and the symptom occurs more often in women than in men (6). Half of all people with LBP visit their GP because of the pain (3, 8); in 2012, more than 1.5 million people sought care for LBP in Dutch general practice (3).

Generally speaking, the natural course of recent onset LBP is favorable: for the majority of patients, pain intensity quickly declines within the first month of follow-up (9). However, about a third of patients experience a new episode of LBP within a year (10, 11) and 19.6% of adults between 20 and 59 years old develop LBP with a duration of more than 12 weeks (known as chronic LBP) (12). The largest impact of LBP is related to this chronic subtype, because of impairment of physical functioning, which is highest in working age groups (2, 4). This in turn leads to productivity loss and work absenteeism, with high indirect costs of LBP as a result. In the Netherlands, the total costs associated with spinal pain were estimated at 1.3 billion euros in 2011, representing 1.5% of all Dutch health expenditures (7). In the United States, these costs were estimated to be 87.6 billion dollars in 2013 (13).

Specific pathologies of the lumbar spine that may cause LBP include, but are not limited to, vertebral fractures, axial spondyloarthritis, malignancy and infections (3, 4, 14); such causes are found in only a minority of patients presenting with LBP in primary care. Up to 90% of patients are labeled as having non-specific LBP (NSLBP), as no specific cause for their pain can be found (14-16).

ANALGESIC MEDICATION FOR LOW BACK PAIN

Analgesic medicines are ubiquitous in the management of LBP (17, 18). It is estimated that 55% of all patients with LBP use analgesics (19); in patients over 55 years of age, this percentage was found to be even higher at 72% (20). In the Netherlands in 2012, 985 LBP-related prescriptions occurred per 1000 LBP patients in general practice (8); this is similar to Australia, where 892 analgesics were recommended per 1000 spinal pain problems managed (21). In a survey in Swiss primary care, the most prescribed medications

for LBP were non-steroidal anti-inflammatory drugs (NSAIDs) (97.4% of respondents) and paracetamol (94.4%) (17). In 2012, 26% of Dutch LBP patients were prescribed NSAIDs; opioids were prescribed to 12% of patients (22). Very likely, this is only "the tip of the iceberg", as over-the-counter medication is also available to patients in many countries.

PARACETAMOL: THE RISE AND FALL OF A SUPERSTAR DRUG

Worldwide, the most used over-the-counter analgesic is paracetamol (also known as acetaminophen) (23, 24). Paracetamol forms the first step of the World Health Organization (WHO) pain ladder (25) and is widely recommended in many clinical practice guidelines for LBP (26). The first clinical results of paracetamol were published in 1893 by German physician Joseph von Mering (27), who claimed an adverse effect of paracetamol was methemoglobinemia (elevated blood levels of methemoglobin which may lead to dangerous tissue hypoxia). Because of this severe adverse effect and due to the introduction of the popular analgesic aspirin in 1899, paracetamol was essentially forgotten for half a century until a series of research articles was published in 1948 by British and American scientists, disputing Von Mering's claims and demonstrating that paracetamol could be suitable as an analgesic or antipyretic (28-30). Paracetamol came to the market in the 1950s in the United States and the rest is history: today, it is hard to imagine a household without paracetamol in the drug cabinet. In the UK, 200 million packs were sold over the counter in 2014 (31). Reflecting its wide use, the most appropriate unit to measure paracetamol sales may not be the milligram, but the ton (31): in the Netherlands, an average of nearly 200 tons of paracetamol is sold every year (557.6 tons of paracetamol sold between January 1st 2005 and December 31st 2007) (32). Although the working mechanism of paracetamol has long been the subject of debate, it is now accepted that the medicine is an inhibitor of the cyclooxygenase (COX) 1 and 2 enzymes, which effectively belong to the NSAID family (31, 33-35). Paracetamol used to be perceived as a harmless drug by both clinicians and patients (23, 36), but globally, paracetamol overdose is the number one cause of acute liver failure (37); furthermore, a systematic literature review of observational studies has shown that patients taking paracetamol also have an increased risk of gastro-intestinal, renal and cardiovascular side effects when compared to no paracetamol use (23).

Naturally, the potential benefits of all therapeutic interventions need to be carefully balanced with their potential harms; however, this is where a problem has arisen for paracetamol (31). Over the last decade, uncertainty has emerged regarding the efficacy of paracetamol for several health conditions, including: cancer pain (38), dysmenorrhea (39), tension-type headaches (40), migraine (41), post-operative pain (42), and arthritis (43, 44). Paracetamol was recommended as the first-choice analgesic for LBP in many

international guidelines (45), until the publication of results from the Paracetamol for Acute Low Back Pain (PACE) trial, the first large randomized placebo-controlled trial investigating the efficacy of paracetamol for the management of acute NSLBP (46).

THE PARACETAMOL FOR ACUTE LOW BACK PAIN (PACE) TRIAL

The PACE trial was conducted between 2009 and 2013 in Sydney, Australia (46, 47). In this randomized controlled trial (RCT), 1652 participants with a new episode of at least moderate intensity NSLBP (measured using an adaptation of item 7 of the 36-item Short Form Health Survey: "How much bodily pain have you had over the last four weeks?", scored from 'none' to 'very severe' (48)) were randomly allocated to receive paracetamol regularly, paracetamol as-needed or placebo until recovery from LBP or for a maximum of four weeks, whichever occurred first (46, 47). In the original trial analyses, there was neither a statistically significant nor a clinically relevant difference between paracetamol (whether taken regularly or as-needed for pain) and placebo for time until recovery from LBP, LBP intensity, physical functioning, health-related quality of life (HRQoL) and sleep quality (46). Based on this trial, a 2016 Cochrane systematic review concluded that there is high-quality evidence for no difference between paracetamol and placebo for pain relief and improvement of physical functioning at the immediate and short term follow-up (49).

Despite the fact that the PACE trial demonstrated that paracetamol had no effect on the outcomes of LBP as compared to placebo, it is still recommended for the treatment of acute LBP in Dutch general practice (3). Over the years, many countries have published clinical practice guidelines for the treatment of NSLBP in order to rationalize the organization and delivery of health care and to optimize treatment outcomes on a societal level (26, 45); the first of these guidelines was already published in 1987 (50). Although these guidelines share one body of evidence, differences may exist between the way this evidence is interpreted by policymakers in different countries. This leads to the first research question of this thesis:

1. **What are the similarities and differences between recommendations for pharmacotherapy of NSLBP from recent national clinical practice guidelines, and how do these recommendations compare to the best available evidence?**

Since the PACE trial is the first and only high-quality RCT that investigated the efficacy of paracetamol for acute NSLBP, evidence from this study is highly influential on clinicians and policymakers. Therefore, the reproducibility of the PACE results remains highly important, as early acceptance of results that cannot be reproduced, may lead to harms

in patients (51). Although reproducibility is one of the cornerstones of scientific research (52, 53), it is often an exception rather than a rule in clinical research. In recent years, reproducibility (or lack thereof) has attracted attention in psychology (54), basic science (55) and cancer research (56, 57). Following the 'new lexicon for research reproducibility' that was published by Goodman and colleagues in 2016, there are three types of reproducibility: methods reproducibility, results reproducibility and inferential reproducibility (58-60). A graphical representation of these different types of reproducibility is presented in Figure 1. In methods reproducibility, an analysis is reproduced using the same data, analysis plan and statistical code; the only difference is the data analyst (58-60). Results reproducibility refers to the collection of new data in the same population, followed by analysis using the same analysis plan (58-60); this type of reproducibility

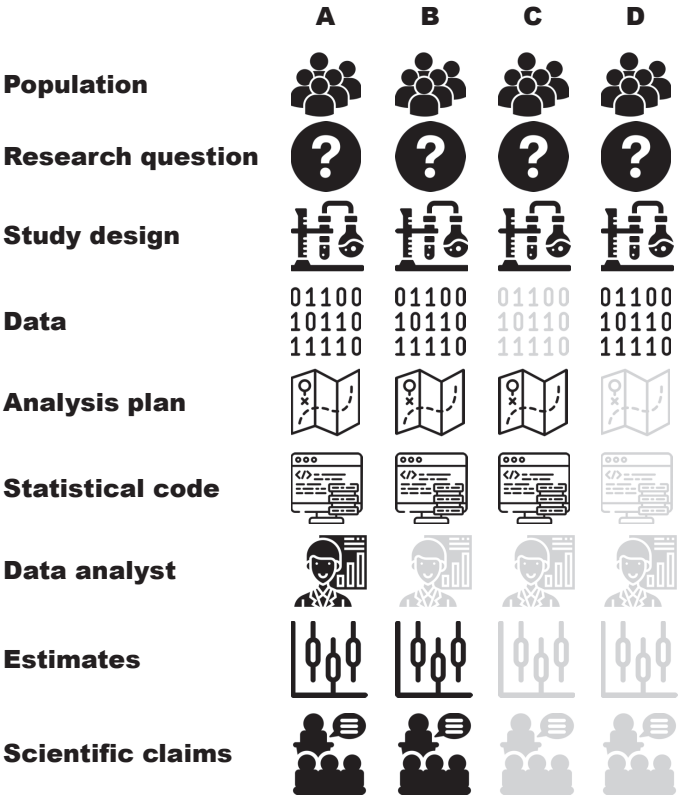

Figure 1: Different types of reproducibility in research according to Goodman's lexicon (58). Column A represents an original study. Columns B, C and D represent reproduction studies, with changes as compared to the original study represented in grey. Column A represents a methods reproduction study. Column B represents a results reproduction study (also known as a replication study). Column D represents an inferential reproduction study. Figure adapted from Patil and colleagues, BioRxiV 2017 (59). Icons made by Daniel Bruce, Eucalyp, Freepik and Smashicon from www.flaticon.com.

is also called 'replication'. Inferential reproducibility is defined as the making of new knowledge claims of similar strength from either a new data collection or a reanalysis of original data (58-60). In the PACE trial, methods reproduction was already performed (46), but results reproducibility and inferential reproducibility are important research priorities before paracetamol is completely dismissed as a treatment for acute LBP. This yields the following research questions related to reproducibility:

2. **Can the results of the PACE trial be reproduced in Dutch general practice?**
3. **Can the causal inferences made in the PACE trial be reproduced in an independent reanalysis of the original data?**

Apart from uncertainty regarding the reproducibility of the results of PACE, the conclusions of the PACE trial have been also been challenged stating non-compliance to treatment could have played a role in the results (61, 62). However, assessing the efficacy of an intervention in participants who comply with treatment is difficult using conventional statistical analysis techniques. In complier average causal effects (CACE) analysis, treatment compliers are compared to participants from the control group who, had they been randomized to the treatment group, would have complied to the intervention as well (so-called would-be compliers) (63-65). This analysis technique has been demonstrated to produce unbiased estimates for the treatment effect in compliers (65). This leads to the fourth research question:

4. **What is the efficacy of paracetamol for acute NSLBP in participants of the PACE trial who complied with the treatment regimen?**

It is already known that treatment outcomes in people with acute LBP are influenced by patient expectations and beliefs (66). Similarly, reporting adverse events (AEs) in PACE could be associated with reporting worse outcomes of LBP. This leads to the fifth and final research question of this thesis:

5. **Is there an association between reporting AEs and the outcomes of acute LBP in the PACE trial?**

THE AIM AND OUTLINE OF THIS THESIS

This thesis aims to strengthen the evidence about the efficacy of paracetamol for acute LBP in general practice. In order to answer the five research questions stated above, six research projects were conducted.

To investigate the similarities and differences between recommendations for pharmacotherapy of NSLBP from recent national clinical practice guidelines, a systematic literature review was conducted. In **Chapter 2**, an overview of recent clinical practice guidelines is presented and compared to the best available evidence regarding the efficacy of pharmacological treatments.

A new RCT to follow-up on the PACE trial (called the PACE Plus trial) was designed to assess if the results of PACE could be reproduced in Dutch general practice; an additional aim of this study was to compare the efficacy of paracetamol to that of diclofenac (an NSAID) and advice only. In **Chapter 3**, the study protocol of the PACE Plus trial is presented. The reality of doing research is that many projects take longer than expected, or are even cancelled completely because of feasibility issues (67). Unfortunately, this was also the case for the PACE Plus trial. Of course, there's only one thing more painful than learning from experience, and that is not learning from experience (Archibald Macleish, American poet). The discontinuation of the PACE Plus trial has therefore been transparently communicated, in the hope that future researchers in this field may avoid the problems that were encountered in this RCT. The results of this communication can be found in **Chapter 4**.

Three secondary analyses of original data collected in the PACE trial were conducted. To begin with, the first independent inferential reproduction analysis in the field of LBP research was conducted to investigate if the causal inferences made in the PACE trial were reproducible; the original researchers of the PACE trial had no influence on the aim, methods and conclusions. The results of this study are presented in **Chapter 5**. Second, the efficacy of paracetamol for acute LBP in participants who complied with the treatment regimen was investigated in **Chapter 6**, using a CACE analysis. Finally, the association between reporting AEs in PACE and outcomes of LBP was assessed in **Chapter 7**.

In **Chapter 8**, the most important findings of this thesis are summarized and the strengths and weaknesses are discussed. Furthermore, these findings are put in context of the current medical literature and finally, implications for clinical practice and unanswered questions for future research are debated.

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Chapter 2

Guideline recommendations on the pharmacological management of non-specific low back pain in primary care – is there a need to change?

Marco Schreijenberg, Bart W. Koes and Chung-Wei Christine Lin

Expert Rev Clin Pharmacol. 2019 Feb;12(2):145-157

ABSTRACT

Introduction

Analgesic drugs are often prescribed to patients with low back pain (LBP). Recommendations for non-invasive pharmacological management of LBP from recent clinical practice guidelines were compared with each other and with the best available evidence on drug efficacy.

Methods

Guideline recommendations concerning opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, antidepressants, anticonvulsants and muscle relaxants from national primary care guidelines published within the last 3 years were included in this review. For each pharmacotherapy, the most recent systematic review was included as the best available evidence on drug efficacy and common adverse effects were summarized.

Results

Eight recent national clinical practice guidelines were included in this review (from Australia, Belgium, Canada, Denmark, The Netherlands, UK and US). Guidelines are universally moving away from pharmacotherapy due to the limited efficacy and the risk of adverse effects. NSAIDs have replaced paracetamol as the first choice analgesics for LBP in many guidelines. Opioids are considered to be a last resort in all guidelines, but prescriptions of these medications have been increasing over recent years. Only limited evidence exists for the efficacy of antidepressants and anticonvulsants in chronic LBP. Muscle relaxants are one of the analgesics of first choice in the US, but aren't widely available and thus not widely recommended in most other countries.

Conclusions

Upcoming guideline updates should shift their focus from pain to function and from pharmacotherapy to non-pharmacologic treatment options.

INTRODUCTION

Low back pain (LBP) is one of the most prevalent musculoskeletal symptoms and the number one cause of disability worldwide (1, 2). Research into the natural course of LBP in the general population demonstrated that recent onset LBP often improves rapidly during the first 2 months of follow up (3). However, the one-year risk of recurrence is estimated to be around 33% (2, 4, 5). Furthermore, 19.6% of all adults between 20 and 59 develop chronic LBP (i.e. LBP with a duration of more than 12 weeks), which is responsible for a high burden due to disability as well as high cost due to direct medical costs, and indirect costs due to work absenteeism and loss of productivity (6). In up to 99% of patients presenting with LBP in primary care, no specific nociceptive source for their complaints is found. These patients are often labeled as having non-specific LBP (NSLBP), which is essentially a basket term for LBP without a known cause (7, 8).

Many LBP patients use analgesics for symptom relief (9). Over recent years, there has been an increase in the prescription of opioids, antidepressants and anticonvulsants for back pain in primary care (10). Estimates of analgesic usage in LBP range from 55% (11) to 72% in elderly patients (age >55 years) (12). A recent Australian study reported analgesics were recommended at a rate of 892.2 per 1000 spinal pain problems managed between 2013 and 2014 (10). Findings from this study showed that the noninvasive pharmacological options that were most often prescribed in primary care were (in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014): opioids (277.2 recommendations), non-steroidal anti-inflammatory drugs (NSAIDs; 165.9 recommendations), simple analgesics such as paracetamol (acetaminophen; 137.2 recommendations), antidepressants and anticonvulsants (76.2 recommendations) and muscle relaxants (<106.1 recommendations, in the category 'other medicine group') (10). Invasive pharmacological options for the treatment of LBP include epidural, spinal, facet joint or sacroiliac analgesic or corticosteroid injections; however, these therapies are not commonly used in primary care and will therefore not be discussed in this review.

In order to rationalize care, many countries have developed and issued clinical practice guidelines containing recommendations for the diagnosis and treatment of LBP (including tools for the recognition of specific causes of LBP and recommendations for the management of NSLBP) (13); the first of these guidelines was published in 1987 by the Quebec Task Force on Spinal Disorders (14). During recent years, many national guidelines for the management of LBP in primary care have been updated. The main aims of this review are twofold: first, to compare the recommendations for pharmacological treatment of NSLBP in primary care between recently published national guidelines and second, to compare these guideline recommendations with best available evidence regarding the efficacy of pharmacological treatments. A secondary aim of this review is to summarize the most common adverse effects (AEs) of noninvasive pharmacological treatments in NSLBP in primary care.

METHODS

This review focuses on recent clinical practice guidelines for the management of NSLBP in primary care and recent (Cochrane) systematic reviews and meta-analyses of randomized controlled trials (RCTs) about noninvasive pharmacological treatment of NSLBP. The search for clinical guidelines was conducted using the following databases: PubMed (key words: low back pain, clinical guidelines), National Guideline Clearinghouse (www.guideline.gov, keyword: low back pain), National Institute for Health and Care Excellence (NICE) (www.nice.org.uk, key word: low back pain) and Physiotherapy Evidence Database (PEDro) (key words: low back pain, guideline). Furthermore, the contents and reference lists of reviews of guidelines were hand searched. Clinical practice guidelines had to meet the following inclusion criteria: (1) the main topic of the guideline was the management of LBP (recommendations regarding the management of sciatica will not be considered), (2) the guideline concerns the primary care setting, (3) the guideline provides recommendations for pharmacotherapy in NSLBP, and (4) the guideline was written in English, German or Dutch as these languages could be read by the reviewers. Guidelines published before January 1st 2016 were not considered to be recent and were excluded from this review. One guideline was included per country. Clinical practice guidelines from the following countries and agencies were included in this review:

- Australia, New South Wales Agency for Clinical Innovation (2016) (15)
- Belgium, Belgian Health Care Knowledge Centre (KCE) (2017) (16)
- Canada, Institute of Health Economics (IHE) (2017) (17)
- Denmark, Danish Health Authority (DHA) (2018) (18)
- Germany, German Association for Quality Assurance in Medicine (ÄZQ) (2017) (19)
- The Netherlands, Dutch College of General Practitioners (NHG) (2017) (20)
- United Kingdom (UK), NICE (2017) (21)
- United States (US), American College of Physicians (ACP) (2017) (22)

Efficacy of pharmacological treatments

Based on the recent study by Mathieson et al (10), we identified the following six pharmacological treatments of NSLBP (in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014): (1) opioids, (2) NSAIDs, (3) paracetamol, (4) antidepressants, (5) anticonvulsants and (6) muscle relaxants. To obtain evidence regarding the efficacy of these treatments, we started by hand-searching the reviews of the Cochrane Back and Neck Group (back.cochrane.org) for all Cochrane reviews and meta-analyses concerning these pharmacological treatments published until May 2018. Six Cochrane reviews and meta-analyses were found in this search (23-28).

An additional search for systematic reviews and meta-analyses published since the above Cochrane reviews was performed in Medline Ovid, PubMed and Embase. Key-

words used for the searches were low back pain and name of the pharmacotherapy, e.g. "low back pain" AND paracetamol. For each pharmacological treatment, the most recent review was selected. Six additional studies were found during this search (29-34).

Next, we determined which articles would be used as best available evidence. For each of the five pharmacological treatments, we chose the most recent review available. For the final selection of systematic reviews, see Box 1.

MS and CL independently scored the quality of the all reviews included for efficacy of the five pharmacological treatments based on the additional search using the AMSTAR 2 tool, a validated critical appraisal tool for systematic reviews (35). This checklist consists of 16 questions that can be answered with Yes, Partial Yes, No or Other. Systematic reviews scoring at least 8 out of 16 items with 'Yes' were considered to have adequate quality for inclusion; systematic reviews scoring 7 or less out of 16 were excluded from the review and replaced by an older available systematic review on the same pharmacological treatment. A consensus meeting was held to discuss articles about which there was disagreement between the reviewers. In case a consensus could not be reached, a third independent reviewer (BK) made the final decision whether or not to include the article into the review.

In order to summarize the most common AEs of noninvasive pharmacological treatments for NSLBP in primary care, we searched for evidence about safety and AEs (observational studies and systematic reviews) in Medline Ovid, PubMed and Embase. Keywords used for the searches were combinations of the name of the pharmacotherapy and the extra keywords "safe" or "adverse", e.g. paracetamol AND safe* OR adverse.

Quality of evidence

All included systematic reviews in Box 1 scored at least 8 out of 16 questions of the AMSTAR 2 tool with 'Yes' and were thus considered to have adequate quality for inclusion in this review.

Box 1: Final selection of systematic reviews

Opioids	Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis (2016) (29).
NSAIDs	Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis (2017) (34).
Paracetamol	Paracetamol for low back pain (2016) (26).
Antidepressants	Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline (2017) (30).
Anticonvulsants	Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials (2017) (31).
Muscle relaxants	Efficacy and tolerability of muscle relaxants for low back pain: Systematic review and meta-analysis (2017) (32).

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NSLBP: Non-Specific Low Back Pain.

RESULTS

Pharmacotherapy recommendations in guidelines

Eight recent national clinical practice guidelines were included in this review (from Australia, Belgium, Canada, Denmark, Germany, The Netherlands, UK and US). Recommendations for each of the pharmacological treatments are summarized in tables (Table 1-6); each pharmacological treatment is discussed separately below in order of descending recommendation rate per 1000 spinal problems managed between 2013 and 2014 (10), preceded by a general section describing the recommendations of the different national guidelines regarding commencement of pharmacotherapy in NSLBP.

Recommendations regarding the initiation of pharmacotherapy for NSLBP in primary care

Variations exist between clinical practice guidelines on when to consider commencing pharmacological management for LBP in primary care. Five guidelines (Australia, Belgium, Canada, The Netherlands and the UK) present pharmacotherapy as a treatment option that may be considered if required by the patient. Both the Dutch and German guideline specifically mention that analgesics are only used to support patients to return to their usual activities.

The guidelines from Denmark and the US are more hesitant in recommending the prescription of analgesics to patients with LBP: the Danish guideline states that physicians should only prescribe pain medication after careful consideration, while the American guideline specifically recommends selecting non-pharmacological treatment with superficial heat, massage, acupuncture or spinal manipulation over pharmacological treatment options.

Guideline recommendations and best available evidence regarding opioids

An overview of guideline recommendations related to opioids for NSLBP is presented in Table 1. Guidelines universally recommend avoiding opioids, specifically stating that the prescription of opioids should only be considered in case other treatment options have been contra-indicated, have not been tolerated or have failed to reduce pain. The Canadian and German guidelines mention reassessment of patients to whom opioids have been prescribed; the latter mentions this should happen with intervals no longer than four weeks. Duration of opioid treatment in acute LBP was mentioned in two guidelines (Canada and The Netherlands); The Canadian guideline reports a period of less than one or two weeks while the Dutch guideline reports a maximum of five days. The Belgian guideline states no specific period but instead mentions opioids should be used for acute LBP for the shortest period possible.

Table 1: Guideline recommendations concerning opioids for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Think about weak opioids (with or without paracetamol) for the shortest period possible for managing acute low back pain with or without radicular pain only if an NSAID is contraindicated, not tolerated or has been ineffective. • Do not routinely offer opioids for managing chronic low back pain with or without radicular pain.
Canada (2017)	• Cautious and responsible use of opioids should only be considered for carefully selected patients with severe acute pain not controlled with acetaminophen and NSAIDs, at a minimum effective dose only for a limited period of time, usually less than one to two weeks. • Ongoing need for opioids is an indication for reassessment. • Evidence is lacking for long-term use of opioids for chronic low back pain. However, there is some evidence of the benefit of opioids for short-term pain and function improvements. • Long-term use of opioids should only follow an unsuccessful trial of non-opioid analgesics. In severe chronic pain, strong opioids require careful consideration. • Long-acting opioids are preferred as they can establish a steady state blood and tissue level that may minimize the patient's experience of unsteady dosing (cyclical improvement and/or withdrawal) from short-acting opioids. Any use of opioids over the long term will lead to physical dependence. • Avoid escalating doses above 50 mg/day if initiating, and above 90 mg/day oral morphine equivalent for ongoing use. • Careful attention to incremental improvements in pain or function is required to justify ongoing use of opioids. Because little is known about the long-term effects of therapy it should be monitored carefully. • A history of addiction is a relative contraindication. Consultation with an addictions specialist may be helpful in these cases.
Denmark (2018)	• Do only offer patients with recent onset LBP opioids in addition to usual care after careful consideration, as the evidence points towards no short-term effect.
Germany (2017)	• Opioid drugs can be a treatment option for acute non-specific low back pain if non-opioid analgesics are contraindicated or have been found to be ineffective in the individual patient. • The indication for opioid drugs should be regularly reassessed at intervals of no longer than 4 weeks. • [opioids] can be used to treat chronic non-specific low back pain for 4 to 12 weeks initially. • If this brief period of treatment brings about a relevant improvement in the patient's pain and/or subjective physical impairment, while causing only minor or no side effects, then opioid drugs can also be a long-term therapeutic option.
The Netherlands (2017)	• Prescribe opioids only to patients with severe acute low back pain, for whom weaker analgesics were ineffective. Inform patients about the side-effects of opioids and minimize duration of treatment, to a maximum of five days. • Prescribe opioids only to patients with chronic non-specific low back pain who experience severe disability, in order to support stepwise increase of activity. Minimize duration of treatment, to a maximum of one to two weeks.

Table 1: Guideline recommendations concerning opioids for non-specific low back pain (continued)

Guideline	Recommendations
UK (2017)	• Do not routinely offer opioids for managing acute low back pain. • Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective. • Do not offer opioids for managing chronic low back pain.
US (2017)	• Opioids should be the last treatment option considered and should be considered only in patients for whom other therapies have failed because they are associated with substantial harms.
Best available evidence	**Main findings**
Efficacy, Tolerability, and Dose-Dependent Effects of Opioid Analgesics for Low Back Pain: A Systematic Review and Meta-analysis. (2016)	• For people with chronic low back pain who tolerate the medicine, opioid analgesics provide modest short-term pain relief but the effect is not likely to be clinically important within guideline recommended doses. • Evidence on long-term efficacy is lacking. • The efficacy of opioid analgesics in acute low back pain is unknown.

LBP: low back pain; mg: milligrams; NSAID: non-steroidal anti-inflammatory drug; UK: United Kingdom; US; United States of America.

For chronic LBP, recommendations concerning opioid prescription are presented with hesitation in nearly all guidelines. The British guideline recommends not prescribing opioids at all for patients with chronic LBP, while the Belgian, Canadian, Dutch and American guidelines advise caution but are generally less strict. The German guideline recommends the use of opioids for the treatment of chronic LBP. The guideline from Canada has by far the most comprehensive recommendations: even the use of long-acting versus short-acting opioids and specific doses for oral morphine are mentioned. Furthermore, this is the only guideline specifically discussing addiction in its recommendations. The Australian guideline only states that opiates are usually less effective for neuropathic pain than other analgesics; for this reason, no recommendation on the prescription of opioids was included in this review.

Duration of opioid treatment in chronic LBP was mentioned in two guidelines (Germany and The Netherlands); the Dutch guideline limits the use of opioids to a maximum of one to two weeks, while the German guideline suggests an initial treatment period of four to 12 weeks, stating that opioid treatment may be continued in the long term if patients experience a relevant improvement in pain or impairments and have only minor or no AEs. The guideline from Denmark only concerns acute LBP and thus presents no recommendations for the use of opioids in chronic LBP.

The 2016 review about opioids for both acute and chronic LBP was considered to be the best available evidence (29). For acute LBP, the efficacy of analgesics remains unknown, as no placebo-controlled trials enrolled patients with acute LBP (29). The review presented moderate-quality evidence that opioids have a small short-term effect on pain (mean difference of 10.1 points on a 100-point pain scale, 95% Confidence Interval (CI) 7.4-12.8 points) (29); however, the authors reported large numbers of patients withdrawing from trials because of AEs or lack of efficacy (29). No trials investigated long term effects (29).

Apart from the aforementioned drug dependence, common AEs of opioids are nausea, dizziness, constipation, vomiting, somnolence, dry mouth and an increased risk of falling and fractures; the risk ratio of experiencing any AE in short term opioid use was found to be 1.4 when compared to placebo (36-38). Furthermore, patients who use opioids for a longer period of time may experience depression and sexual dysfunction (38); meanwhile, patients attempting to stop taking opioids after prolonged use may develop a withdrawal syndrome (with symptoms including agitation, insomnia, diarrhea, rhinorrhea, piloerection and hyperalgesia) (38). Risks of misuse (estimated rates 21-29%, 95% CI 13-38%) and of developing drug-dependence (estimated rates 8-12%, 95% CI 3-17%) have been demonstrated in patients with chronic non-cancer pain (such as LBP) (39).

Guideline recommendations and best available evidence regarding non-steroidal anti-inflammatory drugs (NSAIDs)

An overview of guideline recommendations related to NSAIDs for NSLBP is presented in Table 2. All guidelines recommend NSAIDs for acute LBP; for the guidelines that recommended against the use of paracetamol, NSAIDs are the analgesic of first choice except in the US, where physicians are advised to choose between NSAIDs and skeletal muscle relaxants (SMRs) based on patient preferences and risk profiles. The Danish guideline is the only guideline stating that no effect on LBP is expected of NSAIDs; in the Dutch guideline, it is stated that NSAIDs are not expected to be more effective than paracetamol for LBP.

Cyclo-oxygenase 2 inhibitors (COX-2-inhibitors) are mentioned in the Australian, Canadian, German and American guidelines. The Australian and German guidelines recommend considering contra-indications of COX-2-inhibitors when prescribing them. The guideline from the US does not make a recommendation about prescribing COX-2-inhibitors, as they were not assessed for their effect on pain or function. The Canadian guideline only mentions COX-2-inhibitors in the context of the prescription of proton pump inhibitors (PPIs) to those using NSAIDs over 45 years of age.

Only the Canadian and American guidelines specifically mention chronic LBP. The guideline from Canada recommends paracetamol and NSAIDs for both acute and chronic LBP. The guideline from the US states that in patients with chronic LBP, NSAIDs had a

small to moderate effect on pain and no effect on function, but should be the first option considered nonetheless.

A 2017 review on the effects of NSAIDs for LBP and neck pain (together referred to as 'spinal pain') concluded that although NSAIDs are effective for pain reduction when compared to placebo, differences between NSAIDs and placebo were not clinically relevant (34). In acute LBP, NSAIDs were associated with small improvements in pain intensity within 2 weeks (immediate term) when compared to placebo (mean difference 6.4 points on a 100-point pain scale, 95% CI 2.5 – 10.3 points); furthermore, the short term effects of NSAIDs on pain (follow-up duration 2 weeks to 3 months) were non-significant when compared to placebo (mean difference 1 point on a 100-point pain scale, 95% CI -3.9 – 5.9 points). In chronic LBP, NSAIDs were associated with significant results on pain relief when compared to placebo at both the immediate term (mean difference 11.1 points on a 100-point pain scale, 95% CI 8.4 – 13.8 points) and short term (mean difference 9.8 points on a 100-point pain scale, 95% CI 7.0 – 12.7 points)(34).

For disability, this review found NSAIDs had a significant effect on disability when compared to placebo in patients with acute LBP at the immediate term (mean difference 7.1 points on a 100-point disability scale, 95% CI 1.9 – 12.4 points) but no difference at the short term (mean difference 0.4 on a 100-point disability scale, 95% CI -4.5 – 5.4 points). In chronic LBP, NSAIDs were associated with small but significant differences in disability when compared to placebo at both the immediate term (mean difference 8.4 on a 100-point disability scale, 95% CI 6.3 – 10.6 points) and the short term (mean difference 7.9 on a 100-point disability scale, 95% CI 4.0 – 11.8 points)(34). Furthermore, the risk of gastro-intestinal AEs was reported to have increased 2.5 times (risk ratio; 95% CI 1.2 – 5.2) for those using NSAIDs when compared to placebo; however, observational studies rather than randomized trials are suited to study the prevalence of AEs of medication.

Use of all NSAIDs (both conventional and COX-2-inhibitors) leads to an increased risk of cardiovascular disorders (such as myocardial infarction, cerebrovascular events and heart failure; increase in overall cardiovascular risk of 35-40% for all NSAIDs except naproxen when compared to placebo) (37, 40, 41). Gastro-intestinal AEs are also common (41), but may be avoided by simultaneously prescribing PPIs (42). All but the Danish guidelines directly alert their readers to the risk of AEs when using NSAIDs. The four guidelines that recommend NSAIDs as first choice analgesic (Belgium, Germany, UK and US) all state that NSAIDs should be prescribed in the lowest effective dose and for the shortest possible period of time. The Canadian guideline is the only document that recommends the use of PPIs to all patients over 45 years of age using NSAIDs. Only the guideline from The Netherlands mentions dermal NSAIDs as an alternative to oral NSAIDs in order to avoid systemic AEs.

Table 2: Guideline recommendations concerning NSAIDs for non-specific low back pain

Guideline	Recommendations
Australia (2016)	• NSAIDs are recommended for reducing pain for short periods. However, assessment for contraindications is required before prescribing NSAIDs. These include severe hypertension, renal disease, previous gastrointestinal haemorrhage and current corticosteroid use. The lower incidence of gastrointestinal side effects must be balanced with increased cardiovascular risks associated with some CoX-2 NSAIDs (Cyclo-oxygenase 2 inhibitors are anti-inflammatory medications that have lower gastrointestinal side effects when compared to other NSAIDs).
Belgium (2017)	• If a medication is required for managing low back pain with or without radicular pain (e.g. due to severity of the pain and patients' preferences), consider oral NSAIDs taking into account potential differences between NSAIDs in gastrointestinal, liver and cardio-renal toxicity and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of the evolution of risk factors, and the use of gastro protective treatment. • When prescribing oral NSAIDs for low back pain, select the lowest effective dose for the shortest possible period of time.
Canada (2017)	• Acute low back pain: Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. • Chronic low back pain: Recommend acetaminophen and NSAIDs. • A proton pump inhibitor (PPI) should be considered for patients over 45 years of age when using an oral NSAID/COX-2 inhibitor.
Denmark (2018)	• Do only offer patients with recent onset LBP NSAIDs in addition to usual care after careful consideration, as the evidence points towards no short-term effect
Germany (2017)	• To minimize side effects NSAIDs should be given in the lowest effective dose and for the shortest possible time. • Considering the contraindications, COX-2-inhibitors can be used if NSAIDs are contraindicated or poorly tolerated (off-label-use).
The Netherlands (2017)	• NSAIDs are not expected to be more effective than paracetamol for low back pain. • Dermal NSAIDs may be considered as an alternative to oral NSAIDs. Dermal NSAIDs have fewer systemic side-effects and may therefore be also used in elderly people with reduced renal function or heart failure (given their skin is intact).
UK (2017)	• Consider oral non-steroidal anti-inflammatory drugs (NSAIDs) for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age. • When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment. • Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.

Table 2: Guideline recommendations concerning NSAIDs for non-specific low back pain (continued)

Guideline	Recommendations
US (2017)	• We recommend that the choice between NSAIDs and SMRs be individualized on the basis of patient preferences and likely individual medication risk profile. • Clinicians should therefore assess renovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend the lowest effective doses for the shortest periods necessary. • Although they are associated with lower risk for adverse effects than nonselective NSAIDs, COX-2–selective NSAIDs were not assessed for improvement in pain or function. • Pharmacologic therapy should be considered for patients with chronic low back pain who do not improve with nonpharmacologic interventions. Nonsteroidal anti-inflammatory drugs had a small to moderate effect on pain (moderate-quality evidence) and no to small effect on function (low-quality evidence) and should be the first option considered. • Moderate-quality evidence showed no difference in pain improvement when different NSAIDs were compared with one another.
Best available evidence	Main findings
Non-steroidal anti-inflammatory drugs for spinal pain: a systematic review and meta-analysis. (2017)	• NSAIDs reduced pain and disability, but provided clinically unimportant effects over placebo. • Six participants (95% CI 4 to 10) needed to be treated with NSAIDs, rather than placebo, for one additional participant to achieve clinically important pain reduction. • When looking at different types of spinal pain, outcomes or time points, in only 3 of the 14 analyses were the pooled treatment effects marginally above our threshold for clinical importance. • NSAIDs increased the risk of gastrointestinal reactions by 2.5 times (95% CI 1.2 to 5.2), although the median duration of included trials was 7 days.

CI: confidence interval; COX-2: Cyclo-oxygenase 2; LBP: low back pain; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; UK: United Kingdom; US; United States of America.

Guideline recommendations and best available evidence regarding paracetamol

An overview of guideline recommendations related to paracetamol (acetaminophen) for NSLBP is presented in Table 3. Four out of eight included guidelines recommend paracetamol for acute LBP (Australia, Canada, Denmark and The Netherlands). In both the Australian and Danish guideline, this recommendation is accompanied by a statement that paracetamol has no short-term effect. The Belgian, German, British and American guidelines recommend against the use of paracetamol in acute LBP. Only the Canadian and German guidelines specifically mentioned chronic LBP; in the former, the use of paracetamol is recommended in chronic LBP while the latter advises against using this pharmacological treatment for patients with either acute or chronic LBP.

The 2016 Cochrane review concluded that there is no significant difference between paracetamol and placebo for pain, quality of life, function, impression of recovery, sleep

Table 3: Guideline recommendations concerning paracetamol for non-specific low back pain

Guideline	Recommendations
Australia (2016)	• Regular paracetamol is recommended for acute LBP. However, both clinician and patients should be mindful that a recent trial demonstrated it was no more effective than a placebo plus 'best evidence education'. • If during the course of treatment, patients find that paracetamol is not helping, then cessation and review for additional analgesia, such as non-steroidal anti-inflammatory drugs (NSAIDs), is suggested.
Belgium (2017)	• Do not routinely offer paracetamol (as single medication) for managing low back pain with or without radicular pain.
Canada (2017)	• Acute low back pain: Prescribe medication, if necessary, for pain relief preferably to be taken at regular intervals. First choice acetaminophen; second choice NSAIDs. • Chronic low back pain: Recommend acetaminophen and NSAIDs.
Denmark (2018)	• Do only offer patients with recent onset LBP paracetamol in addition to usual care after careful consideration, as the evidence points towards no short-term effect.
Germany (2017)	• In the light of new evidence, paracetamol (= acetaminophen) should no longer be used. In comparison to placebo, the use of this drug did not lead to any improvement in pain or functional ability in patients with either acute or chronic non-specific low back pain.
The Netherlands (2017)	• Paracetamol may be prescribed regularly or as-needed; there is no difference in effectiveness. • NSAIDs are not expected to be more effective than paracetamol for low back pain.
UK (2017)	• Do not offer paracetamol alone for managing low back pain.
US (2017)	• The updated evidence showed that acetaminophen was not effective at improving pain outcomes versus placebo. […] we recommend against these drugs for treatment of acute low back pain.
Best available evidence	**Main findings**
Paracetamol for low back pain (Cochrane review, 2016)	• For acute LBP, there is high-quality evidence for no difference between paracetamol (4 g per day) and placebo at 1 week (immediate term), 2 weeks, 4 weeks, and 12 weeks (short term) for the primary outcomes. • There is high-quality evidence that paracetamol has no effect on quality of life, function, global impression of recovery, and sleep quality for all included time periods. • There were also no significant differences between paracetamol and placebo for adverse events, patient adherence, or use of rescue medication. • For chronic LBP, there is very low-quality evidence (based on a trial that has been retracted) for no effect of paracetamol (1 g single intravenous dose) on immediate pain reduction. • Finally, no trials were identified evaluating patients with subacute LBP.

LBP: low back pain; g: grams; NSAID: non-steroidal anti-inflammatory drug; UK: United Kingdom; US; United States of America.

quality, AEs, patient adherence and rescue medication in patients with acute LBP (26). There is low quality evidence for no effect of paracetamol in chronic LBP (26).

Paracetamol is generally perceived as safe, but this perception may be misguided (43, 44). Although severe AEs of paracetamol are relatively rare, paracetamol remains the leading cause of acute liver failure worldwide and overdosing may lead to severe liver damage and even death (37, 45). Apart from hepatotoxicity, a review of observational studies suggests that paracetamol may be associated with an increased risk of cardiovascular, gastrointestinal and renal AEs (respective risk ratios 1.19 – 1.68, 1.11 – 1.49 and 1.40 – 2.19) (44).

Guideline recommendations and best available evidence regarding antidepressants

An overview of guideline recommendations related to antidepressants for NSLBP is presented in Table 4. The American, British and Dutch guidelines recommend against prescribing antidepressants for LBP. It is stated in the Canadian guideline that insufficient evidence exists to recommend antidepressants or for acute LBP. For those with chronic LBP with or without leg pain, this guideline suggests TCA's may have a small to moderate effect on pain. The guideline from Belgium advises against prescribing antidepressants to patients with acute LBP and against prescribing selective serotonin reuptake inhibitors (SSRIs) for those with chronic LBP, but keeps the prescription of tricyclic antidepressants (TCAs) or selective serotonin and noradrenalin reuptake inhibitors (SNRIs) for patients with chronic LBP open for consideration. The Danish and German guidelines make no recommendations for or against prescribing antidepressants in LBP; the Australian guideline only makes recommendations about antidepressants for those with neuropathic pain; for this reason, these recommendations were not included in this review.

The recent systematic review on pharmacologic therapies for low back pain was considered to be the best available evidence for the prescription of antidepressants for LBP in primary care (30). The effects of antidepressants were not evaluated in patients with acute LBP (30). For antidepressants in chronic LBP, no difference in the effect on pain was found between TCAs and SSRIs and placebo (30); antidepressants were not associated with reduced depression or improved function in patients with chronic LBP (30). Small but significant effects were found for duloxetine, an SNRI (30).

The AEs of antidepressants have been summarized in a recent review and meta-analysis (46). This study found that dry mouth, dizziness, nausea, headache and constipation were most often reported by patients; the overall risk ratios for AEs ranged from 1.06 for milacipran to 3.78 for fluoxetine (46).

Table 4: Guideline recommendations concerning antidepressants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer selective serotonin reuptake inhibitors (SSRI) for managing low back pain with or without radicular pain. • Do not routinely offer tricyclic antidepressants or non-selective serotonin–norepinephrine reuptake inhibitors (SNRI) for managing low back pain with or without radicular pain. This recommendation is applicable only for chronic pain; the use of antidepressants is not recommended in acute pain.
Canada (2017)	• Acute low back pain: There is insufficient evidence to recommend for or against analgesic antidepressants such as amitriptyline, other tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors (SNRIs) for acute low back pain with or without leg dominant pain. • Chronic low back pain: Tricyclic antidepressants amitriptyline and nortriptyline may have a small to moderate effect for chronic low back pain with or without leg dominant pain at much lower doses than might be used for depression.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• The use of neuropathic pain medication, such as anti-depressants and anti-convulsants, is not recommended for the reduction of pain.
UK (2017)	• Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain.
US (2017)	• Moderate-quality evidence showed that TCAs did not effectively improve pain or function (low-quality evidence) in patients with chronic low back pain, which is contrary to the 2007 guideline. In addition, moderatequality evidence showed that SSRIs did not improve pain.
Best available evidence	**Main findings**
Antidepressants: Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline (2017)	• No trial evaluated antidepressants or antiseizure medications for acute low back pain. • For chronic low back pain, no significant difference was found in pain between tricyclic antidepressants or selective serotonin reuptake inhibitors and placebo. • Antidepressants were not associated with reduced depression or improved function. • Small but significant effects were found for the serotonin norepinephrine reuptake inhibitor (SNRI) duloxetine when compared to placebo.

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; UK: United Kingdom; US; United States of America.

Table 5: Guideline recommendations concerning anticonvulsants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer anticonvulsants for managing low back pain with or without radicular pain in absence of a neuropathic pain component.
Canada (2017)	• Acute low back pain: There is insufficient evidence to recommend for or against anticonvulsants (gabapentin, topiramate) for acute low back pain with or without leg dominant pain.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• The use of neuropathic pain medication, such as anti-depressants and anti-convulsants, is not recommended for the reduction of pain.
UK (2017)	• Do not offer anticonvulsants for managing low back pain.
US (2017)	-
Best available evidence	**Main findings**
Anticonvulsants: Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials (2017)	• Existing evidence on the use of gabapentinoids in CLBP is limited and demonstrates significant risk of adverse effects without any demonstrated benefit. • Given the lack of efficacy, risks, and costs associated, the use of gabapentinoids for CLBP merits caution.

CLBP: chronic low back pain; UK: United Kingdom; US; United States of America.

Guideline recommendations and best available evidence regarding anticonvulsants

An overview of guideline recommendations related to anticonvulsants for NSLBP is presented in Table 5. The Belgian, British and Dutch guidelines recommend against using anticonvulsants. It is stated in the Canadian guideline that insufficient evidence exists to recommend anticonvulsants for acute LBP; no recommendation is made in this guideline about the prescription of anticonvulsants in chronic LBP. The Danish and German guidelines make no recommendations for or against prescribing anticonvulsants in

LBP. The guideline from the US does not make a clear recommendation on the use of anticonvulsants either; however, it is mentioned elsewhere in the guideline document that insufficient evidence exists to make a recommendation about using anticonvulsants in LBP. The Australian guideline only makes recommendations about anticonvulsants for those with neuropathic pain; for this reason, these recommendations were not included in this review.

A systematic review of the commonly used anticonvulsants gabapentin and pregabalin concluded that the existing evidence for the efficacy of these drugs for chronic LBP is limited, while they are associated with substantial risk of AEs as well as high costs (31).

When compared with placebo, patients using gabapentin were more likely to report dizziness (risk ratio 1.99), fatigue (risk ratio 1.85), difficulties with mentation (risk ratio 3.34) and visual disturbances (risk ratio 5.72) (37, 47).

Guideline recommendations and best available evidence regarding muscle relaxants

An overview of guideline recommendations related to muscle relaxants for NSLBP is presented in Table 6. There are significant variations between guidelines in their recommendations on the prescription of muscle relaxants for LBP. The guidelines from Belgium and The Netherlands recommend against prescribing muscle relaxants in LBP. The Canadian guideline only recommends the prescription of muscle relaxants to patients with acute LBP in which pain reduction could not be achieved with paracetamol or NSAIDs. For chronic LBP, the guideline from Canada states that skeletal muscle relaxants (SMRs) may be appropriate for symptomatic relief in selected patients.

Meanwhile, the American guideline recommends SMRs as one of its first choice analgesics, together with NSAIDs; the document states that the choice between NSAIDs and SMRs should be made based on patient preferences and risk profiles. This guideline does warn clinicians for the AEs associated with SMRs.

The Australian, British, Danish and German guidelines make no recommendations for or against prescribing benzodiazepines or SMRs in LBP. However, the British guideline does recommend more research should be done to assess the effectiveness of benzodiazepines, as current evidence in the field of muscle relaxants is either insufficient to make a recommendation or concerns medications that are not licensed for use in the UK (SMRs such as cyclobenzaprine and carisoprodol).

A 2017 systematic review and meta-analysis was used as best available evidence for the efficacy of muscle relaxants; drug groups considered are both benzodiazepines and SMRs (32). This review provides evidence for a clinically significant short-term effect of SMRs on pain relief in acute LBP (21.3 points difference on a 100-point pain scale (95% CI 13.5-29.0 points))(32). For chronic LBP, the efficacy of muscle relaxants remains unknown (32). No evidence exists for the efficacy of benzodiazepines in LBP (32).

Common AEs of muscle relaxants include headache, nausea and dizziness (32, 37); the AE rate for muscle relaxants was found to be similar to that of placebo (14.1% versus 16.0%) (32). Benzodiazepines are known to carry a substantial risk of misuse (3% of users) or drug dependence (2% of users) (48).

Table 6: Guideline recommendations concerning muscle relaxants for non-specific low back pain

Guideline	Recommendations
Australia (2016)	-
Belgium (2017)	• Do not offer skeletal muscle relaxants for managing low back pain with or without radicular pain.
Canada (2017)	• Acute low back pain: Only consider adding a short course of muscle relaxant (benzodiazepines, cyclobenzaprine, or antispasticity drugs) on its own, or added to NSAIDs, if acetaminophen or NSAIDs have failed to reduce pain. • Chronic low back pain: Muscle relaxants (e.g., cyclobenzaprine) may be appropriate in selected patients for symptomatic relief of pain and muscle spasm.
Denmark (2018)	-
Germany (2017)	-
The Netherlands (2017)	• Benzodiazepines are not recommended. A positive effect of muscle relaxation on pain or function has not been demonstrated. Meanwhile, these medicaments do have side-effects and a risk of dependence exists.
UK (2017)	-
US (2017)	• We recommend that the choice between NSAIDs and SMRs be individualized on the basis of patient preferences and likely individual medication risk profile. • Skeletal muscle relaxants are associated with central nervous system adverse effects, especially sedation.
Best available evidence	**Main findings**
Efficacy and tolerability of muscle relaxants for low back pain: Systematic Review and meta-analysis (2017)	• A total of five trials (496 participants) provide high quality evidence that muscle relaxants provide clinically significant pain relief in the short term for acute LBP; MD-21.3, [-29.0,-13.5]. There was no information on long-term outcomes. • The median adverse event rate in clinical trials for muscle relaxants was similar to placebo 14.1% IQR (7.0–28.7%) and 16.0% (4.1–31.2%); p = 0.5, respectively. • There is no evidence for the efficacy of benzodiazepines in LBP. • For people with acute LBP, muscle relaxants provide clinically significant short-term pain relief. • For chronic LBP, the efficacy of muscle relaxants is largely unknown. There was no eligible RCT evidence to support the efficacy of benzodiazepines in LBP. Prolonged use of these medicines in LBP cannot be guided by trial evidence.

IQR: interquartile range; LBP: low back pain; MD: mean difference; NSAID: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; SMR: skeletal muscle relaxant; UK: United Kingdom; US; United States of America.

CONCLUSION

Eight national clinical practice guidelines for the management of LBP have been updated in the last three years. This review aimed to compare the recommendations for pharmacological treatment of NSLBP in primary care of these guidelines with the best available evidence regarding treatment efficacy; these recommendations may not apply to patients for whom a specific cause for LBP has been identified. The findings from systematic reviews that were considered to be best available evidence are echoed in most of the included clinical practice guidelines. Differences exist between guidelines in terms of the first-line analgesic in acute LBP. Although best available evidence suggests paracetamol is ineffective in acute LBP, four out of eight guidelines still recommend prescribing paracetamol for this condition. However, two of these guidelines immediately state that no short-term effect of this medication is to be expected. In the other four guidelines, NSAIDs have become the first choice analgesics in LBP; in the American guideline, clinicians are encouraged to choose between NSAIDs and SMRs based on preferences and risk profile of the patient.

When compared to the previous generation of clinical practice guidelines, where prescription of time-contingent paracetamol or NSAIDs was considered the norm(13), this generation is universally moving away from recommending pharmacotherapy, presenting the prescription of analgesics as an option that may be considered if this is required by the patient. The guidelines from Denmark and the US seem to be the most progressive in this respect, actively discouraging the pharmacological treatment of NSLBP and recommend non-pharmacological options instead.

As has been recently demonstrated in Australian data, opioids are now the most prescribed analgesics for LBP in primary care. All guidelines consider opioids as a last resort option in case all other pharmacological options have failed, but opinions differ concerning reassessment intervals and treatment duration in general. Only limited evidence exists for the efficacy of antidepressants and anticonvulsants in chronic LBP; best available evidence does suggest a small but significant effect of duloxetine (an SNRI) for chronic LBP. Regarding recommendations about muscle relaxants, the field is most divided: four guidelines don't make any recommendations for or against muscle relaxants, while two countries advise against the prescription of this medication, one guideline only recommends muscle relaxants to selected patients and, as mentioned above, the last guideline (from the US) considers SMRs as one of the analgesics of first choice.

EXPERT OPINION

In general, most clinical practice guideline recommendations match review findings. However, pharmacological treatments such as paracetamol and anticonvulsants which have not been shown to be effective in RCTs are still recommended in a number of guidelines. Furthermore, pharmacological treatments for which efficacy has been demonstrated, such as NSAIDs and opioids, only have small to moderate effects at best at the immediate term and short term. Meanwhile, all pharmacological treatments discussed in this article are associated with risks of AEs. This means careful consideration is prudent before recommending the use of any analgesic to patients with NSLBP; this notion has been incorporated in some form or another in all clinical practice guidelines, but could be presented more prominently in some.

Based on the available evidence, NSAIDs and SMRs may be the best possible drug choices in case pharmacotherapy is deemed absolutely necessary for the management of NSLBP. However, in Australia and several European countries, SMRs have not been registered due to risk of abuse or addiction, automatically making NSAIDs the analgesics of first choice. The only guideline discussing NSAIDs and SMRs as equal options is the American guideline; this document however does not provide clear patient characteristics on which a choice between these pharmacological treatments can be based; instead, it recommends individualizing this choice "on the basis of patient preferences and […] individual medication risk profile". This feels like a step away from the 'one size fits all' approach of RCTs and corresponding meta-analyses and towards the unpredictability of clinical practice, although there currently is insufficient information available to determine what medication to prescribe to individual patients in order to maximize treatment effect. Guiding clinicians in personalized medical decisions is a challenge for researchers, and this task is complicated by the fact that NSLBP is a heterogeneous disorder and most RCTs are insufficiently powered to identify subgroups or individuals using typical subgroup analyses (49-51); furthermore, it is often unclear whether observed improvements in LBP symptoms of individual patients are attributable to medication effects or explained by other phenomena such as natural recovery. Alternative statistical approaches such as individual participant data meta-analysis (IPDMA) may be helpful in creating personalized medicine strategies (50); research protocols have been published for IPDMA of exercise therapy and spinal manipulative therapy for chronic LBP (52, 53). So far, no protocols for IPDMA of pharmacological treatments in LBP have been published.

According to the best available evidence, paracetamol has no effect on the outcomes of LBP when compared to placebo. However, one should realize that this evidence is mainly based on a single, though large RCT; quality of evidence regarding the efficacy of paracetamol in LBP is therefore considered to be low in some guidelines (16, 22). Therefore, it is important to replicate the aforementioned efficacy trial, comparing

paracetamol not only to placebo, but also to other available (non-)pharmacological treatment alternatives in order to strengthen recommendations in future guidelines.

The prescription of anticonvulsants and antidepressants for NSLBP should be recommended against in future primary care clinical practice guidelines, as these pharmacological treatments should be reserved for patients with neuropathic pain, which is unlikely to be non-specific. As already stated in the current American guideline, opioids should only be prescribed as a last resort; we suggest new guidelines provide clinicians with clear instructions for duration of treatment and regular reassessment of patients taking opioids, similar to the current recommendations in the Dutch guidelines.

Although most of the guidelines discussed in this article already are hesitant in their recommendations to prescribe analgesics as stated above, none of the publications is as strict as the American guideline, which specifically states that non-pharmacological treatments should be first selected for the treatment of acute NSLBP, as most patients will improve regardless of treatment. The German guideline echoes this recommendation, stating that the treatment of LBP with drugs is purely symptomatic and should only be prescribed in support of non-pharmacological measures. In spite of these recommendations, pharmacotherapy for NSLBP is still ubiquitous in clinical practice and both patients and clinicians often do not consider analgesics to be merely optional. Most alarmingly, there has been a marked increase in the prescription of opioids for non-cancer pain in recent years. This trend was initially seen in the US and Canada (38), but the number of opioid prescriptions has increased in other parts of the world as well (54, 55). This development may reflect a continuing focus on pain rather than function in the field of NSLBP.

We consider the fact that many NSLBP patients still routinely receive analgesic prescriptions as a major challenge for the future, especially in the case of opioids. The authors believe that upcoming guideline updates should therefore follow the American example and explicitly shift their focus from pain to function and from pharmacotherapy to non-pharmacological treatment options (8). Of course this means non-pharmacological treatment options should be credible and feasible; this is where a challenge lies for researchers in the field of NSLBP, as evidence is limited for comparative effectiveness between pharmacological and non-pharmacological treatment options as well as between different non-pharmacological treatment options.

Apart from the recommendations made by guidelines, special attention should be given to the translation of these recommendations to clinical practice. It has been shown that there still are evidence-practice gaps in the management of LBP (56-58). Misconceptions about back pain and focus on a pathophysiological model of care have been identified as barriers to successful implementation of LBP guidelines (59) and excellent initiatives for improving the implementation of guideline recommendations have already

been developed (8); using these strategies on a larger scale may lead to an increased uptake of guidelines and consequently to an improvement in quality of LBP care.

Changing treatment routines from pharmacotherapy to non-pharmacological treatment is not only a challenge for clinicians, but also for NSLBP patients, who will need to understand and accept these changes. Public health interventions such as mass media campaigns to educate patients about the limited benefits and side effects of medication could be a first step in order to achieve this (60); media campaigns have been proven to be successful in changing patients beliefs and behaviors in the past (8). Another possible approach to changing NSLBP patients' beliefs and behaviors may be through patient information websites (61) or using consumer versions of guidelines (62, 63). If both clinicians and patients see the benefits of avoiding analgesics, the rise in prescriptions to NSLBP patients could be halted and maybe even reversed.

As most LBP guidelines are updated approximately every ten years, we don't expect any major changes in policy or clinical practice in the upcoming years. However, we hope new evidence for non-pharmacological treatment options, increased focus on guideline implementation and patient education through mass media campaigns, patient information websites and consumer versions of guidelines can help to slowly steer physicians and patients towards non-pharmacological treatments as the interventions of first choice for NSLBP, with improved quality of care as a result.

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Chapter 3

Efficacy of paracetamol, diclofenac and advice for acute low back pain in general practice: design of a randomized controlled trial (PACE Plus)

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ABSTRACT

Introduction

Low back pain is common and associated with a considerable burden to patients and society. There is uncertainty regarding the relative benefit of paracetamol and diclofenac and regarding the additional effect of pain medication compared with advice only in patients with acute low back pain. This trial will assess the effectiveness of paracetamol, diclofenac and placebo for acute low back pain over a period of 4 weeks. Furthermore, this trial will assess the additional effectiveness of paracetamol, diclofenac and placebo compared with advice only for acute low back pain over a period of 4 weeks.

Methods

The PACE Plus trial is a multi-center, placebo-blinded, superiority randomized controlled trial in primary care, with a follow-up of 12 weeks. Patients with acute low back pain aged 18-60 years presenting in general practice will be included.

Patients are randomized into four groups: 1) Advice only (usual care conforming with the clinical guideline of the Dutch College of General Practitioners); 2) Advice and paracetamol; 3) Advice and diclofenac; 4) Advice and placebo. The primary outcome is low back pain intensity measured with a numerical rating scale (0-10). Secondary outcomes include compliance to treatment, disability, perceived recovery, costs, adverse reactions, satisfaction, sleep quality, co-interventions and adequacy of blinding.

Between group differences for low back pain intensity will be evaluated using a repeated measurements analysis with linear effects models. An economic evaluation will be performed using a cost-effectiveness analysis with low back pain intensity and a cost-utility analysis with quality of life. Explorative analyses will be performed to assess effect modification by predefined variables.

Ethical approval has been granted**.** Trial results will be released to an appropriate peer-viewed journal.

Discussion

This paper presents the design of the PACE Plus trial: a multi-center, placebo-blinded, superiority randomized controlled trial in primary care that will assess the effectiveness of advice only, paracetamol, diclofenac and placebo for acute low back pain.

INTRODUCTION

Low back pain is one of the most common diseases of the musculoskeletal system. It is associated with a considerable burden to patients and society. According to the global burden of disease study, low back pain is the number one disorder responsible for disability in the population (as calculated by the years lived with disability (YLD)) (1). The point prevalence is reported to be as high as 33%. The total costs associated with back pain in The Netherlands are estimated at 3,5 billion euro in 2007 (2). In the United States, the figure is over US$50 billion (3).

Clinical guidelines for the management of low back pain have been issued in many countries around the world in order to promote rational care (4). These guidelines provide clear agreement on the recommendations for first line care of acute low back pain (4). According to most guidelines, first line care should consist of reassurance on the favorable prognosis of non-specific low back pain, advice to stay active and avoid bed rest, and prescription of a simple analgesic medicine using a time-contingent dose regimen, e.g. 1 g paracetamol administered 4 times per day. The clinical guideline for the management of low back pain of the Dutch College of General Practitioners (NHG) also recommends paracetamol as first choice followed by nonsteroidal anti-inflammatory drugs (NSAIDs) as a second option for the prescription of analgesics for patients with acute low back pain (5). The current guideline preference for paracetamol as the first choice analgesic was not based on evidence on its efficacy in patients with back pain, but on its better safety-profile as compared to NSAIDs and other analgesics. Until recently there was no placebo-controlled trial available evaluating the effect of paracetamol for patients with low back pain.

In July 2014, the first placebo controlled trial of paracetamol for acute low back pain (PACE trial) was published (6). Australian researchers showed no difference in clinical outcomes between paracetamol and placebo in patients with acute low back pain. In this large clinical trial, 1652 patients with acute low back pain were randomized to 1) paracetamol on regular doses 2) paracetamol as needed or 3) placebo. Neither on the primary outcome (time to recovery) nor on any secondary outcome such as back pain intensity, disability, symptom change were differences in outcome between the three study groups found (6).

Considering the findings in this Randomized-Controlled Trial (RCT), one relevant question is if the current clinical guideline recommendations should be changed regarding the use of paracetamol. The Australian research team stated that replication of their study findings should take place before dismissing paracetamol as a treatment option for low back pain. Changing the content of guidelines based on the findings of a single trial without verification of the results in other similar populations would seem premature (7). Besides replication of the paracetamol versus placebo contrast of the PACE trial

two other topics are also of importance: firstly, there is ample evidence that the clinical course of many patients with acute low back pain is rather favorable. In the PACE trial the median recovery was 16-17 days in all participating patients, including those receiving placebo, and by 12 weeks about 85% of patients was recovered. All patients in the trial received advice and reassurance of a favorable prognosis in addition to the study medications and apparently did rather well regarding the authors. This raises the question of whether patients with acute low back pain need paracetamol (or other analgesic) at all. What would be the outcome if patients receive advice and reassurance only?

Secondly, the awareness of the limited clinical effect of paracetamol could easily influence the decision to step up more quickly to using NSAIDs which are the next recommended type of pain medication in the clinical guidelines. Should NSAIDs even be recommended as first analgesic treatment option instead of paracetamol for patients with acute low back pain? NSAIDs have been compared with placebo in patients with low back pain and have shown significantly better results for pain reduction (8). However, the magnitudes of the effects are rather small. The between-group differences were less than 10 points on a 0-100 pain scale. In addition, in direct comparisons NSAIDs have not shown consistent superiority above paracetamol in patients with acute low back pain. The Cochrane review only lists 5 RCTs comparing NSAIDS versus paracetamol and all were at risk for high risk of bias (8). The Cochrane review concluded 'whether NSAIDs are more effective than other drugs or non-drug therapies for acute low-back pain still remains unclear'. In the Netherlands, diclofenac has been the most commonly prescribed NSAID over the past decade (9).

Objective

The primary objective of the PACE Plus trial is to compare the clinical effectiveness of paracetamol, diclofenac and placebo for acute low back pain in primary care over 4 weeks of follow-up. Furthermore, this trial aims to determine the added clinical effectiveness of medication and advice (paracetamol, NSAID or placebo) versus advice only for acute low back pain in primary care over 4 weeks of follow-up. Secondary objectives of the PACE Plus trial are to compare disability, patients' perceived recovery, quality of life, costs, time to recovery, compliance to treatment, adverse reactions, patients' satisfaction, sleep quality and co-interventions between advice plus paracetamol, advice plus diclofenac, advice plus placebo and advice only groups.

METHODS

Trial design and setting

The trial will be a four arm, multicenter, placebo-blinded, superiority randomized controlled trial using double dummy technique in general practice with a follow-up period of 12 weeks. The study design and flow of patients in the PACE Plus trial are shown in Figure 1.

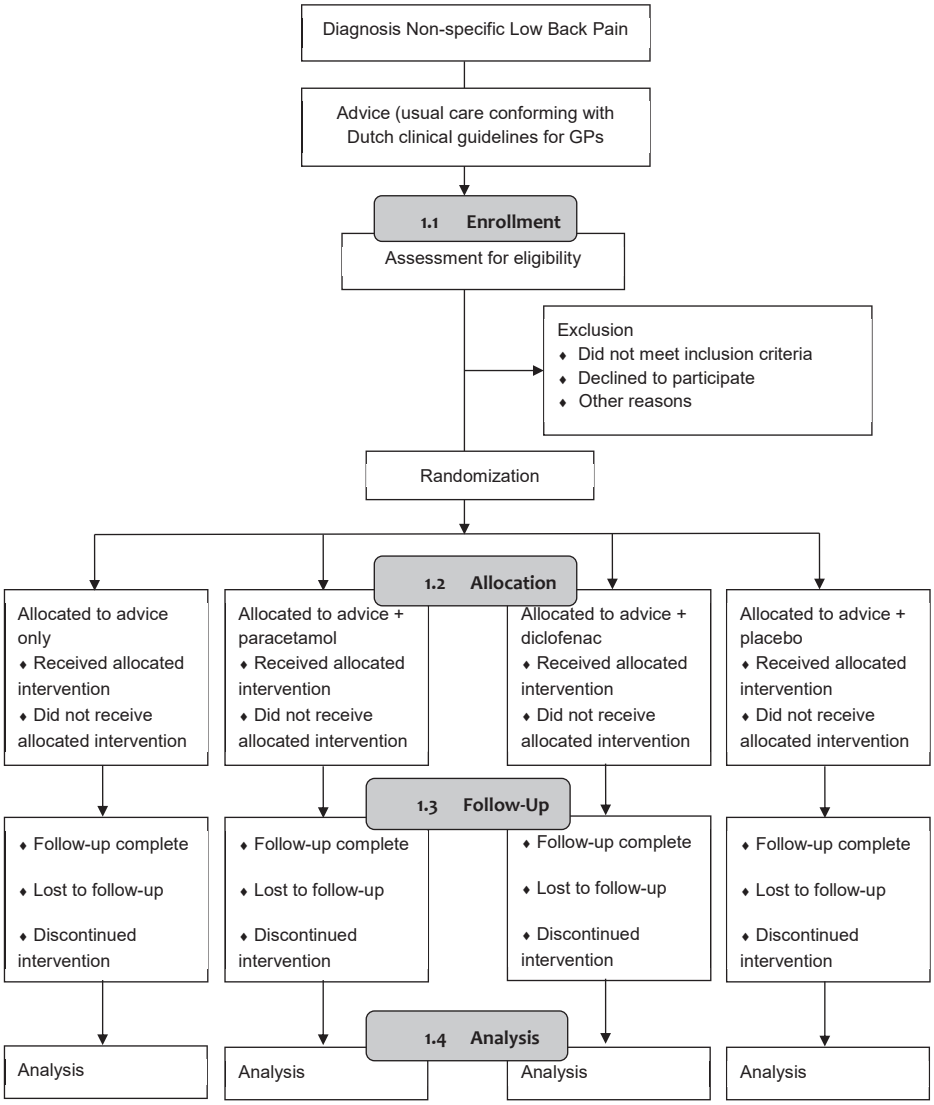

Figure 1: Flow-chart of the PACE Plus trial.

The patient eligibility criteria of the PACE trial are similar to the in- and exclusion criteria that will be used in the PACE Plus trial. Based on the figures in the PACE trial, we will need to assess at least 2231 patients to end up with 800 patients that fulfill eligibility criteria and are willing to participate in the trial. In the PACE trial, 4606 patients were screened by 235 primary care providers during a recruitment period of 3.5 years. This comes down to an average of 5.6 patients per primary care provider per year. The PACE Plus trial has a planned recruitment period of 2 years. We thus need cooperation of at least 200 General Practitioners (GPs) for the referral of patients with acute low back pain for screening. Based on the Dutch National Assessment of Diseases in Primary Care (10), in the average Dutch general practice, the incidence of low back pain is 27 per 1000 patients per year; we therefore assume the proposed referral rate is feasible. Recruitment rate will be monitored closely during the trial recruitment period and if necessary, more GPs will be contacted for participation.

Participants and eligibility criteria

Patients will be recruited in Dutch general practices and referred to the PACE Plus research team. Before enrolment in the trial, all potential patients will be assessed for eligibility and informed consent.

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria: 1) Aged between 18 and 60 years; 2) Low back pain of less than 6 weeks duration; 3) Primary complaint of pain in the area between the 12th rib and buttock crease, with or without radiating leg pain; 4) Experiencing a new episode of low back pain, preceded by a period of at least one month without low back pain; 5) Low back pain severe enough to cause at least moderate pain (≥ 4 on 0-10 numerical rating scale (NRS)).

Exclusion criteria

A potential patient who meets any of the following criteria will be excluded from participation in this study: 1) known or suspected serious spinal pathology (e.g. metastatic, inflammatory or infective diseases of the spine, cauda equina syndrome, spinal fracture); 2) Currently taking recommended regular doses of analgesics, including paracetamol or diclofenac; 3) Spinal surgery within the preceding 6 months; 4) Serious co-morbidities like severe rheumatoid arthritis, cardiac failure, diabetes preventing prescription of paracetamol (e.g.: liver or renal failure) or diclofenac (e.g. gastric ulcers or other gastrointestinal problems); use of proton pump inhibitors before inclusion is not an exclusion criterium, as the patient is considered to be protected (patient will have to continue using this medication during use of study medication); 5) Use of coumarine derivatives, clopidogrel, prasugrel, ticagrelor, acetylsalicylacid derivatives, systemic glucocorticoid,

selective serotonin reuptake inhibitors (SSRIs), venlafaxine, duloxetine, trazodone, spironolactone or other medications that may interact with paracetamol and/or diclofenac; 6) Known intolerance for paracetamol and/or diclofenac; 7) Pregnant or planning to become pregnant during the treatment period.

Recruitment

Patients consulting their GP or doctor's assistant for low back pain and fulfilling simple referral criteria (ages 18 to 60 years, new episode of low back pain (6 weeks maximum duration) and no contraindications for diclofenac) can be referred to the PACE Plus research team. Potential participants will be contacted within 24 hours by a researcher for further information about the trial, assessment of the eligibility criteria and collection of informed consent.

Randomization and blinding

After collection of informed consent, patients will be randomly allocated to one of four intervention groups: 1 advice only group and 3 medication groups. Randomization will be performed using a two-step process. In the first step, patients will be randomized between 'advice only' and 'medication' using a computer-generated randomization list. After the first step of the randomization process, patients and GPs will be informed about the outcome of treatment allocation (either that they receive advice only or that they receive blinded study medication).

In the advice only group, patients will not get study medication, but receive advice and reassurance from their GP or doctor's assistant only (usual care conforming with the clinical guideline of the Dutch College of GPs).

For people who are randomized in the first step to 'medication', a trial medication prescription will be sent to the Erasmus University Hospital Trial Pharmacy. In the second step of randomization, an independent trial pharmacist will use a randomization list with random blocks to determine the medication group that patients will be randomized to (paracetamol, diclofenac or placebo). Both randomization lists used in this two-step process are made by an independent data-manager who is not involved in this trial.

After allocation to 1 of the 3 medication groups, patients will receive a treatment pack containing large oblong tablets and small round tablets prepared and numbered by an independent trial pharmacist. Treatment packs will be sent by mail to the patient, and are expected to arrive the next day. Using the double dummy technique, active medication differs between groups as follows:

- Paracetamol group: active oblong tablets (active paracetamol) and placebo round tablets (placebo diclofenac);
- Diclofenac group: placebo oblong tablets (placebo paracetamol) and active round tablets (active diclofenac);

- Placebo group: placebo oblong tablets (placebo paracetamol) and placebo round tablets (placebo diclofenac).

The placebo tablets that will be used in the PACE Plus trial are identical in appearance and taste to their active counterparts, but do not contain the active component. All medication packaging will be identical between the 3 medication groups, except for a unique randomization number for each participant. Every package contains a reply paid post envelope, in which unused tablets can be returned for counting after 4 weeks of follow-up. The patient, patient's GP and pharmacist and researchers involved in data collection and analysis will be blind to treatment group allocation. Unblinding is permissible in case of a reported suspected unexpected serious adverse reaction (SUSAR).

Treatment

All patients in the PACE Plus trial will receive advice and reassurance from either their GP or doctor's assistant before referral (usual care conforming with the clinical guideline of the Dutch College of GPs).

Patients in the medication groups will be asked to take 4 daily doses of 2 oblong tablets and 2 daily doses of 1 round tablet, until they have experienced two consecutive pain free days (NRS 0 or 1 out of 10), or for a maximum of 4 weeks if a pain free interval does not occur. This means that treatment groups will receive the following drug dosages:

- Paracetamol group: paracetamol (immediate release) 4 daily doses of 1000 mg, placebo diclofenac 2 daily doses.
- Diclofenac group: diclofenac (immediate release) 2 daily doses of 75 mg, placebo paracetamol 4 daily doses.
- Placebo group: placebo paracetamol 4 daily doses, placebo diclofenac 2 daily doses.

Allocated treatment as described above may be discontinued by the patient's own GP in case the patient revisits his or her GP because of persisting low back pain; this will be recorded during follow-up measurements.

Co-interventions

During participation in the PACE Plus trial, patients in the medication groups will be asked not to take paracetamol or NSAIDs because this may lead to overdose of these medications. Participant's GP and Pharmacist will be informed about the participation of their patient in the PACE Plus trial, and for the medication groups, the usage of trial medication. Additional medication taken by the patient for low back pain will systematically be recorded in patients' questionnaires at all follow-up measurements. Physiotherapy as a co-intervention is allowed, but will also be recorded in follow-up measurements.

Outcomes

The primary outcome of the PACE Plus trial is low back pain intensity measured with an 11-point NRS (score range 0-10; higher score means more pain). Pain intensity will be recorded daily over a 4 week follow up period.

Secondary outcome measures that are collected in the PACE Plus trial are:

- compliance to treatment measured daily by asking 'How many large, oblong tablets did you take today?' and 'How many small, round tablets did you take today?' (questions derived from the Brief Medication Questionnaire (BMQ) (11)).
- disability measured using the Roland Morris Disability Questionnaire (RMDQ; score range 0-24; higher score means more disability) (12).
- patients' perceived recovery measured using a 7-point Likert scale that will be dichotomized into recovered (score 1 'complete recovery' and 2 'much improved) and not-recovered (score 3 'improvement' to score 7 'worse than ever').
- quality of life measured using the EuroQol Group 5 Dimensions, 5 Level Questionnaire (EQ-5D-5L) (13).
- costs; all direct medical and patient costs measured using the iMedical Consumption Questionnaire (iMCQ), and productivity costs measured with iProductivity Cost Questionnaire (iPCQ) (14, 15).
- time to recovery assessed using the daily low back pain severity scores. Recovery is defined as the first day of 0 or 1 pain intensity, maintained for seven consecutive days.
- adverse reactions systematically recorded in the follow-up questionnaires; all reported adverse events will be followed until they have abated or until a stable situation has been reached.
- patients' satisfaction measured using an 11-point NRS; score range 0-10, higher score means more satisfaction.
- sleep quality measured using a 4 point Likert scale derived from the Pittsburgh Sleep Quality Index (PSQI) (16). Scores will be dichotomized into good sleep quality (score 1 'very good' and 2 'fairly good') and poor sleep quality (score 3 'fairly bad' and 4 'very bad').
- co-interventions systematically recorded in the follow-up questionnaires.
- adequacy of blinding assessed in medication groups by asking patients to which treatment group they believe to be allocated after 12 weeks of follow-up.

Baseline characteristics that will be measured in the PACE Plus trial (including potentially relevant prognostic factors) are:

- gender, age, height, weight, education and occupational status.
- duration of complaints, history of back complaints, and comorbidity.
- job satisfaction measured with a 7-point Likert scale (score range from extremely unsatisfied to extremely satisfied).

- neuropathic pain measured with the Pain DETECT questionnaire (score range 0-38; higher score means a neuropathic component of back pain is more likely) (17).
- potentially modifiable prognostic indicators measured with the StarT Back Tool (18).

Patient timeline and data collection

Table 1 shows the time schedule of patient enrollment, interventions and assessments according to the SPIRIT-statement (19). After collection of informed consent, patients will fill out the baseline questionnaire. Subsequently, patients will be randomized into one of the four treatment groups. Patients will fill out daily digital questions regarding low back pain severity and compliance to treatment during 4 weeks after baseline measurement. Questionnaires concerning secondary outcomes will be filled out at 2, 4 and 12 weeks of follow-up. All questionnaires used in the PACE Plus trial will be sent to participants using e-mail and filled out using secure hyperlinks. If a questionnaire is not filled out (completely) by a participant, the research team will send a reminder encouraging the participant to complete the questionnaire.

Sample size

For the primary outcome (low back pain intensity (NRS)), between group differences of at least 20% are considered clinically relevant; this difference is expressed in the area under the longitudinal pain trajectories for the four treatment groups. Because low back pain is an episodic condition that is known to fluctuate over time, the correlation between repeated measured was assumed moderate (the parameter rho of a first-order auto-regressive serial correlation structure was set to 0.7). In the sample size calculation, a statistical power of 84% and a random dropout not exceeding 15% were assumed. With group sizes of 200 patients, a between group difference in low back pain intensity of at least 20% can be detected.

Statistical analysis

The statistical analysis will be performed according to the intention-to treat principle.

Primary Statistical Analysis

For clinical effectiveness the between group differences for the primary outcome, low back pain-intensity will be evaluated using a repeated measurements analysis with linear mixed effects models with adequate specification of the fixed and random effects structures to account for possible nonlinear effects. The covariance structure will be unstructured, but we will compare Akaikes' information criterion between the different covariance structures and choose the structure with the lowest value.

Table 1: Schedule of enrolment, interventions and assessments (SPIRIT)

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation (T_{weeks})		Close-out
TIMEPOINT	$T_{baseline}$	0	T_2	T_4	T_{12}
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:		●	—	●	
ASSESSMENTS:					
Socio-demographics	X				
Relevant prognostic factors	X				
LBP Intensity (NRS 0-10)		●	—	●	X
Compliance to treatment		●	—	●	
Disability RMDQ (0-24)	X		X	X	X
Patient's perceived recovery 7-point Likert scale			X	X	X
Quality of life EQ-5D-5L (5-25)	X			X	X
Medical consumption iMCQ				X	X
Productivity loss iPCQ				X	X
Adverse reactions			X	X	X
Patient's satisfaction 11-point NRS scale (0-10)			X	X	X
Sleep quality 4-point Likert scale	X		X	X	X
Co-interventions			X	X	X
Adequacy of blinding					X

LBP = Low Back Pain; NRS = numerical rating scale score; RDMQ = Roland-Morris Disability Questionnaire; EQ-5D-5L = EuroQol Group, 5 dimensions, 5 level questionnaire; iMCQ = institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire; iPCQ = iMTA Productivity Cost Questionnaire.

Secondary Statistical Analysis

A similar approach as described in 'primary study parameter(s)' will be used for the continuous secondary outcomes (e.g. disability and quality of life) to assess between group differences.

A Cox proportional hazards model will be carried out to evaluate the difference in time to recovery (recovery is defined as seven consecutive low back pain NRS scores of 0-1) between the groups.

The effect modification of the allocated treatment strategy by predefined baseline variables (explorative) on low back pain intensity, disability and recovery at 4 and 12 weeks follow-up will be analysed by Cox proportional hazard analyses and logistic regression analyses, respectively. Predefined variables are severe low back pain (defined as NRS≥7) and severe disability (defined as RMDQ≥16) at baseline.

To assess the cost-effectiveness of paracetamol versus diclofenac versus advice only for acute low back pain in general practice, a cost-effectiveness analysis will be performed using the primary outcome low back pain severity (measured daily). A cost-utility analysis will be performed to compare our study with other studies in musculoskeletal disorders research in a more general accepted outcome e.g. quality of life (measured in Quality-Adjusted Life Years (QALYs)). Utility values of the Dutch public for EuroQol health states will be applied to calculate QALY's based on the EQ-5D. Using non parametric bootstrapping (randomly drawing 2500 observations with replacement from the patient sample), the degree of uncertainty for costs and health effects and the cost-utility ratio will be depicted in a cost-effectiveness plane. In addition, an acceptability curve will be drawn, which indicates the probability that the paracetamol or diclofenac versus advice only has lower incremental costs per QALY gained than various thresholds for the maximum willingness to pay for an extra QALY.

The economic analysis will be based on the societal perspective and on the healthcare perspective in which the direct and productivity costs in the groups will be compared. The costs per hour of productivity loss will be updated from the Dutch Guideline for economic evaluations in health care (20). The friction cost method will be used to calculate the productivity costs according to the Dutch guidelines. The costs per unit of medical consumption will be estimated, using information from the Dutch Manual for economic evaluation of health care on costs per unit of medical services (21).

Trial registration

This study protocol was registered with the Dutch Trial Register on September 14th, 2016 (NTR6089; Protocol: Version 4, June 2016).

Data management and safety

All personal data (e.g. demographics, contact-data, questionnaires, diary) will be stored anonymously. The patients' identity will remain confidential at all times. Each patient will be allocated a unique code, which will be used on the Case Report Forms (CRFs). The link between the code and the patients' name will only be assessed by the researchers and the data-manager.

Trial conduct and data integrity will be audited once per year by independent auditors.

DISCUSSION

This paper presents the design for a randomized, placebo controlled trial that will assess the effectiveness of paracetamol, diclofenac and placebo for acute low back pain in primary care. Furthermore, the trial will assess the additional effectiveness of paracetamol,

diclofenac and placebo compared to advice only for acute low back pain in primary care. The primary outcome is low back pain intensity measured daily on a numerical rating scale over a period of 4 weeks. Secondary outcomes are measured at 1 weeks, 2 weeks, 4 weeks and 12 weeks of follow-up and include compliance to treatment, disability, perceived recovery, costs, adverse reactions, satisfaction, sleep quality, co-interventions and adequacy of blinding. Between group differences for the primary outcome will be evaluated using a repeated measurements analysis with linear effects models. An economic evaluation will be performed using a cost-effectiveness analysis with low back pain intensity and a cost-utility analysis with quality of life. Explorative analyses will be performed to assess effect modification by predefined variables. The outcomes of this trial may impact the clinical guideline recommendations concerning first analgesic treatment options in acute low back pain in general practice.

Recruitment of eligible patients is currently ongoing. Substantial protocol amendments will be communicated to participants, cooperating GPs and pharmacists, Medical Research and Ethics Committee (MREC), the Dutch Trial Registry, ZonMw and the journal publishing this protocol. Results of this trial will be published in a peer-reviewed journal. After publication, participating patients and GPs will be informed about trial results (expected in 2020).

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Chapter 4

Discontinuation of the PACE Plus trial: problems in patient recruitment in general practice

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ABSTRACT

Introduction

The PACE Plus trial was a multi-center, double-blinded, superiority randomized controlled trial (RCT) conducted in patients from Dutch general practice to investigate the efficacy of paracetamol and NSAIDs in acute non-specific low back pain (LBP). Because insufficient numbers of patients could be recruited (only four out of the required 800 patients could be recruited over a period of six months), the trial was prematurely terminated in February 2017, six months after the start of recruitment. This article aims to transparently communicate the discontinuation of PACE Plus and to make recommendations for future studies.

Methods

General Practitioners (GPs) from 36 participating practices received a one-question survey in which they were asked to give the three most important factors that in their opinion contributed to failure of patient recruitment.

Results

GPs of 33 out of 36 (92%) participating practices sent a response. A total of 81 factors were reported. These have been categorized into patient factors (26 out of 81 comments, 32%), GP factors (39 out of 81 comments, 48%) and research factors (16 out of 81 comments, 20%).

Discussion

Patient recruitment in the PACE Plus trial may have failed due to inefficient medication distribution, recruitment of incident rather than prevalent cases, a design that was too complicated, adequate self-management of LBP, patient expectations different from the trial's scope and lack of time of participating GPs. Substantial differences in design may explain why the preceding PACE trial did manage to successfully complete patient recruitment.

Conclusion

Although the PACE Plus trial was terminated as a result of insufficient patient inclusion, the research questions addressed in this trial remain relevant but unanswered. We hope that lessons learned from the discontinuation of PACE Plus and corresponding recommendations may be helpful in the design of upcoming research projects in LBP in general practice.

INTRODUCTION

The PACE Plus trial was conducted in Dutch general practice to investigate the efficacy of paracetamol and NSAIDs in acute non-specific low back pain (LBP) (1). The study design was a multi-center, placebo-blinded, superiority randomized controlled trial (RCT). The two main aims of this RCT were to replicate the comparison between paracetamol and placebo as done in the PACE trial (2-4) and to compare the efficacy of paracetamol with diclofenac and advice only. The study protocol was published (1) and was prospectively registered (Dutch Trial Registration NTR6089, registered September 14th 2016). The Erasmus MC Medical Research and Ethics Committee (MREC) has granted approval for the PACE Plus trial (NL54941.078.16). In short, our intention was to recruit 800 patients with acute LBP from Dutch general practices, who would be randomized across four treatment groups (paracetamol, diclofenac, placebo or advice only) and would be followed for 12 weeks. Inclusion and exclusion criteria for patient recruitment in the PACE Plus trial can be found in Table 1.

Table 1: Inclusion and Exclusion criteria for patient recruitment in the PACE Plus trial

Inclusion criteria	Exclusion criteria
• Age between 18 and 60 years; • Low back pain of less than 6 weeks duration; • Primary complaint of pain between the 12th rib and buttock crease; • Experiencing a new episode of low back pain, preceded by a period of at least 1 month without low back pain; • Low back pain severe enough to cause at least moderate pain (≥4 on 0-10 numerical rating scale (NRS)).	• Known or suspected serious spinal pathology; • Currently taking recommended regular doses of analgesics, including paracetamol or diclofenac; • Spinal surgery within the preceding 6 months; • Serious comorbidities preventing prescription of paracetamol or diclofenac; • Use of medication interacting with paracetamol or diclofenac; • Known intolerance for paracetamol or diclofenac; • Pregnancy or planning to become pregnant during the treatment period.

From May 2016, General Practitioners (GPs) were recruited for participation in the trial. Initially, GPs who had experience with patient recruitment in studies conducted by the Erasmus Medical Center (EMC) Department of General Practice were approached for participation. As a second step in the recruitment of GPs, local GPs from the provinces of Zuid-Holland, Noord-Brabant and Zeeland and GPs who were specializing in musculoskeletal disorders at the EMC were approached for participation. Finally, GP residents in their last year of training were asked to participate as part of their training program.

Recruitment of eligible patients for the PACE Plus trial started in September 2016. During the first 10 weeks of the inclusion period of the trial, a total of 79 GPs from 26 practices participated in the trial; GPs from 11 of these practices (42%) had participated in other studies of the EMC Department of General Practice. 22 patients were referred for

participation in the trial by a total number of 12 practices. Four out of these 22 patients (18%) could be included in the trial. 18 out of 22 (82%) referred patients were excluded; nine patients did not meet inclusion criteria, nine patients declined to participate in the trial after being informed by a research assistant over the phone. Reasons why referred patients did not meet inclusion criteria are presented in Table 2. Shortly after inclusion, the first included patient declined further participation and was lost to follow-up.

Table 2: Patient referral and inclusion and exclusion in the PACE Plus trial

Trial period	Before design modification	After design modification	Total
Number of participating GPs	**79**	**96**	**96**
(number of participating practices)	**(26)**	**(36)**	**(36)**
Referrals (number of referring practices)	**22 (12)**	**9 (6)**	**31 (15)**
Exclusions (% of referrals)	**18 (82%)**	**9 (100%)**	**27 (87%)**
Patient did not meet inclusion criteria	9	4	13
Intake of study medicines before inclusion	5	1	6
Pain score (NRS 0-10) <3	1	1	2
Specific cause of low back pain	0	1	1
Age > 60 years	1	0	1
Comorbidity/co-medication with interaction	1	1	2
Insufficient knowledge of Dutch language	1	0	1
Patient declined to participate	9	5	14
Inclusions (% of referrals)	**4 (18%)**	**0 (0%)**	**4 (13%)**

In November 2016, the trial was temporarily suspended due to insufficient patient recruitment and the 'Advice only'-group was removed from the design after approval from the Medical Research and Ethics Committee (MREC) of the Erasmus MC and the funding party (ZonMw), because a majority of participating GPs reported that their patients with LBP did not accept the 25% chance of receiving no medication whatsoever. The 'Advice only'-group was perceived by many patients as well as participating GPs as doing nothing. As a result of the design modification, two of the four included patients were censored from the trial because they had been randomized to the 'Advice-only group'.

After the design modification, a total of 96 GPs from 36 practices participated in the trial; GPs from 13 of these practices (36%) had participated in other studies of the EMC Department of General Practice. Nine more patients were referred for participation in the trial by a total number of six practices. None of the nine patients could be included in the trial; four patients did not meet inclusion criteria and five patients declined participation after being informed over the phone by a research assistant.

Because insufficient numbers of patients could be included despite the study design modification, the PACE Plus trial was terminated in February 2017, approximately six months after the start of recruitment. To investigate the underlying reasons for termination of this RCT, GPs from all participating practices were sent a survey. This publication has two aims: firstly, to provide transparent communication about our unsuccessful patient recruitment, including results from the GP survey and secondly, to make recommendations for future researchers in this field of study in order to avoid the problems encountered in this trial.

METHODS

After the PACE Plus trial was discontinued, a letter explaining the trial had been terminated because of insufficient patient recruitment was sent to all local research collaborators (one GP for each participating practice, n = 36). Attached to this letter was a form with 3 blank answer boxes and a single question: "In your opinion, what are the (3) most important reasons why patient recruitment failed?". GPs were requested to return their answer to this question in a pre-paid envelope that was provided. Reminders were sent two months and three months after the original letter to GPs who had not yet responded to the survey.

MS extracted all responses into Microsoft Excel 2010 as individual reasons. BK, PL and MS created 3 reason categories: patient factors (i.e. factors related to patient expectations and coping mechanisms), GP factors (i.e. factors related to presentation of patients in clinical practice and organization of care) and Research factors (i.e. factors related to trial design and organization). PL and MS categorized all reasons into one of these categories. MS computed percentages using Microsoft Excel 2010 and interpreted initial results. BK and PL checked these computations and interpretation. For categories with a minimum of 8 responses (10% of total reasons), BK and MS selected quotes that represented the opinions of multiple GPs for that specific category. Quotes were translated from Dutch to English by BK and MS.

RESULTS

26 out of 36 GPs responded to the survey after the first letter (19 returned the original filled-out form by post, seven sent an e-mail with their opinion). Six out of the remaining 10 GPs responded after the first reminder (four by post, two by e-mail). After a final reminder, one of the remaining four GPs responded to the question by e-mail. In total, 33 out of 36 practices (94%) sent a response. Not all respondents sent back exactly

three factors, this ranged from one to four factors per response. Responses were usually formulated as short sentences. A total of 81 factors were reported (Table 3). These have been categorized into patient factors (26 out of 81 comments, 32%), GP factors (39 out of 81 comments, 48%) and research factors (16 out of 81 comments, 20%).

Table 3: Results of survey amongst 33 participating GPs

GP opinions on why recruitment failed in the PACE Plus trial	Total number of comments (% of total comments)
1. Patient factors:	26 (32%)
1.1 Patient had other expectations when seeking care for low back pain	14
1.2 Patients were confident they could self-manage their low back pain	7
1.3 Patient declined participation	5
2. GP factors:	39 (48%)
2.1 Insufficient number of patients meeting criteria were seen in practice or spoken to on the telephone	20
2.2 Lack of time or trial forgotten because of other tasks	14
2.3 The trial had just started or had not yet started in the practice	3
2.4 Not all employees of the practice were sufficiently informed about the trial	2
3. Research factors:	16 (20%)
3.1 Medication distribution procedure too complicated	7
3.2 Research question and design irrelevant for clinical practice	4
3.3 Inclusion and exclusion criteria too restrictive	2
3.4 Research logistics disturb usual clinical care	2
3.5 Problems in communication with research department	1
Total number of comments from 33 GPs:	81 (100%)

Most of the comments about patient factors stated that patients had other expectations when seeking care for LBP than participating in a trial (14 out of 26 comments). Examples of these expectations from the survey were patients asking either for alternatives for paracetamol or for stronger pain medication than NSAIDs and patients requesting further diagnostics by x-ray. One GP wrote: "***The study went against expectations of patients and doctors. The idea not to take or prescribe pain medication when someone is in pain requires abstract reasoning. GPs aren't happy to dismiss paracetamol, too much time was invested to promote the usefulness of this drug. This means there is a lose-lose situation; both the patient and the GP lose in this trial (at least from a superficial point of view)***". Other patient factors mentioned by GPs were that patients felt confident they could self-manage their LBPs (using validated online patient information such as the patient information website of the Dutch College of General Practitioners (NHG) (5) or using direct access to physiotherapy, seven out of 26 comments) and patients declining participation in the trial directly in the practice (five out of 26 comments).

Nearly a quarter of all comments mentioned insufficient numbers of patients meeting the inclusion criteria for the PACE Plus trial presenting in the practice or on the phone (20 comments). The quote best capturing this stated: "*I personally see few people in my practice that meet the inclusion criteria. Age, duration of complaints, etcetera. The GP's assistant solves a lot of cases; those patients could otherwise have participated in the trial*". Another reason that was often stated was lack of time due to patient care and administration tasks (14 comments). Several GPs mentioned forgetting about the trial because of the high workload; one respondent wrote: *"It's very hectic! I only remembered to ask my patient to participate after he'd already left".* Other GP factors considered organizational issues in the GP practices: two GPs stated that not all employees in the practice were sufficiently informed about the trial, three GPs had only just or not yet started participating in the trial.

Research factors reported could be related to both study design choices and trial organization by the research department. Apart from the GPs mentioning insufficient numbers of patients presenting in their practice, two GPs explicitly stated that inclusion and exclusion criteria were too restrictive to be realistic. Seven GPs found the medication distribution procedure too complicated and the subsequent time delay before the patient received medication unacceptable. Four GPs believed the trial research question was irrelevant for clinical practice. Two GPs stated that the trial design caused disturbance of usual clinical care. Finally, one GP mentioned that communication with the research department was not clear enough.

DISCUSSION

Termination of the PACE Plus trial may be attributable to research logistics and design, patient related and GP related factors. We will discuss these factors considering the survey described above as well as reflecting on design choices made in this trial's predecessor, the PACE trial, which did manage to successfully recruit 1650 patients with comparable complaints.

In retrospect, an important weakness in the logistics of PACE Plus was the complicated medication distribution procedure, as mentioned by several GPs in the survey. Patients could only be randomized once informed consent was signed and the baseline questionnaire had been filled out; very often, patients could not find the time to do this immediately after referral, which meant randomization and preparation of a medication pack would be delayed. As GP practices participating in the trial were spread across three Dutch provinces, 24-hour postal delivery was used to get medication packs to participants. In practice, this meant that patients who were in pain had to wait at least 24 to 48 hours before receiving medication; in contrast, if patients declined to participate

in the trial and asked their GP for a prescription, they would usually be able to pick up pain medication at their local pharmacy within an hour. Alternatively, patients could buy paracetamol and NSAIDs as over-the-counter medication without a prescription. Although our medication distribution procedure did fit within the limitations of Dutch law on medical research in humans, we have underestimated the potential for delay to arise in practice, the discomfort this meant for the participants and the unfavorable position of the trial in comparison to conventional treatment options.

During the design phase of PACE Plus, an alternative medication distribution procedure was considered. In this scenario, GPs would be asked to inform patients about the trial, collect informed consent, randomize patients and give them a medication pack immediately. However, under Dutch law on medical research in humans, this meant medication packs would have to be stored in a locked, temperature controlled environment, for which extra records would have to be kept by participating GPs. Although this scenario more closely resembled clinical practice and diminished delay, the procedure was dismissed because it would ask a substantially larger investment of time of participating GPs (who were already on a very tight schedule) and would require purchasing special medication storage equipment for all participating practices, for which trial budget did not allow.

Apart from logistics, alternative target populations were also considered during design of the trial. We chose to recruit patients with a new episode of acute LBP (incident cases) as opposed to prevalent cases of acute LBP (less than 6 weeks of pain) for two reasons. Firstly, our main aim was to replicate the PACE trial, which used incident cases. Secondly, many patients with prevalent LBP would already be using recommended doses of paracetamol or NSAIDs and would therefore be ineligible for participation in the trial. A more feasible alternative might have been to recruit patients with chronic LBP, but this of course would mean investigating a completely different research question and a design with a much longer follow-up period. Therefore, although more challenging than the alternatives, recruitment of incident cases of acute LBP seemed the most appropriate choice considering the aim of our trial. The discontinuation of this trial supports the previous finding that recruiting incident cases during the GP's consultation is associated with a lower probability of complete and timely patient recruitment (6). For future research, other designs such as an RCT embedded in a cohort of patients with recurrent LBP could be considered as an alternative to recruitment of incident cases during the first consultation.

Another design choice that may have impacted the feasibility of this trial was the objective to both repeat PACE and explore the alternatives to paracetamol in one trial. Not only did this mean that double the number of patients had to be recruited than when comparing just paracetamol and placebo, it also meant that the trial was more complicated to explain to both participating GPs and eligible patients. In hindsight, it might have been better to focus on one of our objectives and design the trial accordingly.

In terms of patient factors, effective self-management of LBP may have had an impact on patient recruitment. This is supported by the fact that the most important reason for exclusion during PACE Plus was patients already taking one of the study medicines; furthermore, several GPs mentioned in the survey their patients were confident they could self-manage their LBP. Several societal developments could have contributed to this improved self-management. Firstly, since 2006, patients have access to physiotherapy without referral from a GP, although research suggests this does not influence the number of GP visits (7). Secondly, it was demonstrated that the introduction of a patient information website of the NHG (5) has led to a decrease in healthcare usage of 12% (8). Finally, both paracetamol and NSAIDs are available without a doctor's prescription, as they are registered as over-the-counter medications in the Netherlands.

In PACE Plus, 14 of 27 excluded patients declined to participate in the trial. This is highly related to the comments of GPs that patients had other expectations and that patients declined participation. The trial did not provide any new treatment or in fact, any intervention that the patient could not obtain over-the-counter as mentioned above; instead, it relied on altruism of patients to answer the research question. The reason why patients declined to participate may have been because the underlying problem and research question were not considered relevant enough by many patients, as was mentioned in the survey by four GPs. This may have been avoided by discussing research ideas with a group of acute low back pain patients and taking their specific preferences and expectations for both treatments and outcomes into consideration.

Lack of GP's time was often mentioned as a factor affecting patient recruitment. This statement appears to reflect recent trends in increasing workload for Dutch GPs because of changes in the national health care system (9). As a result of this increasing workload, less time is available for participating in clinical research, which affects the feasibility of conducting clinical trials in general practice (10).

GPs participating in the PACE Plus trial reported a lower incidence of acute LBP than was initially expected based on incidence figures reported in the NHG practice guideline (11). This may have been because of Lasagna's law(6, 12, 13), the phenomenon that researchers overestimate the number of available patients meeting inclusion and exclusion criteria of a trial (originally formulated as "the incidence of patient availability sharply decreases when a clinical trial begins").

Considering PACE Plus investigated a highly similar patient group and similar interventions to the original PACE trial, we looked into differences between the two studies that may explain why PACE successfully completed patient recruitment while PACE Plus failed to do so. Firstly, the total budget in the PACE trial was substantially higher than in PACE Plus, which meant that in PACE, three fulltime research assistants could be employed as opposed to 1.2 fulltime equivalent in PACE Plus. Furthermore, both GP's and participants could be reimbursed for their time invested in the trial in PACE, whereas there was no

compensation in PACE Plus. Other strategies used in PACE but omitted in PACE Plus included conducting a pilot trial and rewarding participating GPs with Mandatory Continuing Education (MCE) points. In PACE, a 'novel' treatment (modified release paracetamol) was investigated that could potentially have been added to conventional treatment options, whereas in PACE Plus, two of the treatments were somewhat controversial both for GPs and patients (diclofenac and no medication); additionally, some GPs feared losing paracetamol as a treatment option. Finally, as opposed to the complex medication distribution procedure used in PACE Plus, medication was allowed to be directly provided by the GP preventing delay in patients commencing their pain relief medicine.

CONCLUSION

Although the PACE Plus trial was terminated as a result of insufficient patient inclusion, the research questions addressed in this trial remain relevant but unanswered. This is especially true in light of recent international LBP guidelines (14-17), in which the use of any medication for LBP is discouraged. Lessons learned from the discontinuation of PACE Plus and corresponding recommendations have been summarized in Table 4. We hope that these lessons and recommendations may be helpful in the design of upcoming research projects in LBP in general practice.

Table 4: Lessons learned from discontinuation of the PACE Plus trial and corresponding recommendations for future research

Lessons learned	Recommendations for future research
• Even though treatment distribution follows legislation and works on paper, they may have issues in practice that affect patients. • Asking GPs to recruit incident cases during the first consultation seems unlikely to be successful considering the current workload in general practice. • Attempting to answer several research questions at once not only requires more patients but is also more complicated to explain to GPs and potential participants. • Interests and expectations of patients can collide with scientifically interesting questions in practice. • The number of available patients meeting inclusion criteria is easily overestimated (Lasagna's Law). • Negative perception of trial treatment may influence participation of both GPs and patients.	• Keep treatment distribution as simple as possible and provide an attractive alternative to conventional therapy. • Try to answer your research question in prevalent cases or use alternative designs such as a trial within a cohort study. Take into account reimbursement of GPs in grant application and budgeting (especially if you do end up recruiting incident cases). • Choose your most important research question and design your trial to be as simple as possible. • Before starting a trial, ask a patient panel for their preferences and expectations of treatments and outcomes. Ask GPs if they know of any reservations about treatments you consider using. • Take Lasagna's law into account when planning your trial. • Consider conducting a pilot trial and taking part in Mandatory Continuous Education.

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Chapter 5

Can the inferences of the Paracetamol for Acute Low Back Pain (PACE) trial be reproduced?

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Submitted

ABSTRACT

Introduction

The aim of this study was to reanalyze and reinterpret data obtained in PACE, the first large randomized controlled trial evaluating the efficacy of paracetamol in acute low back pain, to assess the inferential reproducibility or the original conclusions.

Methods

Mixed effects models were used to reanalyze pain intensity (primary outcome; 11-point Numeric Rating Scale), and physical functioning, health-related quality of life, sleep quality and time until recovery (as secondary outcomes), according to the intention-to-treat principle. The original authors of the PACE study were not involved in the development of the methods for this reanalysis.

Results

The reproduction analyses indicated no effect of treatment on pain intensity and confidence intervals excluded clinically worthwhile effects (coefficient for regular paracetamol versus placebo 0.00 (-0.02- 0.01, p = 0.85); coefficient for paracetamol as-needed versus placebo 0.00 (-0.02 – 0.01, p = 0.92)). Similar results were obtained for all secondary outcomes.

Conclusions

This study indicates that the conclusions of the PACE trial are inferentially reproducible, even when using a different analytical approach. This reinforces the notion that management of acute low back pain should focus on providing patients advice and reassurance without the addition of paracetamol.

INTRODUCTION

Paracetamol (acetaminophen) used to be the first-choice analgesic for acute low back pain (LBP), but several recent clinical practice guidelines have abandoned this recommendation due to new evidence about its lack of efficacy (2-6). This evidence came from a 2016 Cochrane Review, which mainly based its results on the Paracetamol for Acute Low Back Pain (PACE) trial, the first and only large placebo-controlled randomized controlled trial (RCT) concerning the efficacy of paracetamol in acute LBP (7, 8). As this trial was highly influential on recent guidelines, the reproducibility of its results is of great importance (9).

Although the importance of reproducibility of scientific results is universally agreed upon, the terminology describing different types of reproducibility is not. In 2016, Goodman and colleagues introduced their 'new lexicon for research reproducibility', in which they described 3 types of reproducibility: methods reproducibility, results reproducibility and inferential reproducibility (10, 11). Methods reproducibility refers to the reproduction of an analysis using the same data, analysis plan and code, with the only difference being the analyst (12, 13). In results reproduction (also called 'replication'), new data is collected in the same population and consequently analyzed using the same analysis plan (12, 13). Finally, inferential reproducibility is the making of knowledge claims of similar strength from either a study replication or reanalysis of original data (10). In clinical research, reproduction studies are often the exception rather than the rule. However, early acceptance of scientific claims that are subsequently not reproducible may lead to harms; furthermore, reproduction is important in case only little evidence exists about a certain topic (14).

In the PACE trial, methods reproducibility was already addressed, as ***"Two statisticians who were masked to allocation independently did statistical analyses…"*** (8). Another RCT evaluating the result of the PACE trial (called the PACE Plus trial) was discontinued in 2017 due to insufficient recruitment of participants (15, 16). The primary outcome in the PACE trial was time until recovery from LBP, but this outcome is not among the outcome domains most relevant to patients with LBP (17). A core outcome set for LBP, published after the PACE trial had already been completed, included pain intensity, physical functioning, health-related quality of life (HRQoL) and number of deaths as core outcome domains (18). The first three core domains were included in the PACE original analysis as secondary outcomes, while no patients died during trial participation (8). In the analysis plan of the discontinued PACE Plus trial, pain intensity recorded in the daily pain diary was the primary outcome (15). The original analysis of the PACE trial reported results for pain intensity at one, two, four and 12 weeks of follow-up and presented only part of the data from the pain diary (up to 14 days of follow-up) in the appendix; not all collected diary data were used (8). The aim of this study is to reanalyze the original data obtained in the PACE trial in order to assess the inferential reproducibility of results obtained in PACE.

METHODS

Participants and data collection in the PACE trial

A brief description of participants and data collection in the original PACE trial is provided here; for a detailed description, see the original manuscripts (8, 19). The PACE trial was a randomized, placebo-controlled clinical trial that was conducted from November 2009 until March 2013 in Sydney, Australia. This RCT was conducted in a multicenter setting with a double-dummy design. The study protocol, analysis plan and main results of the PACE trial have been published (8, 19, 20). 1652 patients with a new episode of at least moderate-intensity LBP were randomly allocated to take paracetamol regularly (1330 mg of modified-release paracetamol 3 times a day, n = 550, which all were analyzed) or as-needed (up to a maximum of 1000 mg of regular paracetamol four times a day, n = 549, of which 546 were analyzed), or to receive placebo (n = 553, of which 547 were analyzed). Placebo tablets were identical in appearance to paracetamol tablets but did not contain the active component. Participants were instructed to use study medication until they had experienced seven consecutive days with pain scores of 0 or 1 out of 10 (measured on a numerical pain rating scale (NRS)), or for a maximum of four weeks, whichever occurred first. During the trial, participants, clinicians and researchers remained blinded to allocation of treatment.

Pain scores and number of tablets used were recorded by participants into a daily pain and drug diary until recovery or for a maximum of 12 weeks. At one, two, four and 12 weeks after randomization, follow-up questionnaires were collected.

Outcomes used in this reanalysis

For this reanalysis, the predefined and published analysis plan from the PACE Plus trial was used (15). The PACE Plus trial was a randomized, placebo-controlled clinical trial that aimed to reproduce the results obtained in the PACE trial; however, this trial was discontinued due to insufficient patient recruitment (15, 16). As the groups and outcomes were similar but not identical between PACE and PACE Plus, we present primary and secondary outcomes of the current reproduction analysis here. The primary outcome of the PACE Plus trial was LBP-intensity measured with an 11-point Numeric Rating Scale (NRS, score range 0–10; higher score means more pain) (21); this outcome was therefore used as the primary outcome for this study. Data from the daily pain and drug diary collected up to 28 days of follow-up were used for the current analyses rather than data from the follow-up questionnaires that were collected after one, two, four and 12 weeks. Secondary outcome measures from the PACE Plus analysis plan that were also collected in the PACE trial were:

- Time to recovery assessed with the daily low back pain severity scores. Recovery is defined as the first day of 0 or 1 pain intensity on a 0-10 pain scale, maintained for seven consecutive days (primary outcome of the PACE trial).
- Physical functioning measured with the Roland Morris Disability Questionnaire (RMDQ; score range 0–24; higher score indicates poorer functioning) (22).
- HRQoL measured with the physical and mental component summary scores of the Short Form 12 (SF-12, range 0-100; higher score indicates better HRQoL) (23).
- Sleep quality measured with a 4-point Likert scale derived from the Pittsburgh Sleep Quality Index (PSQI). Scores will be dichotomized into good sleep quality (score 1 'very good' and 2 'fairly good') and poor sleep quality (score 3 'fairly bad' and 4 'very bad') (24).

Statistical analysis

The researchers who performed the original analysis of the PACE trial were not involved in the reanalysis of the data; two co-authors of the original trial (CM, CL) involved in this study were only allowed to view the results and to give their comments in a separate box at the end of the article, after the reanalysis and interpretation had already been completed. The statistical analysis was performed according to the intention-to-treat (ITT) principle. Software used for the statistical analysis was R version 3.5.3 (25). An overview of differences between the original analysis and the current inferential reproduction analysis can be found in Table 1.

Primary statistical analysis

For clinical effectiveness the between-group differences for the primary outcome, LBP-intensity, were evaluated using a repeated measurements analysis with Poisson mixed effects models with adequate specification of the fixed and random effects structures to account for possible nonlinear effects. The covariance structure was unstructured. Poisson mixed effects models rather than linear mixed effects models were used as pain data was found to be zero-inflated and non-normally distributed (Supplementary Figure 1A); Poisson models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data such as data obtained from the NRS (26, 27). The GLMMadaptive R package was used to create the Poisson mixed effects models (28). Results are presented as corrected coefficients for treatment with corresponding 95% confidence intervals and p-values.

Secondary statistical analysis

We used Poisson mixed effect models for physical functioning as data obtained using the RMDQ was found to be zero-inflated and non-normally distributed (see distribution of data in Supplementary Figure 1B), linear mixed effect models for HRQoL, a logistic

Table 1: Differences between the original analysis by Williams et al and the current inferential reproduction analysis for outcomes of PACE.

Outcome	Original Analysis (Williams et al, Lancet 2014)				Inferential Reproduction Analysis			
	P/S	Method	Presented outcome	SA	P/S	Method	Presented outcome	SA
Time until recovery	P	Cox Proportional Hazards Model; Recovery time and status considered after 12 weeks of follow-up	Hazard Ratios for recovery for overall comparisons between groups after 12 weeks of follow-up	No	S	Cox Proportional Hazards Model; Recovery time and status considered after 28 days of follow-up	Hazard Ratios for recovery for overall comparisons between groups after 28 days of follow-up	Yes
Pain intensity	S	Linear Mixed Model on pain data at 1, 2, 4 and 12 weeks follow-up;	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up; results for analysis of diary data presented up to 14 days	No	P	Poisson Mixed Model on pain diary data up to 28 days of follow-up	Coefficients for change in log average pain intensity for overall comparisons between groups	Yes
Physical functioning	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Poisson Mixed Model	Coefficients for change in log average physical functioning for overall comparisons between groups	Yes
Sleep Quality	S	Log-Binomial Regression	Fractions and percentages of poor sleep quality in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Logistic Regression	Odds ratios for poor sleep quality for overall comparisons between groups	No
HRQoL	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	S	Linear Mixed Model	Coefficients for change in average HRQoL for overall comparisons between groups	No
Global rating of symptom change	S	Linear Mixed Model	Mean and SD in each group at 1, 2, 4 and 12 weeks follow-up	No	NA	-	-	-

HRQoL: Health-Related Quality of Life; NA: Not analyzed (not in PACE Plus trial protocol); P: Primary outcome; PACE: Paracetamol in Acute Low Back Pain; S: Secondary outcome; SA: Subgroup Analyses for participants with severe pain intensity (defined as NRS ≥ 7) or severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline; SD: Standard Deviation.

regression model for sleep quality and a Cox proportional hazards model for time until first recovery from LBP to assess between-group differences (26, 27); respective R packages used for the analyses were GLMMadaptive, lme4, Stats and Survival (25, 28-30). Sensitivity to missing data in the recovery analysis was investigated by calculating a best-case scenario and a worst-case scenario for recovery from LBP. In the best-case scenario, we assumed all missing participants recovered after the first day of follow-up. In the worst-case scenario, we assumed none of the missing participants recovered within 28 days of follow-up.

As specified in the PACE Plus study protocol, exploratory subgroup analyses were conducted for participants with severe LBP intensity (defined as NRS ≥ 7) or severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline (15); for these subgroups, estimates were obtained for LBP intensity, physical function and time until recovery using Poisson mixed effects models and Cox proportional hazard analyses respectively. Results are presented as corrected coefficients for treatment with corresponding 95% confidence intervals and p-values.

RESULTS

Reproduced baseline characteristics of participants of the PACE trial can be found in Table 2. Treatment groups were comparable at the start of the trial.

Results for the intention-to-treat analysis of the primary and secondary outcomes are presented in Table 3. Comparisons between regular paracetamol and placebo, paracetamol as-needed and placebo, and regular paracetamol and paracetamol as-needed are presented. As an example, the coefficient for regular paracetamol versus placebo (0.00, 95% CI -0.02 – 0.01) is interpreted as no change in the log average pain intensity for regular paracetamol when compared to placebo, when all other predictors remain constant.

Pain intensity diary data was available for 1601 participants (538 from the regular paracetamol group, 530 from the paracetamol as-needed group and 533 from the placebo group). All treatment coefficients indicated no effect of treatment on pain intensity during 28 days of follow up (Table 3A); no estimates exhibited between-group differences (even without correction for multiple testing). Furthermore, confidence intervals for the coefficients were between-0.1 and +0.1 and did not include a clinically worthwhile effect of treatment with paracetamol (taken regularly or as-needed) on pain intensity when compared to placebo.

The estimates for treatment coefficients for physical functioning and HRQoL, odds ratios for poor sleep quality, and hazard ratios for recovery from LBP indicated no effect of treatment without correction for multiple testing (Table 3B). Furthermore, clinically worthwhile differences were not included in the confidence intervals for these estimates.

Table 2: Patients and episode characteristics

Patient characteristics	Regular group (N = 550)	As-needed group (N = 546)	Placebo group (N = 547)
Age (years)	44.1 (14.8), N = 550	45.5 (16.5), N = 546	45.4 (15.9), N = 546
Women	263/547 (48%)	256/546 (47%)	245/544 (45%)
Private health insurance	275/550 (50%)	240/545 (44%)	248/544 (46%)
Currently employed	424/550 (77%)	403/546 (74%)	389/542 (72%)
Household income per week (per year)			
Negative or no income	19/540 (4%)	11/531 (2%)	22/531 (4%)
AUD 1-649 (1-33799)	133/540 (25%)	167/531 (31%)	168/531 (32%)
AUD 650-1699 (33800-88399)	243/540 (45%)	243/531 (46%)	226/531 (43%)
AUD 1700-3999 (88400-207999)	119/540 (22%)	92/531 (17%)	97/531 (18%)
≥AUD 4000 (≥208000)	26/540 (5%)	18/531 (3%)	18/531 (3%)
Use of drugs for another disorder	201/550 (37%)	227/543 (42%)	202/544 (37%)
Episode characteristics	**Regular group (N = 550)**	**As-needed group (N = 546)**	**Placebo group (N = 547)**
Days since onset of pain	10.1 (10.1), N = 550	9.8 (10.0), N = 546	9.7 (9.8), N = 546
Number of previous episodes	6.3 (13.7), N = 547	7.2 (14.9), N = 544	7.2 (16.8), N = 544
Presence of pain extending beyond the knee	108/547 (20%)	113/546 (21%)	99/544 (18%)
Number of days reduced usual activity	3.8 (6.5), N = 548	3.6 (5.9), N = 546	3.4 (5.3), N = 545
Physical functioning (RMDQ)	12.8 (5.6), N = 543	13.2 (5.4), N = 532	13.3 (5.5), N = 531
Feelings of depression in last week	3.2 (2.9), N = 547	3.1 (2.9), N = 546	3.1 (2.9), N = 546
Perceived risk of persistent pain	4.6 (2.8), N = 548	4.6 (2.8), N = 546	4.4 (2.8), N = 545
Back pain episode compensable	31/546 (6%)	44/543 (8%)	43/546 (8%)
Pain intensity (NRS)	6.3 (1.9), N = 550	6.3 (2.0), N = 545	6.2 (1.8), N = 546
Global rating of change	0.0 (2.1), N = 548	-0.1 (2.2), N = 545	-0.1 (2.1), N = 546
Poor sleep quality	273/549 (50%)	272/545 (50%)	272/546 (50%)
Function (Nominated Activity)	3.5 (1.7), N = 547	3.6 (1.9), N = 544	3.7 (1.9), N = 545
Quality of life – physical (SF-12)	42.7 (9.1), N = 537	41.8 (9.7), N = 543	42.1 (9.2), N = 538
Quality of life – mental (SF-12)	44.1 (7.7), N = 537	44.6 (7.7), N = 543	44.4 (7.9), N = 538
Credibility score (CEQ)	19.0 (4.9), N = 544	18.5 (5.2), N = 542	19.4 (4.9), N = 540
Expectation score (CEQ)	19.7 (5.3), N = 544	19.6 (5.1), N = 542	20.2 (5.1), N = 542

Data are mean (SD) or n/N (%). AUD: Australian Dollars; CEQ: Credibility/Expectancy Questionnaire; LBP: Low Back Pain; NRS: Numerical Rating Scale; PSQI: Pittsburgh Sleep Quality Index; RMDQ: Roland Morris Disability Questionnaire; SF-12; 12-item Short Form Survey.

Table 3: Coefficients for effect of treatment on log average pain intensity (primary outcome) during 28 days of follow-up and for secondary outcomes during 12 weeks of follow-up.

A. Primary outcome	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	0.0 (-0.02, 0.01) p = 0.85	0.0 (-0.02, 0.01) p = 0.92	0.00 (-0.02, 0.01) p = 0.92
B. Secondary outcomes	**Regular Paracetamol vs Placebo [β (95% CI)]**	**Paracetamol as needed vs Placebo [β (95% CI)]**	**Regular Paracetamol vs Paracetamol as needed [β (95% CI)]**
Physical functioning (RMDQ, scale range 0-24)	-0.06 (-0.13, 0.01) p = 0.11	-0.03 (-0.10, 0.04) p = 0.39	-0.03 (-0.09, 0.04) p = 0.46
hrQoL-mental (SF-12)	-0.13 (-0.72, 0.47) p = 0.67	0.17 (-0.42, 0.76) p = 0.58	-0.30 (-0.89, 0.30) p = 0.33
hrQoL-physical (SF-12)	0.0 (-0.77, 0.77) p = 1.00	-0.14 (-0.91, 0.62) p = 0.71	0.14 (-0.62, 0.91) p = 0.71
Sleep Quality (PSQI)	OR 1.03 (0.90, 1.19) p = 0.62	OR 1.04 (0.91, 1.19) p = 0.59	OR 1.00 (0.87, 1.14) p = 0.97
Time until first recovery	HR 1.02 (0.88, 1.18) p = 0.82	HR 1.02 (0.88, 1.19) p = 0.76	HR 0.99 (0.86, 1.15) p = 0.93

All numbers rounded to 2 decimal places. All models were corrected for sex, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; NRS: Numerical Rating Scale; OR: Odds Ratio; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-12: Short Form 12.

A graphical representation of the effects of treatment during follow-up is shown in Figure 1; graphs were obtained from uncorrected regression models containing only treatment and time as covariates. The lines for different treatment groups are very close in all graphs (and sometimes nearly indistinguishable), emphasizing no difference in effect between paracetamol and placebo. Pain intensity (Figure 1A) steadily declines over time in all treatment groups. For physical functioning (Figure 1B), a sharp decline can be observed during the first four weeks of follow-up followed by a stable phase until 12 weeks of follow-up. While the mental component of HRQoL remained constant during the trial (Figure 1C), the physical component of HRQoL steadily increased during 12 weeks of follow-up, indicating an improvement of HRQoL over time (Figure 1D). The probability of poor sleep quality steadily declined during 12 weeks of follow-up.

Figure 1F illustrates the recovery curves as well as median recovery times for the 3 treatment groups; recovery information could be obtained from pain diary information for 1601 participants; for 13 additional patients with all pain diary data missing, a recov-

ery date was available, yielding a total of 1614 patients for the analysis (542 in the regular paracetamol group, 535 in the paracetamol as-needed group and 537 in the placebo group). 1186 out of 1614 participants (73%) had recovered from LBP after 28 days of follow-up. Median recovery times were 13 days (95% CI 11-14 days), 14 days (95% CI 13-15 days) and 12 days (95% CI 10-14 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no difference between the 3 recovery curves (log-rank p = 0.7).

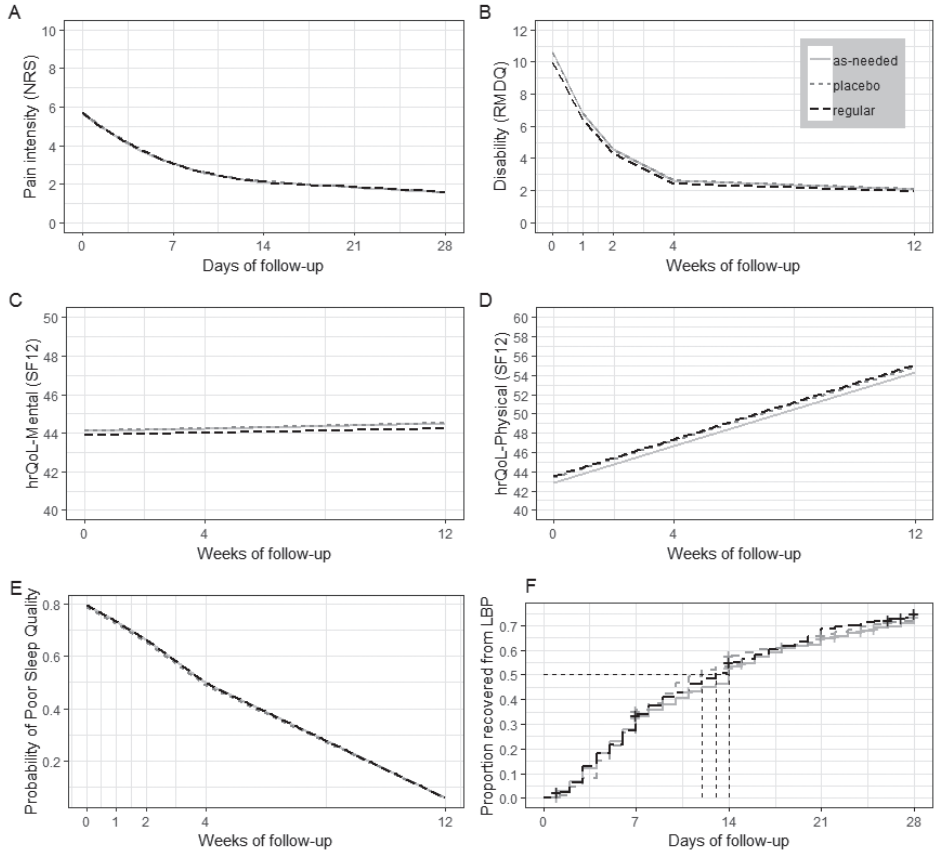

Figure 1: Effects of treatment on core outcomes of LBP (Pain intensity (A), Physical functioning (B) and hrQoL (C and D), Sleep Quality (E) and Time until first recovery from LBP (F). Graphs obtained from uncorrected regression models containing only treatment and time as covariates. Y-axis was truncated for plots B, C, D, E and F in order to improve visibility of results. Red line indicates placebo group, green line indicates paracetamol as-needed group, blue line indicates regular paracetamol group. hrQoL: health-related Quality of Life; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF12: Short Form 12

In Supplementary Figure 2, results of the analysis for the sensitivity to missing data were presented. Results did not substantially change in the sensitivity analyses when compared to the available data analysis.

In Table 4, results for the subgroups for severe baseline LBP intensity (defined as NRS ≥ 7) and severe baseline impairment of physical functioning (defined as RMDQ ≥ 16) are displayed. Results did not substantially change in the subgroups when compared to the main analysis. Figure 2 shows recovery curves for these subgroups. In the severe baseline LBP intensity subgroup, 547 out of 776 participants (70%) had recovered from LBP after 28 days of follow-up. Median recovery times were 14 days (95% CI 13-19 days), 16 days (95% CI 14-18 days) and 13 days (95% CI 11-17 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no difference be-

Table 4: Coefficients for subgroups for effect of treatment on average pain intensity (primary outcome) and time until first recovery during 28 days of follow-up and on average physical function during 12 weeks of follow-up.

Subgroup 1: Severe baseline LBP intensity (defined as NRS ≥ 7)	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	-0.02 (-0.09, 0.05) p = 0.49	0.0 (-0.07, 0.07) p = 0.96	-0.02 (-0.09, 0.05) p = 0.53
Physical functioning (RMDQ, scale range 0-24)	-0.01 (-0.11, 0.08) p = 0.80	-0.01 (-0.10, 0.09) p = 0.88	-0.01 (-0.10, 0.09) p = 0.91
Time until recovery	HR 1.04 (0.83, 1.30) p = 0.74	HR 1.09 (0.88, 1.36) p = 0.44	HR 0.95 (0.77, 1.19) p = 0.67
Subgroup 2: Severe baseline impairment of physical functioning (defined as RMDQ ≥ 16)	Regular Paracetamol vs Placebo [β (95% CI)]	Paracetamol as needed vs Placebo [β (95% CI)]	Regular Paracetamol vs Paracetamol as needed [β (95% CI)]
Pain intensity (NRS, scale range 0-10)	0.0 (-0.10, 0.10) p = 0.99	0.03 (-0.07, 0.12) p = 0.58	-0.03 (-0.12, 0.07) p = 0.59
Physical functioning (RMDQ, scale range 0-24)	0.02 (-0.06, 0.11) p = 0.56	-0.03 (-0.11, 0.05) p = 0.50	0.05 (-0.03, 0.13) p = 0.20
Time until recovery	HR 1.02 (0.79, 1.30) p = 0.89	HR 1.08 (0.84, 1.38) p = 0.53	HR 0.94 (0.73, 1.21) p = 0.64

Subgroups were: severe LBP intensity (defined as NRS ≥ 7) and severe impairment of physical functioning (defined as RMDQ ≥ 16) at baseline. All numbers rounded to 2 decimal places. All models were corrected for sex, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire.

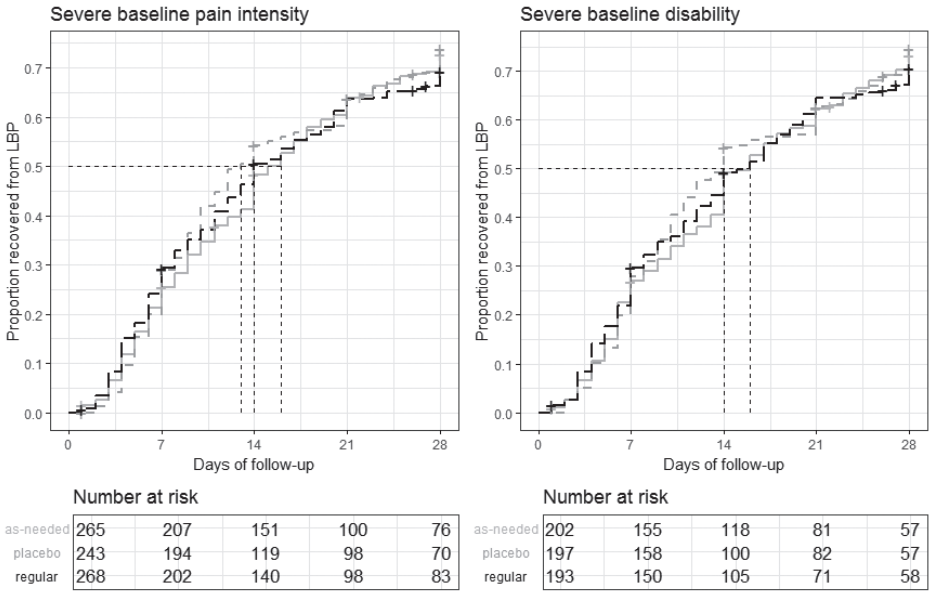

Figure 2: Survival curves for time until first recovery in subgroups. Subgroups were: A: severe baseline LBP intensity (defined as NRS ≥ 7) and B: severe baseline physical functioning (defined as RMDQ ≥ 16).

tween the 3 recovery curves (log-rank p = 0.8). In the severe baseline impairment of physical functioning subgroup, 420 out of 592 participants (71%) had recovered from LBP after 28 days of follow-up. Median recovery times were 16 days (95% CI 13-19 days), 16 days (95% CI 14-19 days) and 14 days (95% CI 11-21 days) in the regular paracetamol, paracetamol as-needed and placebo groups, respectively. There was no significant difference between the 3 recovery curves (log-rank p = 0.9).

DISCUSSION

We performed an inferential reproduction analysis of data collected in the PACE trial, using the predefined and published analysis plan from the PACE Plus trial; key differences between the original analysis and the current reanalysis include a different primary outcome and different analysis methods, follow-up time points, presented outcomes and subgroup analyses (8, 15). In our reanalysis of the PACE-trial data the treatment of patients with acute LBP with paracetamol (taken regularly or as-needed) had no effect on pain intensity, physical functioning, HRQoL and time until recovery from LBP when compared to placebo; our study thus confirmed the original results of the PACE trial (8).

A strength of this study is the fact that the predefined and published analysis plan from a discontinued replication trial of PACE was used (15). Furthermore, Poisson mixed

models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data such as data obtained from the NRS and the RMDQ than linear mixed models (26, 27). A weakness of this study is the fact that the published analysis plan could not be completely used as intended, due to differences between the PACE trial and the PACE Plus trial (15). Whereas the PACE trial had 3 treatment groups (regular paracetamol, paracetamol as-needed and placebo), the PACE Plus trial had four treatment groups (regular paracetamol, regular diclofenac, placebo and advice-only). Furthermore, as mentioned in the 'Methods' section, not all outcome domains were the same between both trials, meaning we could only use part of the analysis plan as well as part of the available data collected in the PACE trial; however, despite some differences, the core outcome domains and instruments for LBP were included in the reproduction analysis (18, 21). Finally, the authors deviated from the original protocol by using Poisson mixed effect models rather than the predefined linear mixed effects models, but the nature of the data obligated this change.

As the PACE Plus protocol only specified the collection of pain diary data up to 28 days of follow-up (upon which the recovery analysis was based), the authors decided not to use any data gathered in the PACE trial after 28 days of follow-up, as this would not have been available in the PACE Plus study; furthermore, the analysis for this reproduction analysis was conducted on available data with sensitivity analyses for missing data, whereas in the original report, data was imputed in order to obtain complete groups for the recovery analysis. A consequence of these decisions is that patients who recovered after 28 days of follow-up will be considered censored in the current version of the recovery analysis; this may be an explanation for the difference in median recovery times (13, 12 and 14 days in the regular paracetamol, paracetamol as-needed and placebo groups, respectively versus 17, 16 and 17 days as reported in the original report).

This reanalysis of the PACE data yielded no substantially different results and therefore, the interpretation of the PACE trial remains the same: paracetamol (taken regularly or as needed) did not improve outcomes of LBP when compared to placebo. Thus, this study supports the notion that paracetamol has a limited role in the management of acute LBP in general practice. Furthermore, this reanalysis confirms that prognosis of acute LBP is favorable and that natural course or regression to the mean (Figure 1), rather than pharmacological treatment, are important factors influencing core outcomes' trajectory in patients with acute LBP.

While method reproducibility and inferential reproducibility have now been addressed for the PACE trial, results reproducibility (also called replication) has not (8, 10, 11). In other words, the highest level of evidence for the (lack of) efficacy of paracetamol for acute LBP is still based on a single trial that was conducted in a single country (7, 8). In order to definitively rule out efficacy of paracetamol for acute LBP, the authors highly recommend a replication of PACE, ideally in a multi-country collaboration.

CONCLUSION

This inferential reproduction analysis indicates that treatment of patients with acute LBP with paracetamol (taken regularly or as-needed) has no effect on core outcomes of LBP when compared to placebo, and thus confirms the original results of the PACE trial (8). This means the original conclusions of the PACE trial are inferentially reproducible, even when using a different approach to the statistical analysis.

Box 1: Comments on this inferential reproduction analysis of PACE by the original authors:
The inferential reproduction analysis of the PACE study, conducted by an independent group based on a pre-defined statistical analysis plan of a similar study (PACE Plus), agrees with the conclusion from the original PACE analysis – that paracetamol has no effects on pain or other core outcomes compared to placebo in patients with acute low back pain.
This study joins other secondary analyses of the PACE study showing the lack of benefits of paracetamol: we have also found that paracetamol did not improve pain intensity even in patients who complied with the regular treatment regimen (article to be published in 2019), and taking paracetamol did not confer any economic benefits in patients with acute low back pain (1). However we await the most important and currently missing step in definitively confirming the results of PACE – a replication of the PACE study. We would encourage other triallists to make their data sets available to allow reanalysis of the data by independent groups.

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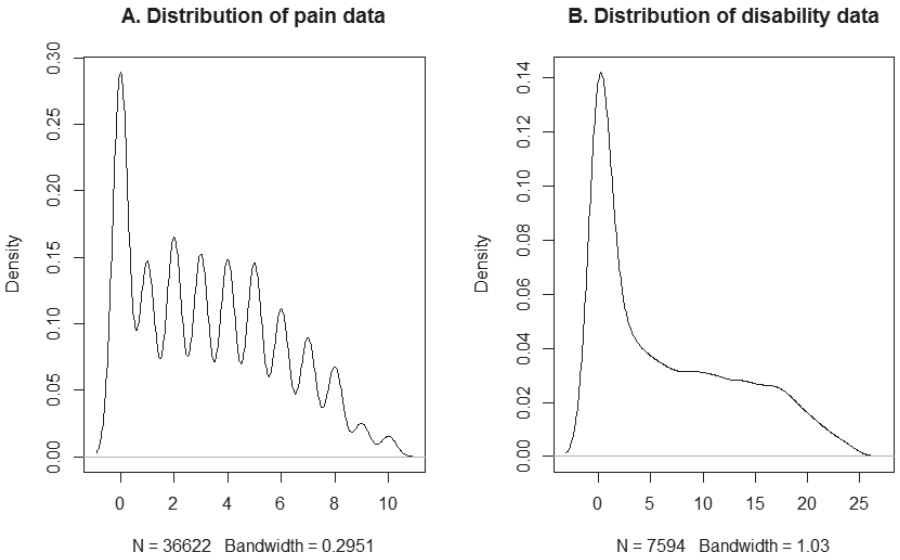
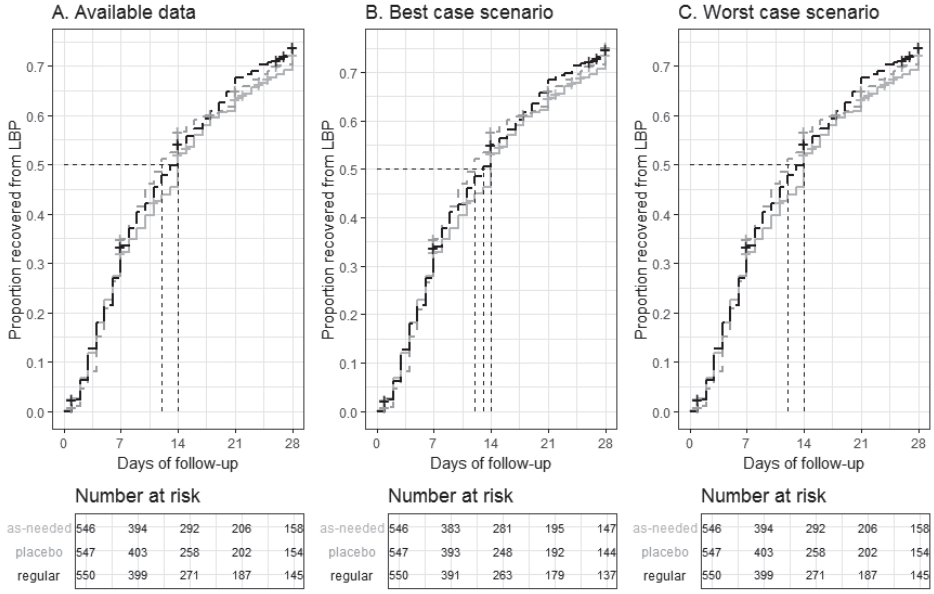


Supplementary Figure 1: Distribution of pain data (A) and physical functioning data (B) in the PACE trial.



Supplementary Figure 2: Sensitivity analysis for missing data in the recovery analysis for time until first recovery. A: Recovery curve using available data for recovery (n = 1614). B: Recovery curve with best case scenario assumed for missing cases (i.e. all missing participants recovered after 1 day of follow-up; n = 1643). C: Recovery curve with worst case scenario assumed for missing cases (i.e. none of the missing participants recovered within 28 days of follow-up; n = 1643).

Chapter 6

Paracetamol is ineffective for acute low back pain even for patients who comply with treatment: Complier Average Causal Effect Analysis of a Randomized Controlled Trial

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PAIN, 2019

ABSTRACT

Introduction

In 2014, the PACE trial demonstrated that paracetamol had no effect compared to placebo in acute low back pain (LBP). However, non-compliance was a potential limitation of this trial. The aim of this study was to investigate the efficacy of paracetamol in acute low back pain among compliers.

Methods

Using individual participant data from the PACE trial (ACTN12609000966291), Complier Average Causal Effects (CACE), Intention-to-treat (ITT) and Per Protocol (PP) estimates were calculated for pain intensity (primary), and disability, global rating of symptom change and function (all secondary) after two weeks of follow-up. Compliance was defined as intake of an average of at least four of the prescribed six tablets of regular paracetamol per day (2660 milligrams in total) during the first two weeks after enrolment. Exploratory analyses using alternative time points and definitions of compliance were conducted.

Results

Mean between-group differences in pain intensity on a 0-10 scale using the primary time point and definition of compliance were not clinically relevant (propensity weighted CACE 0.07 (-0.37, 0.50) p = 0.76; joint modelling CACE 0.23 (-0.16, 0.62) p = 0.24; ITT 0.11 (-0.20, 0.42) p = 0.49; PP 0.29 (-0.07, 0.65) p = 0.12); results for secondary outcomes and for exploratory analyses were similar.

Conclusions

Paracetamol is ineffective for acute low back pain even for patients who comply with treatment. This reinforces the notion that management of acute low back pain should focus on providing patients advice and reassurance without the addition of paracetamol.

INTRODUCTION

The Paracetamol for Acute Low Back Pain (PACE) trial was the first placebo-controlled randomized controlled trial (RCT) investigating the efficacy of paracetamol (acetaminophen) for acute low back pain (LBP) (1-3). In this RCT, 1652 people seeking care for LBP were randomized to take paracetamol regularly, paracetamol ***as needed for pain,*** or placebo using a blinded double-dummy design. The unexpected result that paracetamol had no effect compared to placebo on pain intensity, time until recovery, disability and function in acute LBP received worldwide attention in the medical literature and the lay-press. Nonadherence to study medication was identified as a potential limitation in the original publication of the PACE results as well as in a number of commentaries discussing the impact of the trial (1, 4-6); in a descriptive analysis of nonadherence in PACE, 70% of patients were found to be non-adherent over the four-week treatment period, and overall adherence to guideline-recommended care for acute LBP was described as 'poor' (5). In RCTs, noncompliance has always been an issue and may even influence their results (7). However, the question as to whether there is benefit of an intervention in participants who adequately adhere to treatment is difficult to answer using conventional techniques used in the analysis of RCTs (i.e. intention to treat analysis and per protocol analysis).

Complier average causal effects (CACE) analysis involves comparing participants who were randomized to the intervention and complied, to participants from the control group who would have complied to the intervention had they been randomized to the intervention (so called 'would be compliers'). As participants in the control group are never offered the active treatment in reality, there is no observed data in the control group for adherence to active treatment. CACE analysis is therefore essentially a missing data problem. CACE analyses have been used to assess the efficacy among compliers of intervention programs in substance abuse, behavioral interventions and a multifactorial intervention in physiotherapy (8-16). In the field of LBP, CACE analysis has been used to assess the influence of non-compliance on effectiveness of a cognitive behavioral intervention (17).

This analysis aims to investigate the efficacy of paracetamol in acute LBP among participants who complied with regular paracetamol treatment in the PACE trial using a CACE analysis, to address the uncertainty that compliance may have influenced drug efficacy (14, 15). Additionally, we conducted intention to treat analysis and per protocol analysis to compare to the CACE analysis.

METHODS

Ethics

The University of Sydney Human Research Ethics Committee granted ethical approval of the PACE trial protocol. Written informed consent was provided by all participants. The PACE trial was registered with the Australian and New Zealand Clinical Trial Registry, number ACTN12609000966291.

Participants and procedures

The PACE trial was a multicenter, double-dummy, randomized, placebo-controlled trial that was conducted from November 2009 until March 2013. The study protocol, analysis plan and main outcomes have been published (1-3). In summary, 4606 people seeking care for acute non-specific low-back pain or responding to a community advertisement were screened by 235 primary care clinicians across Sydney, Australia. The trial included 1652 participants with a new episode of moderate, or severe-intensity low back pain with or without leg pain. Participants were randomly allocated (in a 1:1:1 ratio) to receive 2 tablets of 665 mg modified-release paracetamol tablets 3 times a day regularly (n = 550), or 2 tablets of 500 mg immediate-release paracetamol tablets up to 4 times a day ***as-needed*** for pain (n = 549), or placebo (n = 553). Participants, clinicians and researchers were blinded to allocation of treatment during the trial. Participants were instructed to use study medication until they had experienced 7 consecutive days with pain scores of 0 or 1 out of 10 (measured on a numerical pain rating scale (NRS)), or for a maximum of four weeks, whichever occurred first. Participants were asked to return to their clinician for review after 1 week, at which time the use of study medication was reviewed. Rescue medication (naproxen 250 mg) was available for participants with continuing ongoing pain as required.

Participants recorded pain scores and number of tablets taken in a daily pain and drug diary until recovery or for a maximum of four weeks. Follow-up data was collected at 1, 2, 4 and 12 weeks after randomization. Data were either entered directly by the participant into an online database or recorded by participants in a booklet and transcribed to a case report form during a telephone interview with research staff. Returned tablets were counted by research staff to confirm self-reported compliance. In this CACE analysis, data from the ***as-needed*** treatment group were not used because the 'need' to take medication would have been different for each individual participant, preventing the use of one universal definition of compliance in this treatment group.

Outcome measures

For this CACE analysis, pain intensity measured on a NRS from 0 (no pain) to 10 (worst possible pain) was the primary outcome; analyses were also performed for disability (Ro-

land Morris Disability Questionnaire, scored from 0 (no disability) to 24 (high disability)), Global rating of symptom change (scored from-5 (vastly worse) to +5 (completely recovered)) and function (Patient Specific Function Scale, with the average of 3 items scored from 0 (unable to perform) to 10 (able to perform at preinjury level), these outcomes represent two of the three core outcome domains for non-specific LBP (18). Although measurements were conducted in the PACE trial for the third core outcome domain (health-related quality of life), this outcome was omitted from the CACE analysis because of missing data (the Short Form 12 (SF12)), which we expected would compromise the CACE estimation. Time until recovery, the primary outcome of the original PACE analysis, was omitted as methods for survival CACE analysis have not yet been developed.

Definitions of compliance to the study intervention and time points

Compliance was defined as taking an average of at least 4 tablets per day (approximately 66% of the prescribed dosage or 2660 mg per day) of modified-release paracetamol until recovery or for a maximum of 2 weeks for the primary outcome of the CACE analysis (pain intensity at 2 weeks of follow-up).

Two alternative cut-off points for compliance were defined ***a priori*** to assess whether the treatment effect differed according to the level of compliance: taking an average of 5 tablets per day (83% of the prescribed dosage or 3325 mg per day) and taking 6 tablets per day (100% of the prescribed dosage or 3990 mg per day). The two-week questionnaire was chosen as the primary time point as this was closest to the median recovery time (1); exploratory analyses were performed at 1 week and 4 weeks follow-up for pain intensity only. For the exploratory analysis of pain intensity at 4 weeks, the definition of compliance was expanded to 'until recovery or for a maximum of 4 weeks'.

Statistical analysis

Using individual participant data from the PACE trial, baseline participant and back pain episode characteristics were compared between observed compliers and observed non-compliers in the regular paracetamol treatment group, using standardized differences (St.Diffs). For binary variables, the St.Diff was calculated as the difference in proportions divided by the standard deviation i.e. (p1 – p2) / sqrt ([p1 (1 – p1) + p2 (1 – p2)] / 2). For categorical variables with more than 2 levels, we used a method proposed by Yang and Dalton based on a multivariate Mahalanobis distance method which generalizes the St.Diff metric (19). St.Diffs larger than 0.1 were considered to be relevant and were reported in the results section.

We calculated ITT, CACE and Per Protocol (PP) estimates for the 4 outcomes of interest (pain intensity, disability, global rating of symptom change, and function). ITT analyses were performed consistent with the original analysis of the PACE trial, comparing outcomes between all participants randomized to the regular paracetamol group and

all patients randomized to the placebo group using linear mixed models adjusted for all baseline characteristics (1, 3). Based on our definition of compliance, we created a dichotomous variable indicating observed compliance status. We used this dichotomous variable for the PP analysis, where we compared outcomes of observed compliers from the regular paracetamol group to outcomes of observed compliers in the placebo group using linear mixed models adjusted for all baseline characteristics. Outcomes of the PP analysis are not included in the main results of this article, but are added to the supplementary information. The reason for this is that we were interested in comparing results of the CACE analysis to results of a PP analysis, which may provide biased estimates of efficacy for compliers, as the reasons for noncompliance could be different for the regular paracetamol group than for the placebo group. For example, noncompliance in the regular paracetamol group could be related to side effects despite efficacy, whereas noncompliance in the placebo group may be due to lack of efficacy (20). In the Supplementary Information, the difference between PP and CACE analyses is discussed in more detail.

As the underlying assumptions for CACE analysis are untestable, we obtained CACE estimates using both a propensity weighted estimation approach and a joint modeling estimation approach, which serve as each other's sensitivity analysis (15). More information about the underlying assumptions for these CACE estimation techniques can be found in the Supplementary Information. For the propensity weighted CACE estimation, compliance to regular paracetamol was predicted on baseline covariates using logistic regression with a dichotomous variable indicating the observed compliance status. The prediction model was developed using only data from the regular paracetamol group. This model was then used to calculate the likelihood of compliance (propensity score) in the placebo group. To prevent missing propensity scores due to missing baseline data, missing baseline variables were imputed once using fully conditional specification (i.e. imputation on a variable-by-variable basis in an iterative fashion, with an imputation model specified for each incomplete baseline variable (21)). The imputed dataset was used to predict the propensity score. Once derived, the propensity scores were added back to the original non-imputed baseline data set and each participant was weighted as follows: in the regular paracetamol treatment arm, compliers received a weight of 1 and non-compliers a weight of 0; in the placebo treatment arm, the weight was calculated as the odds of the propensity score p (odds=p/(1-p)). We investigated if any residual imbalances existed after weighting by calculating St.Diffs between baseline variables between compliers in the regular paracetamol group and weighted placebo group participants (see Supplementary Information). Finally, we performed an analysis comparing compliers in the regular paracetamol group to odds-weighted patients in the placebo group. Propensity weighted CACE analyses were adjusted for all baseline characteristics in order to correct for residual imbalances. To assess a potential "dose-response" ef-

fect we performed a pre-specified subgroup analysis according to quintiles of likelihood of compliance (using the propensity scores created for the propensity weighted CACE analysis). For this subgroup analysis, the primary cut-off point for compliance (taking an average of at least 4 tablets of modified-release paracetamol per day) and primary time point (two weeks of follow-up) were used); for each quintile group, a mean difference and corresponding confidence interval was calculated.

For the CACE analysis using joint modeling, 2 models were simultaneously estimated: a model for compliance and a model for the outcome (pain intensity). Estimates were adjusted for all baseline characteristics. This estimation approach resulted in a comparison between observed compliers in the regular paracetamol group to inferred compliers (would-be-compliers) in the placebo group.

Results of all the analyses (ITT, CACE propensity and CACE joint modeling and PP) are presented as mean differences between paracetamol and placebo groups with 95% confidence intervals and corresponding p-values. ITT, PP and propensity weighted CACE analyses were performed in SAS version 9.4 (SAS Institute, Inc., Cary, NC), joint modeling CACE estimation was performed in Mplus version 7 (22).

RESULTS

Characteristics of compliers to regular paracetamol

The baseline characteristics of participants in the regular paracetamol group are presented in Table 1; participants were split into compliers and non-compliers based on our main definition of compliance (an average of at least 4 tablets of 665 mg regular paracetamol per day during the first 2 weeks). Table 1 also shows St.Diffs between observed compliers and non-compliers. At the primary time point of the CACE analysis (2 weeks), 394 out of 550 participants in the paracetamol group (72%) were classified as compliers.

When comparing compliers and non-compliers, compliers tended to be somewhat older (44.9 vs 42.4 years, St.Diff 0.17); were more likely to be male (54% vs 46%, St.Diff 0.15); were more likely to have private health insurance (52% vs 46%, St.Diff 0.12); had a different distribution of household income (St.Diff 0.23); were less likely to have pain extending beyond the knee (17% vs 26%, St.Diff 0.22); had a longer period of reduced usual activity (4.1 vs 3.2 days, St.Diff 0.13); scored higher for feelings of depression (3.4 vs 2.8, St.Diff 0.18); reported a higher perceived risk of persistent pain (4.8 vs 4.1 out of 10, St.Diff0.22); more often reported poor sleep quality (51% vs 46%, St.Diff 0.10); scored lower on function (3.4 vs 3.7, St.Diff 0.15) and scored lower for physical quality of life (42.4 vs 43.3, St.Diff 0.11).

Table 1: Baseline characteristics for observed compliers and non-compliers in the regular paracetamol group, including standardized mean differences between observed compliers and observed non-compliers.

Patient characteristics	Regular Paracetamol (N = 550)		Standardized differences
	Observed compliers (N = 394)	Observed non-compliers (N = 142)	
Age (years)	44.9 (14.9) N = 394	42.4 (14.5) N = 142	0.171*
Women	182/393 (46%)	75/140 (54%)	0.146*
Private health insurance	203/394 (52%)	65/142 (46%)	0.115*
Currently employed	305/394 (77%)	107/142 (75%)	0.048
Household income per week (per year)			0.342*
Negative or no income	13/384 (3%)	6/142 (4%)	
AUD 1-649 (1-33799)	89/384 (23%)	42/142 (30%)	
AUD 650-1699 (33800-88399)	174/384 (45%)	59/142 (42%)	
AUD 1700-3999 (88400-207999)	86/384 (22.4%)	32/142 (23%)	
≥AUD 4000 (≥208000)	22/384 (6%)	3/142 (2%)	
Use of drugs for another disorder	148/394 (38%)	49/142 (35%)	0.064
LBP Episode characteristics			
Days since onset of pain	10.2 (10.3) N = 394	9.8 (9.6) N = 142	0.037
Number of previous episodes	6.4 (12.8) N = 392	6.5 (16.4) N = 141	0.009
Presence of pain extending beyond the knee	68/392 (17%)	37/141 (26%)	0.217*
Number of days reduced usual activity	4.1 (7.0) N = 393	3.2 (4.9) N = 141	0.134*
Disability (RMDQ)	12.7 (5.5) N = 390	12.9 (5.9) N = 139	0.027
Feelings of depression in last week	3.4 (2.9) N = 392	2.8 (3.0) N = 141	0.175*
Perceived risk of persistent pain	4.8 (2.7) N = 392	4.1 (2.9) N = 142	0.224*
Back pain episode compensable	20/392 (5%)	10/140 (7%)	0.085
Pain intensity (NRS)	6.3 (1.9) N = 394	6.2 (2.0) N = 142	0.039
Global rating of symptom change	0.0 (2.1) N = 393	0.1 (2.0) N = 141	0.054
Poor sleep quality	200/393 (51%)	65/142 (46%)	0.103*
Function (Nominated Activity)	3.4 (1.7) N = 392	3.7 (1.9) N = 141	0.151*
Quality of life – physical (SF-12)	42.4 (9.0) N = 384	43.3 (9.4) N = 140	0.112*
Quality of life – mental (SF-12)	44.3 (7.7) N = 384	43.7 (7.8) N = 140	0.071
Credibility score (CEQ)	19.1 (4.9) N = 390	18.8 (4.8) N = 140	0.064
Expectation score (CEQ)	19.8 (5.4) N = 389	19.4 (5.3) N = 141	0.080

St.Diffs: Standardized Differences; Data are mean (SD) or n/N (%);* under standardized differences indicate St.Diffs > 0.1. AUD: Australian Dollar; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; SF-12; 12-item Short Form Survey; CEQ: Credibility/Expectancy Questionnaire.

Estimates of the CACE models

Table 2 presents ITT and CACE estimates for pain intensity, disability, global rating of symptom change, and function in the PACE trial at week 2 with compliance defined as an average intake of at least 4 tablets per day during the first 2 weeks.

For the primary outcome measure, none of the analyses indicated a difference in pain intensity (ITT: mean difference 0.11 (-0.20, 0.42) p = 0.49; joint modeling CACE: mean difference 0.23 (-0.16, 0.62) p = 0.24; propensity weighted CACE: mean difference 0.07 (-0.37, 0.50) p = 0.76). Similar results were obtained for the secondary outcomes disability, global rating of symptom change, and function. Confidence intervals of estimates for pain intensity, global rating of symptom change and function were all between-1 and 1 and therefore exclude clinically meaningful differences; the confidence interval of the estimate of disability exceeded 1 in both the propensity weighted CACE estimation and the joint modelling CACE estimation; however, this difference is still smaller than the minimal clinically important difference (MCID) of 30% change from baseline (in PACE, approximately 4 points) (23).

Table 2: Outcomes of PACE trial (Pain Intensity, Disability, Global Rating of Symptom Change and Function) at week 2 with compliance defined as an average intake of ≥4 tablets per day for regular paracetamol group vs placebo group.

Outcome	ITT	Propensity weighted CACE	Joint Modeling CACE
Pain Intensity (NRS) (scale range 0-10)	0.11 (-0.20, 0.42) p = 0.49	0.068 (-0.37, 0.50) p = 0.76	0.23 (-0.16, 0.62) p = 0.24
Disability (RMDQ) (scale range 0-24)	0.11 (-0.60, 0.82) p = 0.76	0.054 (-0.93, 1.04) p = 0.91	0.37 (-0.55, 1.30) p = 0.43
Global Rating of Symptom Change (scale range-5 to +5)	0.0019 (-0.26, 0.27) p = 0.99	0.059 (-0.33, 0.44) p = 0.76	-0.083 (-0.42, 0.25) p = 0.62
Function (Patient Specific Function Scale) (scale range 0-10)	-0.069 (-0.38, 0.24) p = 0.67	0.0043 (-0.45, 0.45) p = 0.99	-0.28 (-0.67, 0.11) p = 0.16

All values represent mean difference (lower limit of 95% CI, upper limit of 95% CI) p value; mean differences calculated by subtracting placebo group mean from regular paracetamol group mean. All analyses were adjusted for gender and baseline age, private health insurance, employment status, household income, use of drugs for another disorder, days since onset of pain, number of previous episodes, presence of pain extending beyond the knee, number of days reduced usual activity, disability (RMDQ), feelings of depression, perceived risk of persistent pain, back pain episode compensability, pain intensity, global rating of symptom change, sleep quality, function, quality of life (mental and physical components of the 12 item short form survey (SF-12)) and credibility and expectation scores (CEQ). Values rounded to 2 significant figures. Abbreviations: CACE: Complier Average Causal Effect; CEQ: Credibility/Expectancy Questionnaire; ITT: Intention-to-Treat; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire.

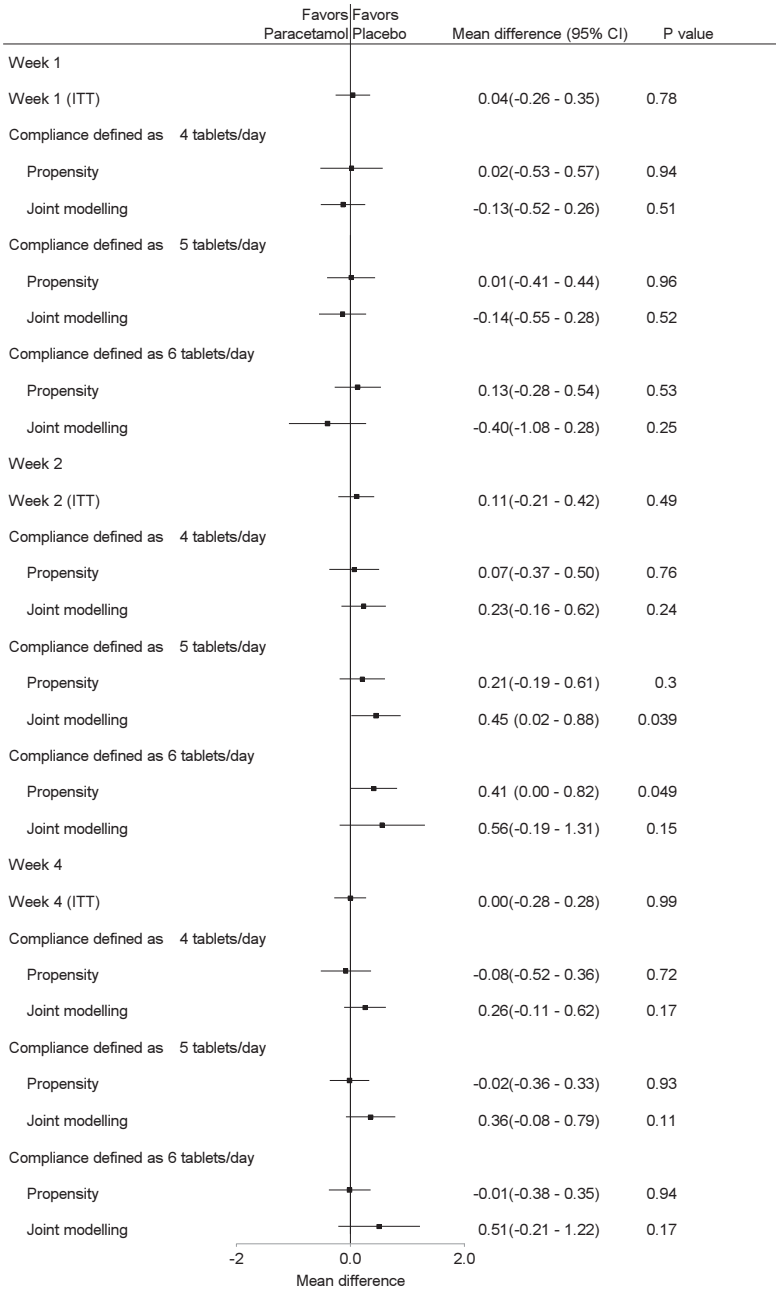

Figure 1: Exploratory ITT and CACE analyses for pain intensity including both primary and alternative cut-off points for compliance (an average of at least 5 tablets per day and 6 tablets per day, calculated over the periods of interest) as well as primary and alternative time points (1 week and 4 weeks). Values rounded to 2 significant figures. ITT: intention to treat, CACE: Complier Average Causal Effect, CI: Confidence Interval.

Exploratory analyses

Figure 1 shows results of the exploratory ITT and CACE analyses using primary and alternative cut-off points for compliance (an average of at least 5 tablets per day, and 6 tablets per day) and primary and alternative time points (1 week and 4 weeks). Mean differences in pain intensity between regular paracetamol and placebo were calculated for 3 definitions of compliance at 3 time points using 3 analysis techniques, yielding a total of 21 estimates.

Minimal differences in pain intensity were only found for 2 of the 21 analyses: the joint modeling CACE estimate after 2 weeks with compliance defined as an average of at least 5 paracetamol tablets per day (mean difference 0.45 (0.02, 0.88), p = 0.039) and for the propensity weighted CACE estimate after 2 weeks with compliance defined as 6 paracetamol tablets per day (mean difference 0.41 (0.00, 0.82) p = 0.049); however, no correction was made for multiple testing. Furthermore, the confidence intervals for these estimates do not include clinically meaningful differences. For all other time points, no differences in pain intensity were found.

Results of the ITT analysis for pain intensity at 2 weeks for quintiles of compliance (defined as an average of at least 4 tablets per day over 2 weeks) are depicted in Figure 2. No difference in pain intensity was found between regular paracetamol and placebo for any of the compliance subgroups. There appears to be no clear dose-response relationship between compliance and effect of paracetamol.

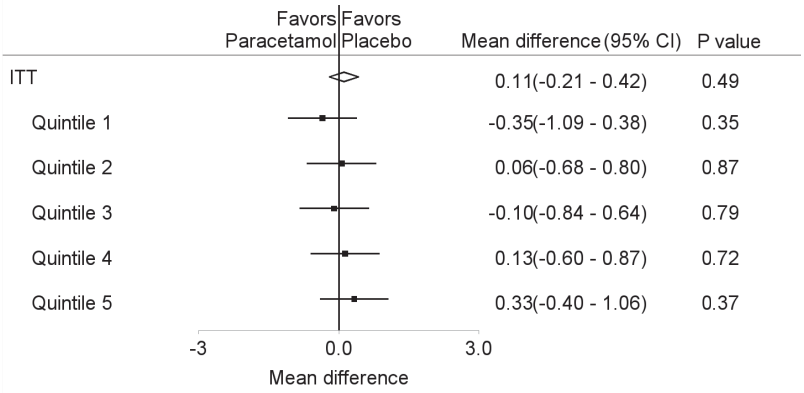

Figure 2: Exploratory ITT analysis for pain intensity at 2 weeks for quintiles of likelihood of compliance (with compliance defined as taking an average of at least 4 tablets of modified-release paracetamol per day during 2 weeks of follow-up). Quintile groups are presented in order of increasing likelihood of being compliant, with Quintile 1 representing the group that was least likely to be compliant and Quintile 5 representing the group that was most likely to be compliant. ITT: intention to treat, CI: Confidence Interval.

DISCUSSION

In this secondary analysis of the PACE trial we found that paracetamol had no clinically-meaningful effect when compared to placebo on pain intensity, disability, global rating of symptom change and function in people with acute LBP who complied with regular paracetamol.

The CACE analysis technique produces robust estimates of efficacy amongst compliers; furthermore, we applied 2 distinct methods to estimate complier average causal effects, which serve as each other's sensitivity analysis (15). The credibility of our findings is supported by the fact that no large differences exist between these 2 estimation techniques (15). Data used in this analysis were collected in a large and well-conducted RCT (1, 24).

The CACE analysis technique has two main weaknesses. First, no universally accepted definition of compliance to paracetamol for low back pain exists. Using our main definition of compliance, 72% of participants in the regular paracetamol group were classified as compliers. We explored stricter definitions of compliance and found results consistent with the primary analysis; however, as the percentage of compliers was lower using these definitions, CACE estimates using these definitions are less robust. Second, CACE estimates were based on patient-reported compliance filled out in paper drug diaries, which may not have perfectly represented actual consumption of tablets. However, counts of returned medicines and results from the brief adherence rating scale were consistent with patient-reported compliance (1).

The findings of this secondary analysis should be placed in context of the original analysis of the PACE trial, which is still the only RCT that has assessed the efficacy of paracetamol for acute LBP and is considered to be the best available evidence (24). As mentioned in the introduction, non-compliance to study medication was considered a potential limitation of the PACE results (1, 4-6). The results of this analysis suggest this is not the case and thus support the conclusion from the original analysis of the PACE trial that paracetamol is ineffective for acute LBP when compared to placebo. It is important to note that CACE analysis is a technique that accounts for a very specific participant group, namely those who comply with treatment. Although this analysis technique may be useful in trials where non-compliance is an issue, results of the ITT analysis remain the most relevant to clinical practice.

After a lack of efficacy of paracetamol for acute LBP was demonstrated by the PACE trial, paracetamol was no longer recommended as first choice analgesic in four out of eight recently published national clinical practice guidelines (25-28). However, other recent guidelines still endorse the prescription of paracetamol for acute LBP (29-32). One possible justification was that paracetamol may be effective in those who comply with the dosing regimen. Our CACE analyses have demonstrated that the efficacy of paracetamol is unlikely to change even in patients with total compliance to the regular

regimen, reinforcing that management of acute low back pain should focus on providing patients advice and reassurance without the addition of paracetamol.

In conclusion, paracetamol is not more effective than placebo for acute LBP in compliers of the treatment regimen. CACE analyses using different cut points showed that paracetamol had no effect on pain intensity and secondary outcomes when compared to placebo for participants that complied to regular paracetamol in the PACE trial. These results support the original findings of the PACE trial.

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APPENDIX 1: SUPPLEMENTARY INFORMATION

Background to Complier Average Causal Effect (CACE) analysis

Conventional Intention-to-Treat (ITT) analysis produces the overall mean effect for all participants randomized, regardless of compliance status. While an ITT analysis provides an unbiased estimate of the effect of treatment allocation, it does not estimate the efficacy of treatment in compliers. Common analysis strategies used to estimate treatment effect in compliers are Per Protocol (PP) analysis, where effects for compliers in the intervention group are compared to effects for participants in the control group, and As-treated (AT) analysis, where effects for those who received the intervention are compared to effects for those who did not receive the intervention. However, the use of PP and AT analyses to account for compliance may lead to biased results (1). The reason for this is that likelihood of compliance to placebo is fundamentally different from likelihood of compliance to an active treatment; this could actually work in two directions: participants receiving an active drug may be more likely to comply to treatment if they experience a drug effect that participants receiving placebo cannot experience. On the other hand, participants receiving an active drug may be less likely to comply to treatment if they experience adverse effects that participants receiving placebo don't experience. Compliers to an active treatment in one group and compliers to placebo in another group may thus be incomparable, while the overall treatment groups would of course be comparable due to randomization.

To obtain unbiased estimates for complying participants in the intervention group of a trial, the effect estimates for compliers in the intervention group could be compared to the effects for those in the control group, who would have complied to the treatment had they been randomized to the intervention group (so-called 'would-be-compliers'). This comparison can be made using an average causal effects (CACE) analysis (2, 3). Of course, the active treatment was never offered to the control group participants in real life; therefore we have no observed compliance data in this group. Therefore, the CACE analysis is essentially a missing data problem in the control group; once 'would-be-compliers' in this group have been identified, a normal ITT analysis can be performed.

Underlying assumptions in CACE analysis (3) and their translation to the PACE trial

1. **Ignorable Treatment Assignment:** Treatment assignment is independent of the potential outcomes, conditional on the observed baseline covariates (3).
   PACE: This assumption is automatically satisfied in randomized experiments.
2. **Stable Unit Treatment Value Assumption (SUTVA):**

a. **The potential outcomes for each person are unaffected by the treatment assignment of other individuals:** this means there is no interference between patients in different groups (3).

   PACE: Although interference between individuals in different treatment groups could not be ruled out in PACE, it is unlikely that this has played a significant role in the outcomes as all participants were blinded to the treatment they observed and everyone received medication through the double-dummy design; this means that unblinding because of dosage scheme is highly unlikely. SUTVA is therefore considered to be fulfilled.

b. **There is only one version of each treatment:** the treatments given to each individual within each treatment condition do not vary across individuals (3).

   PACE: Both active and control groups had one fixed treatment protocol in PACE. SUTVA is therefore considered to be fulfilled.

3. **Monotonicity:** This assumption states there are no Defiers (i.e. participants who do the exact opposite of the instructions given in the trial; they take the intervention if they're in the control group and they don't take the intervention when they are in the active group) (3).

   PACE: Because of the blinded double-dummy design used in PACE, patients in all groups received the same instructions and were blinded for the intervention they received (this means in this case, active paracetamol group and placebo group do not get contradicting instructions). It seems unlikely that there were Defiers in PACE.

4. **Exclusion Restriction:** Treatment assignment does not affect the outcome if it does not affect the treatment actually received (no direct effect of treatment assignment on outcome). This means there is no effect of the treatment assignment for always takers or never takers; therefore Always-Taker Average Causal Effect (AACE) = 0 and Never-Taker Average Causal Effect (NACE) = 0 (3).

   PACE: Translation of the assumption to terms used in the PACE trial: patients who never take or always take paracetamol for low back pain won't experience an effect of being randomized in the PACE trial. This assumption is may not be fulfilled if trial randomization (i.e. telling people to take the given medication) has an effect on outcome through other behavior than taking pills; for example if always-takers or never-takers start exercising more for their back pain because of the attention given to the back pain during the trial.

5. **Principal Ignorability:** Potential outcomes are the same across compliance strata, conditional on covariates. In other words, principal stratum membership is independent of the potential outcomes given the observed covariates. This assumption implies that we can identify principal stratum membership using only the observed covariates. This is what enables us to find the "likely compliers" in the control group, using the model of compliance behavior as a function of covariates fit among treat-

ment group members; i.e., it implies that the outcomes of the control group members identified as "likely compliers" actually reflect well what the potential outcomes under control would have been had the treatment group compliers been in the control group instead (3).

PACE: This assumption is very likely to hold as the intervention and control are so similar in PACE due to the blinded double dummy design.

6. **Missing Values Assumptions:**
   a. **Missing At Random (MAR) Assumption:** Non-response is associated with non-compliance only among individuals with observed compliancy information. The probability of the outcome being recorded is not associated with the outcome conditional on treatment assignment, observed treatment receipt status and pre-treatment covariates. Under this assumption, missingness is not attributable to unobserved data, including unobserved compliance status (3).

      PACE: This assumption is unlikely to hold in PACE, as nonresponse in the placebo group is very likely to be associated to the trial outcomes (i.e. participants who have recovered are less likely to continue filling out the trial questionnaires). However, the vast majority of patients provided data for the primary outcome in PACE (97%). For this reason, missing data were not considered influential in the CACE analyses presented in this article.

   b. **Response Exclusion Restriction (RER) Assumption:** For never-takers, the probability of outcomes being recorded is not affected by treatment assignment status. This assumption will be violated if response probability is affected by treatment assignment. This means it is violated if never-takers provide outcome data more when assigned to the intervention condition then when assigned to the control condition (3).

      PACE: This assumption may hypothetically be violated in 2 ways:
      - Poorly complying participants may have felt some benefit from active paracetamol and might have felt more obliged to provide outcome information when assigned to the active regular paracetamol group than when assigned to the placebo group.
      - Poorly complying participants might have been demoralized when assigned to the intervention condition, by failing to comply with the intervention. This might not have happened if they had been assigned to the placebo group.

   c. **Stable Complier Response (SCR) Assumption:** For compliers, the probability of outcomes being recorded is not affected by treatment assignment status. This assumption will be violated if response probability is affected by treatment assignment. This means it is violated if compliers provide outcome data more when assigned to the intervention condition then when assigned to the control condition (3).

PACE: This assumption may hypothetically be violated in 2 ways:

- Compliers may have felt some benefit from active paracetamol and might have felt more obliged to provide outcome information when assigned to the active regular paracetamol group than when assigned to the placebo group.
- Compliers might have been demoralized when assigned to the placebo condition because they did not feel any effect despite taking the prescribed medication. This might not have happened if they had been assigned to the intervention group.

Supplementary Results

Baseline characteristics of the complete regular paracetamol and placebo groups (as shown in the original analysis) are presented with corresponding standardized differences (St.Diffs) in Supplementary Table 1; due to chance, significant differences were found for employment status and household income. Because no significant differences could be found in all other baseline characteristics, we still assume correct randomization.

Estimates of the CACE models compared to Per Protocol analysis

Mean differences and corresponding p-values were very similar between Per Protocol analysis and joint modeling CACE for all outcomes that were assessed (Supplemental Table 2). A reason for this may be that in this trial, inferred compliance behavior to regular paracetamol in the placebo group was similar to observed compliance to placebo in this group. However, it should be noted that Per Protocol analysis should not be routinely used to account for non-compliance, as using this statistical technique may lead to biased effect estimates (3, 4).

Technical considerations about this CACE analysis

Three assumptions are used in CACE analysis (3). The first assumption is ignorable treatment assignment, which states that treatment assignment is independent of the potential outcomes, conditional on the observed baseline covariates. This assumption is automatically satisfied in randomized experiments. The second assumption is stable unit treatment value assumption (SUTVA), which states two things: firstly, the potential outcomes for each person are unaffected by the treatment assignment of other individuals and secondly, there is only one version of each treatment, meaning that treatments given to each individual within each treatment condition do not vary across individuals. It is unlikely that SUTVA has been violated in PACE due to the fixed treatment protocols and double-dummy design, which prevents unblinding and thus interference between participants. The third assumption is monotonicity, which states that there are no defiers (participants who do the exact opposite of the instructions given in the trial. Because all patients received the same instructions and blinding was shown to have been successful, it is unlikely the monotonicity assumption has been violated in PACE (5).

In joint modeling CACE estimation, exclusion restriction is an additional underlying assumption; this assumption states that treatment assignment does not affect the outcome if it does not affect the treatment actually received (i.e., there is no direct effect of treatment assignment of the outcome). In propensity-weighted CACE estimation, exclusion restriction is replaced by principal ignorability; this assumption states that principal stratum membership is independent of the potential outcomes given the observed covariates. In practice, exclusion restriction is unverifiable and can hardly ever be completely dismissed; in PACE, it could very well be that receiving instructions to

take medication may lead to always-takers or never-takers of medication being more active, which in turn could affect the outcomes of their back pain. However, in settings like the PACE trial where there is no effect of the intervention at all, the exclusion restriction assumption is automatically satisfied and joint modeling CACE estimation is likely to perform very well (given no severe deviations from normality of outcome variables); although the assumption is not necessarily violated, principal ignorability propensity-weighted CACE estimation does not necessarily perform well in this scenario (3). For this reason, we expect the joint modeling approach will have resulted in the more reliable CACE estimates of the two methods used.

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APPENDIX 2: SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table 1: Baseline characteristics for complete patient groups (ITT).

Patient characteristics	All patients (ITT)		
	Paracetamol (N = 550)	Placebo (N = 547)	Standardized difference
Age (years)	44.1 (14.8) N = 550	45.4 (15.9) N = 546	0.085
Women	263/547 (48%)	245/544 (45%)	0.061
Private health insurance	275/550 (50%)	248/544 (46%)	0.088
Currently employed	424/550 (77%)	389/542 (72%)	0.122*
Household income per week (per year)			0.179*
Negative or no income	19/540 (4%)	22/531 (4%)	
AUD 1-649 (1-33799)	133/540 (25%)	168/531 (32%)	
AUD 650-1699 (33800-88399)	243/540 (45%)	226/531 (43%)	
AUD 1700-3999 (88400-207999)	119/540 (22%)	97/531 (18%)	
≥AUD 4000 (≥208000)	26/540 (5%)	18/531 (3%)	
Use of drugs for another disorder	201/550 (37%)	202/544 (37%)	0.012
Episode characteristics			
Days since onset of pain	10.1 (10.1) N = 550	9.7 (9.8) N = 546	0.039
Number of previous episodes	6.3 (13.7) N = 547	7.2 (16.8) N = 544	0.058
Presence of pain extending beyond the knee	108/547 (20%)	99/544 (18%)	0.039
Number of days reduced usual activity	3.7 (6.3) N = 548	3.4 (5.3) N = 545	0.075
Disability (RMDQ)	12.8 (5.6) N = 543	13.3 (5.5) N = 531	0.081
Feelings of depression in last week	3.2 (2.9) N = 547	3.1 (2.9) N = 546	0.048
Perceived risk of persistent pain	4.5 (2.8) N = 548	4.4 (2.8) N = 545	0.050
Back pain episode compensable	31/546 (6%)	43/546 (8%)	0.088
Pain intensity	6.3 (1.9) N = 550	6.2 (1.8) N = 546	0.054
Global rating of symptom change	0.0 (2.1) N = 548	-0.1 (2.1) N = 546	0.046
Poor sleep quality	273/549 (50%)	272/546 (50%)	0.002
Function (Nominated Activity)	3.5 (1.7) N = 547	3.7 (1.9) N = 545	0.069
Quality of life – physical (SF-12)	42.7 (9.1) N = 537	42.1 (9.2) N = 538	0.065
Quality of life – mental (SF-12)	44.1 (7.7) N = 537	44.4 (7.9) N = 538	0.040
Credibility score (CEQ)	19.0 (4.9) N = 544	19.4 (4.9) N = 540	0.078
Expectation score (CEQ)	19.7 (5.3) N = 544	20.2 (5.1) N = 542	0.093

St.Diffs: Standardized Differences; Data are mean (SD) or n/N (%);* under standardized differences indicate St.Diffs > 0.1. AUD: Australian Dollar; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; SF-12; 12-item Short Form Survey; CEQ: Credibility/Expectancy Questionnaire.

Supplementary Table 2: Outcomes of PACE trial (Pain Intensity, Disability, Global Rating of Symptom Change and Function) at week 2 with compliance defined as an average intake of ≥4 tablets per day for regular paracetamol group vs placebo group.

Outcome	Per Protocol	Joint Modeling CACE
Pain Intensity (NRS) (scale range 0-10)	0.29 (-0.074, 0.65) p = 0.12	0.23 (-0.16, 0.62) p = 0.24
Disability (RMDQ) (scale range 0-24)	0.41 (-0.40, 1.22) p = 0.32	0.37 (-0.55, 1.30) p = 0.43
Global Rating of Symptom Change (scale range-5 to +5)	-0.13 (-0.44, 0.18) p = 0.41	-0.083 (-0.42, 0.25) p = 0.62
Function (Patient Specific Function Scale) (scale range 0-10)	-0.28 (-0.65, 0.089) p = 0.14	-0.28 (-0.67, 0.11) p = 0.16

All values represent mean difference (lower limit of 95% CI, upper limit of 95% CI) p value; mean differences calculated by subtracting placebo group mean from regular paracetamol group mean. Values rounded to 2 significant figures. NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire.

Supplementary Table 3: Assessment for residual imbalances between the regular paracetamol group and weighted placebo group in the distribution of categorical variables after the weighting procedure in propensity-weighted CACE analysis at week 2 with compliance defined as an average intake of ≥4 tablets per day.

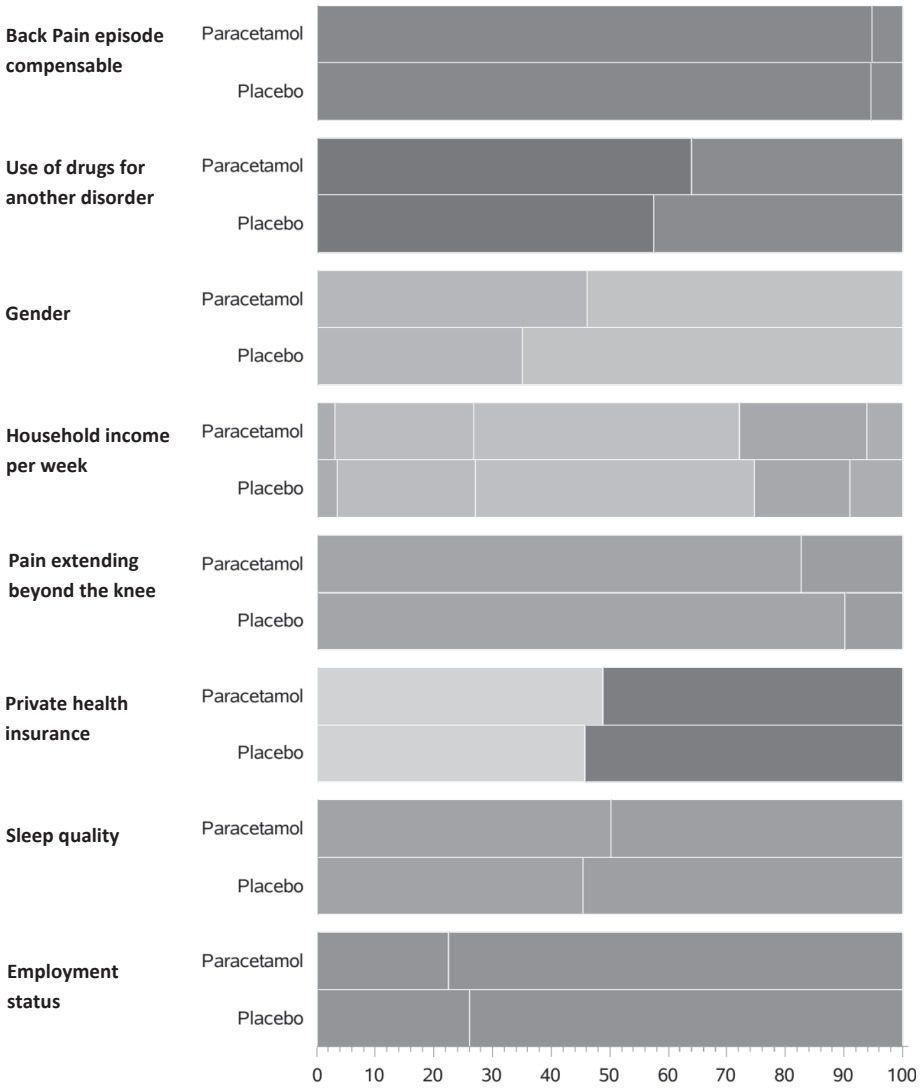
Variable	Placebo (proportion)	Paracetamol (proportion)	Standardized difference
Back Pain episode compensable	0.054	0.053	0.00314
Use of drugs for another disorder	0.42	0.36	0.134*
Women	0.35	0.46	0.226*
Household income per week (per year):	0.035	0.031	0.0228
Negative or no income	0.24	0.24	0.00158
AUD 1-649 (1-33799)	0.48	0.46	0.0440
AUD 650-1699 (33800-88399)	0.16	0.22	0.137*
AUD 1700-3999 (88400-207999)	0.090	0.062	0.106*
≥AUD 4000 (≥208000)	0.098	0.17	0.223*
Private health insurance	0.54	0.51	0.0618
Poor sleep quality	0.55	0.50	0.0962
Currently employed	0.74	0.78	0.0838

St.Diffs: Standardized Differences; * under standardized differences indicate St.Diffs > 0.1; AUD: Australian Dollar.

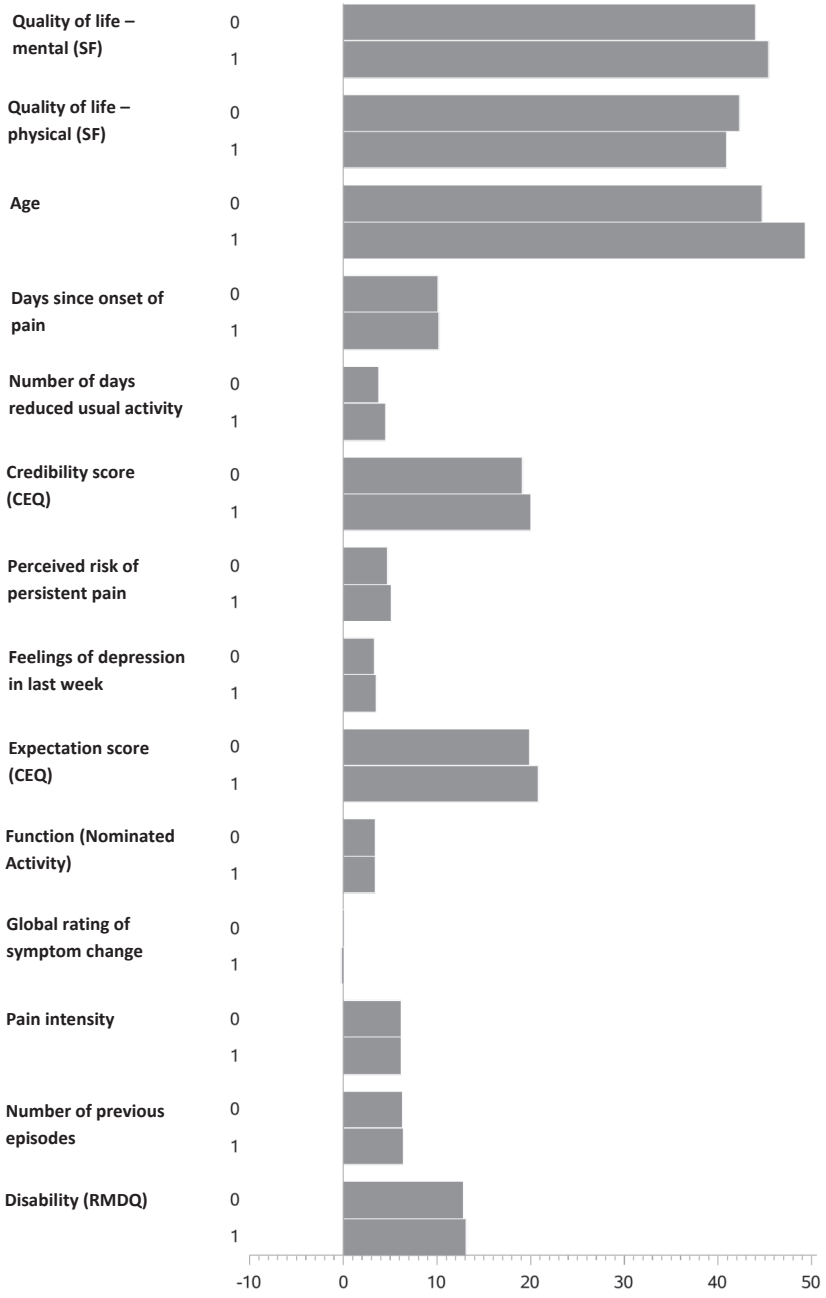
Supplementary Table 4: Assessment for residual imbalances between the regular paracetamol group and weighted placebo group in the means of continuous variables after the weighting procedure in propensity-weighted CACE analysis at week 2 with compliance defined as an average intake of ≥4 tablets per day.

Variable	Placebo mean (SD)	Paracetamol mean (SD)	Standardized difference
Quality of life – mental (SF-12)	45.46 (15.19)	44.08 (6.72)	0.0908
Quality of life – physical (SF-12)	40.91 (17.26)	42.34 (7.82)	0.0831
Age	49.33 (31.27)	44.77 (12.86)	0.146*
Days since onset of pain	10.28 (19.31)	10.12 (8.63)	0.00862
Number of days reduced usual activity	4.57 (12.95)	3.83 (5.53)	0.0571
Credibility score (CEQ)	20.04 (9.02)	19.13 (4.19)	0.100*
Perceived risk of persistent pain	5.14 (5.32)	4.77 (2.35)	0.0700
Feelings of depression in last week	3.57 (6.04)	3.34 (2.49)	0.0381
Expectation score (CEQ)	20.81 (9.00)	19.94 (4.64)	0.0967
Function (Nominated Activity)	3.40 (3.63)	3.43 (1.41)	0.00664
Global rating of symptom change	-0.12 (4.11)	-0.01 (1.81)	0.0262
Pain intensity	6.20 (3.53)	6.29 (1.59)	0.0251
Number of previous episodes	6.39 (27.04)	6.31 (11.33)	0.00326
Disability (RMDQ)	13.11 (10.65)	12.87 (4.67)	0.0233

St.Diffs: Standardized Differences; * under standardized differences indicate St.Diffs > 0.1; RMDQ: Roland Morris Disability Questionnaire; SF-12; 12-item Short Form Survey; CEQ: Credibility/Expectancy Questionnaire.



Supplementary Figure 1: Graphical assessment for residual imbalances between the regular paracetamol group and weighted placebo group in the distribution of categorical variables after the weighting procedure in propensity-weighted CACE analysis at week 2 with compliance defined as an average intake of ≥4 tablets per day.



Supplementary Figure 2: Graphical assessment for residual imbalances between the regular paracetamol group and weighted placebo group in the means of continuous variables after the weighting procedure in propensity-weighted CACE analysis at week 2 with compliance defined as an average intake of ≥4 tablets per day.
0: Paracetamol; 1: Placebo.

Chapter 7

Is there an association between reporting adverse events and outcomes of patients with acute low back pain?

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Submitted

ABSTRACT

Introduction

In people with acute low back pain (LBP), there may be an association between reporting adverse events (AEs) of treatment and outcomes of LBP. This study aimed to 1) investigate the association between baseline characteristics of participants and reporting AEs and 2) the association between reporting treatment related AEs and outcome in people with acute LBP.

Methods

Data from the PACE-trial, evaluating paracetamol versus placebo in acute LBP, was used in this analysis as an observational cohort. The association between baseline characteristics and reporting AEs by participants was investigated using a logistic regression model. The association between reporting AEs and outcomes of LBP was investigated using mixed effects models for LBP intensity, physical functioning and health-related quality of life (hrQoL) and Cox proportional hazards models for time until recovery.

Results

Reporting any AE was strongly associated with the use of medicines for a health problem other than LBP (odds ratio (95% CI) 1.42 (1.07-1.88)). Reporting any AE was not associated with less favorable outcomes for LBP intensity, physical functioning, hrQoL or time until recovery (respective coefficients 0.00 (-0.07-0.07), 0.02 (-0.05-0.10), -0.44 (-1.08-0.20), -0.54 (-1.37-0.29) and HR 1.09 (0.94-1.26)). Due to the very low number of serious AES (death or hospitalization) there was insufficient information to investigate the association between reporting these AEs and baseline characteristics or the association with outcomes of LBP.

Conclusions

In the PACE trial, reporting adverse events after using paracetamol or placebo was associated with the use of medicines for other health problems, but not with (unfavorable) outcomes of LBP.

INTRODUCTION

Paracetamol has represented the first-choice pain medication for patients with acute low back pain (LBP) (1). Although it has been more recently demonstrated that paracetamol is not more effective than placebo in acute LBP (2), paracetamol is still recommended in 4 out of 8 recently updated national clinical practice guidelines for the management of LBP (3-11). Paracetamol is one of the most widely used analgesics and is perceived as a relatively safe medicine by consumers and clinicians (12-14). However, paracetamol overdose is a major cause of acute liver failure globally (15). furthermore, observational studies have found paracetamol ingestion to be associated with an increased risk of cardiovascular, gastro-intestinal and kidney-related AEs in some patient groups (13).

Treatment outcomes in people with acute LBP are influenced by patient expectations and beliefs (16). Haanstra and colleagues demonstrated that expectations related to the effectiveness of treatment were associated with pain intensity after 4 weeks of follow-up and recovery from LBP (17). Similarly, there may be an association between reporting AEs and the outcomes of LBP. The impact of AEs on outcomes can be best studied in large observational cohort studies; however, in the available cohort studies of people with recent onset low back pain, AEs were not rigorously investigated (18). A suitable alternative available data source is to investigate the impact of AEs in patients with acute LBP in a large randomized controlled trial (RCT). With 1652 participants, the PACE trial, which investigated the efficacy of paracetamol, is one of the largest RCTs in people with acute LBP (2).

The aim of this study is to identify baseline socio-demographic and clinical characteristics associated with reporting AEs in trial participants with acute LBP; and second, to investigate the association between reporting AEs and outcomes of acute LBP.

METHODS

Participants and design:

The PACE trial was a multicenter, double-dummy, randomized, placebo-controlled trial that was conducted from November 2009 until March 2013 in Sydney, Australia. The study protocol (19), analysis plan (20) and main results (2) have been published elsewhere. In short, the PACE trial recruited 1643 participants with a new episode of at least moderate LBP (measured by an adaptation of item 7 of the Short Form 36 Health Survey (21)) which were randomly allocated (in a 1:1:1 ratio) to receive 2 x 665 mg modified-release paracetamol tablets administered 3 times a day regularly (n = 550), or 1 to 2 tablets of 500 mg immediate-release paracetamol tablets taken up to 4 times a day as-needed for pain (n = 549), or identical placebo (n = 553) until recovery from LBP or for a maximum of four weeks. Participants recorded pain intensity scores and number

of tablets taken in a daily pain and drug diary. Follow-up data were collected at 1, 2, 4 and 12 weeks after randomization. No treatment effects were observed between study groups (2); therefore for the current study, the complete study population was used and analyzed as an observational cohort study such that allocation to treatment was not included in the analysis.

Ethics

The PACE trial had approval from University of Sydney Human Research Ethics Committee and was prospectively registered with the Australian and New Zealand Clinical Trial Registry (ACTN12609000966291).

Measures

In the PACE trial, AEs were recorded after 1, 2, 4 and 12 weeks of follow-up; for each AE, start date, end date, details and ICD-10 code (obtained using the International Classification of Diseases and Related Health Problems, 10th edition (22)) were recorded (2). AEs were defined as the occurrence or diagnosis of any new medical disorder or exacerbation of any old medical disorder since the most recent contact with the researchers (2). Serious adverse events (SAEs) were defined as any event resulting in death or hospital admission, including pregnancy (2).

To investigate the association between baseline characteristics and reporting AEs, the baseline characteristics as presented in the PACE trial-publications were used (2, 19). These included dichotomous, categorical and continuous variables: sex, age, employment status, income, use of medication for other health conditions, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days of reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations, and physical and mental health-related quality of life (HRQoL) (2, 19).

For the analysis regarding the association between reporting AEs and outcomes of LBP, the core outcome domains for LBP (i.e. pain intensity, physical function and HRQoL (23)) and time until recovery from LBP (the primary outcome of PACE) were used. These outcomes were measured as follows:

- LBP-intensity recorded as average pain intensity the last 24 hours using an 11-point NRS (score range 0–10; higher score means more pain) (24). LBP-intensity was measured at baseline and daily until 12 weeks follow-up or until recovery from LBP.
- Physical functioning measured with the Roland Morris Disability Questionnaire (RMDQ; score range 0–24; higher score indicating poorer back-related physical functioning) (25). Physical functioning was measured at baseline and at 1, 2, 4 and 12 weeks follow-up.

- HRQoL measured with the physical and mental aggregate scores of the Short Form 12 (SF-12, with a population mean of 50 and standard deviation of 10; higher score indicating better HRQoL) (21). HRQoL was measured at baseline and at 4 and 12 weeks follow-up.
- Time until recovery from LBP as assessed with the daily low back pain severity scores. Recovery was defined as the first day of 0 or 1 pain intensity on a 0-10 pain scale, maintained for seven consecutive days.

Statistical analysis

Software used for the statistical analysis was R version 3.5.3 (26). For the descriptive statistics of AEs, frequency tables were created including the number of AEs reported per participant, the minimum, maximum, mean and median were calculated.

To investigate the association between baseline characteristics and reporting of AEs ('yes/no'), initially a full logistic regression model was created with the reporting of any AE as dependent variable and with all baseline covariates and treatment allocation as covariates. Subsequently, a backward stepwise model selection procedure based on Akaike's Information Criterion (AIC) was performed using the stepAIC function from the MASS package in R (27). For covariates in the final model, Odds Ratios (ORs) and their corresponding 95% confidence intervals (CIs) and p-values were calculated.

To explore the association between reporting AEs ('yes/no') and repeated measurements for outcomes of LBP, uncorrected mixed effects models (including covariates for time and the reporting of AEs) and corrected mixed effects models (including covariates for time, the reporting of AEs, treatment allocation and all baseline covariates) were constructed with outcomes of LBP as dependent variables and AEs as a covariate. For pain intensity and physical functioning, Poisson mixed effects models were constructed as pain data was zero-inflated and non-normally distributed in the PACE trial (Supplementary Figure 1). Poisson models have been demonstrated to be more appropriate for the analysis of zero-inflated ordinal data (28, 29). The GLMMadaptive R package was used to create the Poisson mixed effects models (30). For HRQoL, linear mixed effects models were constructed as the aggregate scores for mental and physical HRQoL were normally distributed. The lme4 R package was used to create the Poisson mixed effects models (31). Regression coefficients with 95% CIs for the association of reporting any adverse event on average pain intensity, physical functioning and mental and physical HRQoL were calculated. For the time until recovery analysis, Cox proportional hazards models were constructed; for this outcome, hazard ratios (HRs) with 95% CIs for recovery for participants reporting AEs were calculated; furthermore, median recovery times and survival differences were calculated. The Survival R package was used to create the Cox proportional hazards models (32).

RESULTS

Descriptive statistics for AEs in the PACE trial are presented in Table 1. In total, 1594 out of 1643 participants provided information about AEs, of which 296 participants (19%) reported at least one AE. The number of AEs reported per participant ranged from a minimum of 0 to a maximum of 3; the median was 0. There were no differences in number of participants reporting AEs and SAEs between treatment groups. Only 1% of all 1643 participants reported a SAE (14 events in total; 5 in the regular paracetamol group, 4 in the paracetamol as-needed group and 5 in the placebo-group).

Table 1: Descriptive statistics for adverse events in the PACE trial.

	Regular Paracetamol group (n = 550)	Paracetamol As-needed group (n = 546)	Placebo group (n = 547)	Total (n = 1643)
Any adverse event	99/534 (19%)	99/529 (19%)	98/531 (18%)	296/1594 (19%)
Serious adverse event	5/550 (1%)	4/546 (1%)	5/547 (1%)	14/1643 (1%)

Data are n/N (%)

Reporting any AE by PACE trial participants was associated with baseline age, days since onset of pain, feelings of depression and use of medicines for other health conditions (Table 2). The use of medicines for health conditions other than LBP had the strongest association with reporting any AE; participants who used drugs for other health problems had an adjusted OR for reporting any AE of 1.42 (95% CI 1.07-1.88) when compared to participants not taking medicines for other conditions.

Table 2: Association between the reporting of adverse events (dependent variable) and baseline characteristics (covariates) in the PACE trial.

Covariate	Regression coefficient	Odds Ratio (exp(Coefficient)	Lower limit 95% CI of OR	Upper limit 95% CI of OR	P-value
Intercept	-2.81	0.06	0.04	0.09	<0.01
Age	0.01	1.01	1.01	1.02	<0.01
Days since onset of pain	0.03	1.03	1.01	1.04	<0.01
Feelings of depression in last week	0.06	1.07	1.02	1.11	<0.01
Use of drugs for another disorder	0.35	1.42	1.07	1.88	0.01

All covariates measured at baseline. Values rounded to 2 decimals.

Coefficients for the association between reporting any AE and outcomes of LBP in PACE are presented in Table 3 and a graphical representation of the uncorrected association between reporting any AE and outcomes of LBP during follow-up is shown in Figure 1.

Table 3: Coefficients for the association of outcomes of LBP (dependent variables) and the reporting of adverse events (covariates) in the PACE trial.

	Pain intensity (NRS, scale range 0-10)	Physical functioning	HRQoL-mental (SF-12)	HRQoL-physical (SF-12)	Time until recovery
Regression coefficient for reporting any adverse event - uncorrected	0.08 (0.00, 0.16) p = 0.04	0.13 (0.04, 0.22) p = 0.01	-0.89 (-1.56,-0.23) p = 0.01	-2.13 (-3.08,-1.18) p = 0.00	HR 0.92 (0.81, 1.06) p = 0.25
Regression coefficient for reporting any adverse event - corrected	0.00 (-0.07, 0.07) p = 0.93	0.02 (-0.05, 0.10) p = 0.57	-0.44 (-1.08, 0.20) p = 0.17	-0.54 (-1.37, 0.29) p = 0.20	HR 1.09 (0.94, 1.26) p = 0.24

All numbers rounded to 2 decimal places. 'Corrected' models were corrected for treatment group, gender, age, employment status, income, use of medication for other disorders, health insurance status and back pain compensability, days since onset of pain, number of previous episodes, radiating pain beyond the knee, number of days reduced activity, feelings of depression, perceived risk of persistent pain, pain intensity, global rating of symptom change, physical functioning, patient specific function, sleep quality, credibility, expectations and physical and mental health-related quality of life (all measured at baseline). HR: Hazard Ratio; NRS: Numerical Rating Scale; OR: Odds Ratio; RMDQ: Roland Morris Disability Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SF-12: Short Form 12.

As an example, the uncorrected coefficient for reporting any AE versus reporting no AEs (0.08, 95% CI 0.00 – 0.16) is interpreted as the change in the log average pain intensity for participants reporting any AE when compared to participants that reported no AEs, when all other predictors remain constant. The associations between reporting any AE and pain intensity, physical functioning and HRQoL were not apparent in the corrected mixed effects models.

Reporting any AE was not associated with time until recovery from back pain in both the uncorrected and the corrected Cox proportional hazards analysis (Table 3). Information for both recovery from back pain and AEs was available for 1588 out of 1643 participants (for this analysis, data were missing for 55 participants (3%)). After 12 weeks of follow-up, 1398 out of 1588 participants recovered from LBP. Uncorrected median time until recovery from LBP was 12 days (95% CI 11-14 days) in the participants that did not report any adverse events and 16 days (95% CI 14-18 days) in the participants that reported adverse events; this survival difference is not considered substantial (p = 0.3).

DISCUSSION

In people with acute LBP that participated in the PACE trial, reporting any AE was associated with older age, more days since onset of pain, increased feelings of depression and use of medicines for another health condition; there was no association between

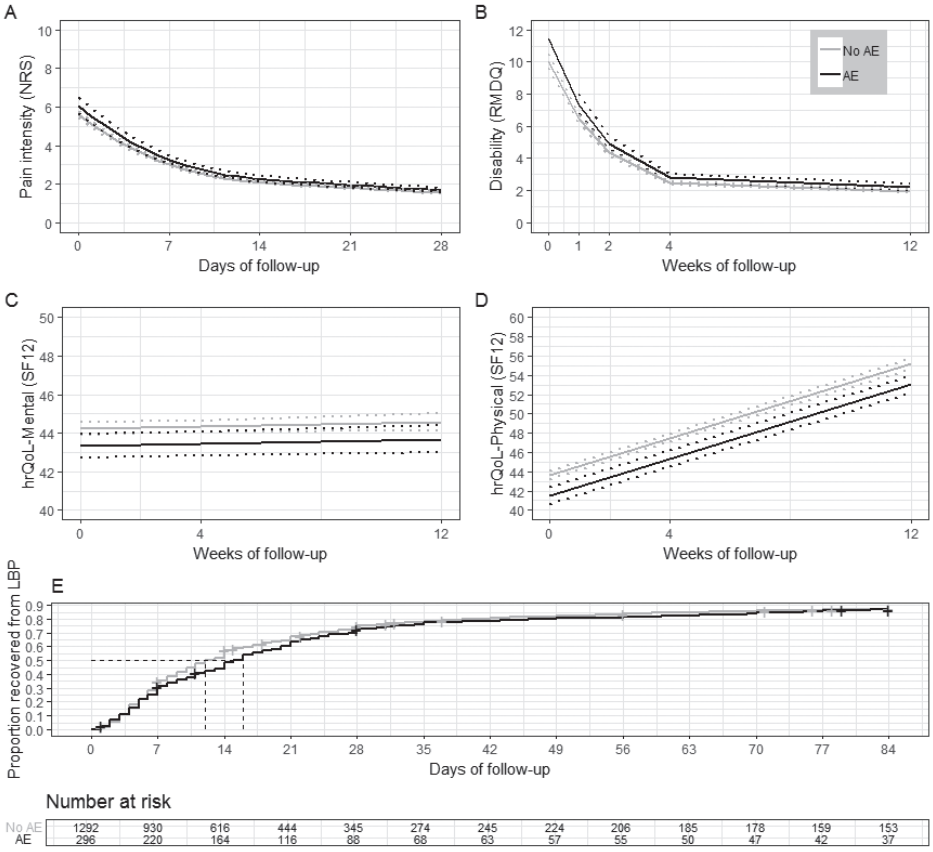

Figure 1: Effects of reporting any adverse event on core outcomes of LBP (Pain intensity (A), Physical functioning (B) and HRQoL (C and D) and Time until first recovery from LBP (E). Graphs obtained from uncorrected regression models containing only the reporting of adverse events and time as covariates. Y-axis was truncated for plots B, C, D, and E in order to improve visibility of results. The blue line indicates the participant group that did not report any adverse events, the red line indicates the participant group that reported adverse events. HRQoL: health-related Quality of Life; LBP: Low Back Pain; NRS: Numerical Rating Scale; RMDQ: Roland Morris Disability Questionnaire; SF12: Short Form 12

treatment group and reporting AEs. Reporting any AE was not associated with (less favorable) outcomes for LBP intensity, physical functioning, HRQoL or time until recovery in participants of PACE.

The strength of this study is the use of a very large dataset of people with acute LBP where data on AEs were reliably captured over the treatment course and up to 8 weeks following the end of the treatment period. Given the fact that paracetamol has a half-life between 1 and 4 hours, it is unlikely that paracetamol-related AEs have occurred after this follow-up period. This study has a number of limitations: first, although the sample size of 1643 patients may be large for an RCT in LBP, it is relatively small compared to the large

observational cohort studies that AEs are ideally investigated in. Second, information bias may have arisen in the registration of AEs, as AEs were a patient-reported secondary endpoint in the PACE trial. Third, although in this study we assessed the association between AEs and baseline characteristics, and AEs and outcomes, we did not assess if the reported AEs were related to the study medicines. The findings that reporting an AE was associated with use of medicines for another health condition would suggest that not all AEs would be related to the study treatment.

Two recent systematic reviews discuss the safety of paracetamol for low back pain (12, 33); both included the PACE trial in their meta-analyses. These systematic reviews focused primarily on the risk of experiencing AEs for patients taking paracetamol when compared to patients taking placebo. No differences were found in number of patients reporting AEs or SAEs or withdrawing from the study because of AEs, which is in line with our findings in the present study (12, 33). Machado and colleagues reported that participants taking paracetamol were 3.8 times more likely than participants taking placebo to have abnormal liver function tests results, although the clinical relevance of this is unclear (12) In the PACE trial, liver function testing was not performed; the reported risk ratio for abnormal liver function tests could therefore not be investigated in the current analysis. Hepatic failure was reported in 1 participant from the placebo group of the PACE trial (2). Apart from the hepatic AEs reported in systematic reviews of RCTs in back pain, a systematic review of observational studies also found an association between paracetamol use and cardiovascular, gastro-intestinal and renal AEs (13). The current study attempts to place the risk of reporting AEs as found in these recent systematic reviews in the context of clinical practice by presenting associations between reporting AEs and the outcomes of LBP.

The best evidence that is currently available suggests that paracetamol is not more effective than placebo for LBP (3, 12, 33); therefore, paracetamol should no longer be recommended to patients for the management of acute LBP in primary care. However, this study suggests that if patients with acute LBP do take paracetamol and consequently experience AEs, overall this is not associated with less favorable outcomes of LBP either. Patients with acute LBP who are older, have had back pain for a longer period before seeking care, had feelings of depression in the last week or use medicines for other health conditions may be more likely to report AEs of paracetamol; these characteristics could represent a more vulnerable patient group of older people with more comorbidities and polypharmacy.

Future studies into the AEs associated with taking paracetamol for LBP could investigate the associations between objective AEs and SAEs (e.g. as confirmed with liver function tests) and the baseline characteristics and outcomes of patients with LBP in order to identify patient groups that have an increased risk of experiencing SAEs.

CONCLUSIONS

In people with acute LBP that participated in the PACE trial, reporting any AE was associated with older age, more days since onset of pain, increased feelings of depression and use of medicines for health conditions; there was no association between treatment group and reporting AEs. Reporting any AE after using paracetamol or placebo was not associated with worse results in the core outcomes for LBP or in time until recovery from LBP.

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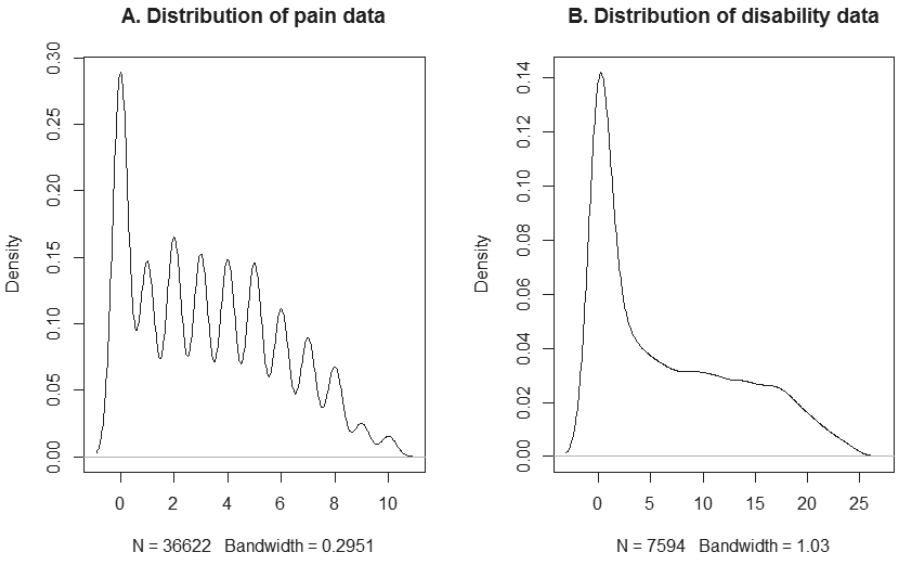
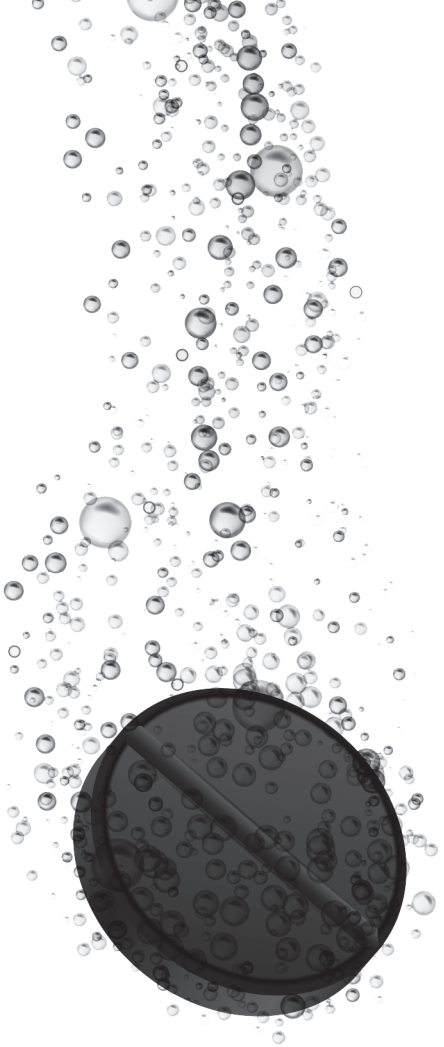


Supplementary Figure 1: Distribution of pain data (A) and Physical function data (B) in the PACE trial.



Chapter 8

General Discussion

The aim of this thesis was to elucidate the current role of paracetamol in the treatment of low back pain (LBP) in primary care. In order to do so, we first compared the recommendations on the pharmacological management of LBP in national clinical practice guidelines. Subsequently, we intended to reproduce the results of the Paracetamol for Acute Low Back Pain (PACE) trial (1) in a follow-up clinical trial (i.e. the PACE-plus trial), but had to discontinue this trial due to insufficient patient recruitment. Finally, we conducted three secondary analyses using data collected in the PACE trial: we tested the inferential reproducibility of the conclusions drawn in PACE, we investigated the efficacy of paracetamol in acute LBP among participants who complied with regular paracetamol treatment, and we explored the association between reporting adverse events of paracetamol and outcomes of LBP. In the current chapter, we place the most important findings from these research projects in the context of prior knowledge and discuss the methodological limitations of this thesis. We end this chapter by discussing the implications of these findings for clinical practice and future research.

8.1 INTERPRETATION OF THE PRINCIPAL FINDINGS IN THE CONTEXT OF PRIOR KNOWLEDGE

8.1.1 Variation in guideline recommendations for the pharmacological management of low back pain

In **Chapter 2**, we presented the results of our systematic literature review of recommendations on the pharmacological management of LBP. The most striking result of this review was the difference between the analgesics of first choice of the eight recent national clinical practice guidelines. Four out of eight guidelines (Australia, Canada, Denmark and the Netherlands (2-5)) still recommend the prescription of paracetamol for LBP, while the other four guidelines (Belgium, Germany, Britain and the US (6-9)) recommend non-steroidal anti-inflammatory drugs (NSAIDs) as first-choice analgesic; furthermore, the American guideline offers a choice between NSAIDs and skeletal muscle relaxants.

There may be a number of explanations why the results from the PACE trial (1) have not been taken up by four recent guidelines. First of all, policymakers behind the guidelines may have considered the results of a single randomized-controlled trial (RCT) as insufficient evidence to change their recommendations. Second, the lack of a safe and effective alternative could have played a role; in fact, NSAIDs, i.e. the next step on the WHO pain ladder (10), are contra-indicated in many primary care patients (for instance due to gastro-intestinal or cardiovascular comorbidity (11)). More importantly, both the review by Machado and colleagues (12) and the upcoming revision of the Cochrane systematic review regarding the efficacy of NSAIDs for acute LBP (Van der Gaag ***et al***, submitted work) question whether the difference between NSAIDs and placebo is clini-

cally relevant. For pain intensity, Machado and colleagues found a mean difference of 9.2 on a 100-point scale in favor of NSAIDs up to 2 weeks of follow-up, which is very similar to Van der Gaag and colleagues' mean difference of 7.3 up to 3 weeks of follow-up. For physical function, the two meta-analyses used different scales: Machado and colleagues found a mean difference of 8.1 points on a 100-point scale in favor of NSAIDs up to 2 weeks of follow-up, where Van der Gaag and colleagues found a mean difference of 2.02 point on the 24-point Roland-Morris Disability Questionnaire (RMDQ) up to 3 weeks of follow-up. These mean differences correspond to a 20% extra improvement in people receiving NSAIDs as compared to people receiving placebo; this generally considered to be the smallest worthwhile effect (13, 14). Furthermore, in head-to-head comparisons of NSAIDs and paracetamol, it was found that these medicines are equally effective for pain intensity and physical functioning in patients with acute LBP, while NSAIDs were associated with more adverse effects as compared to paracetamol (15-19). Third, the four mentioned guidelines may not have implemented the PACE results because of the safety profile of paracetamol, which is still perceived as relatively safe (20). However, results from observational research have shown that this may not be justified (21); paracetamol overdose is the number one cause of acute liver failure worldwide (22), and patients taking paracetamol have an increased risk of gastro-intestinal, cardiovascular and renal AEs (21). Finally, the results of PACE have been challenged as due to non-compliance to treatment (23, 24); uncertainty regarding the efficacy of paracetamol in compliers may have been a reason for policymakers not to change the existing recommendations regarding this drug. This uncertainty is addressed in detail in **Chapter 6**.

At first glance, it seems counterintuitive that only the American and Canadian guideline recommend skeletal muscle relaxants for acute LBP as these drugs could provide a clinically relevant effect on pain on the short term (9). Abdel Shaheed's meta-analysis found a mean difference of 21.3 points on a 100-point scale in favor of skeletal muscle relaxants at 3 months follow-up (25). The main reason why the other guidelines did not make any recommendations about skeletal muscle relaxants may be because they are not widely available outside North America. This begs the question of whether we are missing out on these drugs in Europe or not. Surprisingly, the correct answer to this question may be that we are not. Although the effect on pain was considered to be clinically relevant, the effect on disability was not: the mean difference was 6.5 points on a 100-point scale in favor of skeletal muscle relaxants (25). Furthermore, a recent RCT, which could not yet be included in Abdel Shaheed's meta-analysis, that compared a combination of ibuprofen and skeletal muscle relaxants (baclofen, metaxalone or tizanidine) to a combination of ibuprofen and placebo concluded that adding skeletal muscle relaxants to ibuprofen did not improve pain or physical functioning after one week of follow-up in patients that visited the emergency department for acute LBP (26). Moreover, skeletal muscle relaxants are associated with unpleasant adverse events (sedation, nausea, vomiting, vision

problems, headaches and dizziness), a potential for abuse and dependency and substantial costs (27). As there is still uncertainty about the balance between benefits and harms of skeletal muscle relaxants, more research is needed before adequate guideline recommendations can be made about the use of these drugs for the treatment of acute LBP.

The most important conclusion from the systematic review presented in **Chapter 2** is that although guidelines are universally moving away from recommending pharmacotherapy, there is currently no consensus regarding the analgesic of first choice in case patients do require medication. From the meta-analyses that we considered as best available evidence for the efficacy on drug efficacy, it can be concluded that all pharmacological treatments only have small to moderate short-term effects for non-specific LBP at best. Considering that for the majority of patients, the natural course of acute LBP is favorable (28), the best treatment of non-specific LBP in primary care may therefore not be the one with the best efficacy, but the one with the least side effects. Following this principle, the American guideline recommends nonpharmacological treatments (the efficacy of which is also small to moderate at best) rather than pharmacological treatment for recent-onset non-specific LBP (9). It is now up to policymakers from other countries whether they choose to follow this example in the upcoming revisions or not.

Limitations

The most important limitation of **Chapter 2** is that it was a narrative review, in which a number of arbitrary decisions were made in the methods. An example is the criterion to include only 'recent' clinical practice guidelines, which we defined as published after January 1st, 2016. However, as it was our aim to compare recent guidelines to the best available evidence, a limit would have been necessary in any case, and the definition of recentness would always have been subjective. Another design choice that could have influenced the results was restriction of languages to English, German or Dutch. Because of these criteria, we could have missed clinical practice guidelines. However, when we compare the guidelines included in our review to another recent overview aiming to investigate the consensus among clinical practice guidelines, we can see we did not miss any guideline because of language restrictions (29). Finally, it is difficult to judge what the 'best available evidence' is. As new studies are constantly published, we decided the best available evidence regarding the efficacy of pharmacological treatments would be in the most recent systematic reviews and meta-analyses, which constitute the top of the evidence pyramid (30). Alternatively, we could also have chosen to include only adequately powered RCTs with low risk of bias (31). Irrespective of these limitations, this review provided a valuable overview to provide context for other projects in this thesis.

8.1.2 The development and discontinuation of the PACE Plus trial

A protocol for a clinical trial to follow-up the Australian PACE trial (1) was presented in **Chapter 3**. With the PACE Plus trial, we attempted to reproduce the results of PACE by comparing paracetamol and placebo for the treatment of acute non-specific LBP in primary care; simultaneously, we also intended to compare paracetamol to diclofenac, the most prescribed NSAID in the Netherlands (32), and one of the most used NSAIDs worldwide (33). Finally, we planned to compare the combination of advice and medication (paracetamol or diclofenac) to advice alone. Together, these comparisons were designed to answer three important research questions that arose after publication of the results of the PACE trial. First, can the results of the PACE trial be reproduced? Second, considering that NSAIDs have not been demonstrated to be consistently superior to paracetamol (15-19), which in turn has been shown not to have a clinically relevant effect on LBP as compared to placebo (1), what is the comparative effectiveness of paracetamol, diclofenac and placebo for acute LBP? Third, would treating patients with acute LBP with advice and reassurance only be inferior to treating these patients with paracetamol or diclofenac?

After 6 months of recruitment in the PACE Plus trial, only four of the required 800 patients with LBP had been recruited, leading to the discontinuation of the RCT. In order to investigate the underlying reasons for termination of this RCT, we conducted a survey among local research coordinators of the participating GP practices; results of this survey have been shown in **Chapter 4**. GPs mentioned an insufficient number of patients meeting the study's eligibility criteria, lack of time in daily practice, and different patient expectations as the three main reasons for failed patient recruitment in PACE Plus (in order of descending number of comments); together, these three reasons formed over half of all reasons reported in the survey (48 out of 81 reported reasons). In a systematic literature review investigating factors that limit the progress of RCTs, common barriers to participation in clinical trials were very similar to what was found in the survey in **Chapter 4** (34).

The reduced number of patients with acute LBP seeking help in general practice when compared to the reported incidence of acute LBP in the Netherlands (35) could be explained by Lasagna's law (36, 37), the observation that once a trial starts, the number of available patients is between a tenth and a third of what was originally expected by the researchers (37). This was first described by American physician Louis Lasagna, who defined this phenomenon as "the incidence of patient availability sharply decreases when a clinical trial begins" (38). Explanations for Lasagna's law may be that researchers and clinicians overestimate the number of available patients before the study (for instance because not all patients with a new episode of disease are willing to be randomized), or that clinicians have insufficient time to recruit available cases. Another reason for this suspected drop in incidence could be due to a true decline in GP visits between the mea-

surement of the incidence of LBP (which was in 2012) and the start of the PACE Plus trial (which was in September of 2016). An explanation of such a development could be the launch of the patient information website of the Dutch College of General Practitioners, which happened in March 2012 (39, 40). In 2014, this website already had 2.9 million unique views per month, and a decline of 12% in consultations in general practice was attributed to the website launch; it is highly likely that this reduction in consultations has become even larger in the five years that have passed since then, as the number of unique views per month has increased to 4.6 million in June 2019 (39, 41). The recommendations on the web page about LBP are mainly aimed at improving self-management of complaints: they focus on the favorable prognosis of LBP, the limited benefits of medication and imaging and the necessity to remain active. This information could have directly contributed to one of the other reasons for insufficient patient recruitment mentioned in the survey, namely the effective self-management of LBP. Another explanation of a true decline in GP visits of patients with LBP could be the increasing popularity of direct access to physiotherapy; in 2017, 56% of patients used direct access to physiotherapy as compared to 35% in 2009 (42, 43). Apart from the change in number of patients visiting their GP with recent onset LBP, there may also have been a change in type of patients with LBP presenting in general practice. Patients who recovered using self-management skills only might not visit their GP, whereas the patients seeking care with their GP may have had LBP for a longer period, with greater limitations of their usual daily activities and with unsatisfactory results using over-the-counter medication such as paracetamol and NSAIDs. If this is the case, it seems logical that these patients have different expectations than participating in a trial that offers them exactly the same interventions they have been using for a number of weeks. In light of this suspected changing population of patients presenting to general practice with recent onset LBP, recruiting incident cases of LBP from Dutch general practice for research into first-choice interventions may remain a challenge. However, conducting research in clinical practice is not just a challenge in the Netherlands, but also in other countries such as the United States and the United Kingdom (44); the feasibility of such a study is thus not automatically guaranteed if it were to be conducted in another country.

The second most frequent reason (i.e. lack of time in general practice) seems to reflect the current state of general practice in the Netherlands. Because of changes in the national health care system, the range of tasks of the Dutch GP has vastly increased, as has the related administrative workload; similar increases in workload have been reported in England, which has a similar organization structure of primary care (45). In 2015, this even led to an action group presenting a manifesto to the House of Representatives of the Netherlands signed by two-thirds of all Dutch GPs (a total of 7800 signatures), in which they asked for health care system reforms (46). In an international comparison of the workload of general practitioners, it was found that Dutch GPs spent a large percent-

age of time on tasks that were not directly patient-related, such as administration, when compared to GPs from other countries (47). Although some positive changes have been made in recent years, such as the decrease in number of patients per practice, conducting clinical trials in Dutch general practice (for any clinical condition) will probably remain difficult in the foreseeable future.

GPs could be encouraged to participate in research by allowing for adequate reimbursement of their invested time. Even though a Dutch study investigating the factors related to success and failure of patient recruitment did not identify GP reimbursement as a factor influencing trial success (36), the comparison between PACE Plus and the original PACE trial revealed this may have been an important difference between the Australian and the Dutch trial. However, this would require an increase in the budget of research projects, which would probably only be possible in collaborations with the pharmaceutical industry. Contrary to the reasoning in the Cochrane Risk of Bias assessment tool (31), industry involvement does not always have to be a cause for concern, as long as corporate sponsors are not involved in study design and analysis and interpretation of results, as demonstrated by the PACE trial (1); however, it will very likely be difficult to obtain industry funding under these terms in practice. As an alternative solution, the Australian system for mandatory continuing education, in which part of the points obligatory for re-registration as a GP can only be earned by participating in research, could be implemented in the Netherlands.

Limitations

The most significant limitation of the PACE Plus trial was by far its feasibility. With different study design choices, the trial may have been more likely to succeed. A number of general recommendations for future research have already been made in **Chapter 3**. As the specific research questions of PACE Plus remain relevant but unanswered, an alternative approach to PACE Plus is presented in **Section 8.3**.

From a technical perspective, a limitation of the PACE Plus trial was the fact that it is not strictly speaking a results reproduction study according to Goodman's new lexicon of research reproducibility (48). Goodman describes results reproduction as the collection of new data in the same population and consequently analyzing this data using the same analysis plan (48). Although the first criterion was met (both trials were set in primary care, albeit on opposite sides of the globe), the second was not. While the original PACE trial had three treatment groups (paracetamol taken regularly, paracetamol as-needed for pain and placebo), PACE Plus had four (paracetamol, diclofenac, placebo and advice only), meaning a different analysis plan was needed. Furthermore, not all outcomes were identical between the two trials, the most notable difference being the measurement of health-related quality of life (HRQoL), which we intended to record using the EuroQol Group 5 Dimensions, 5 Level Questionnaire (EQ-5D-5L (49)) rather than the Short Form

12 (SF-12 (50)) that was used in the original trial. These instruments provide different HRQoL scores (i.e. the EQ-5D-5L provides overall utility and visual analogue scale scores, whereas the SF-12 provides a physical and a mental summary score) that make a comparison very difficult to do (Chiarotto 2018 Pain). But although PACE Plus was not strictly speaking a results reproduction study, data on pain intensity, disability and time until recovery from LBP from PACE Plus could have been combined with data of PACE in an individual patient data (IPD) meta-analysis (51), had the PACE Plus trial been completed.

An important technical consideration about the survey in **Chapter 3** was the way the survey was conducted. Although the response rate among local research coordinators was high (92%), it is debatable whether these 33 research coordinators were representative of all 96 GPs that participated in the trial. Furthermore, the survey was not a structured combination of open- and close-ended questions, as it solely consisted of a single open question. By performing a more elaborate survey among all participating GPs rather than only the local coordinators, a more valid picture could have been obtained; however, given the high workload of GPs, a more elaborate survey would likely have had a much lower response rate and thus a poorer representation of the participating clinicians.

8.1.3 Secondary analyses of data collected in the PACE trial

Three projects presented in this thesis were based on secondary statistical analyses of data collected in the PACE trial (1). Our first re-analysis of PACE focused on the reproducibility of the knowledge claims made in the original data analysis. One of the reasons for failed patient recruitment in PACE Plus mentioned by four GPs in the survey in **Chapter 4** was that the research question of the PACE Plus trial was irrelevant for clinical practice, since the original PACE trial had already sufficiently investigated efficacy of paracetamol for LBP. However, reproducibility is one of the cornerstones of scientific research (52) and many scientific claims are found not to be reproducible (53-55). In **Chapter 5**, we presented the results of the first independent inferential reproducibility study in the LBP research field. This study focused on the reproduction of the causal inferences of the PACE trial for the core outcome domains of LBP: pain intensity, physical functioning and HRQoL (56). We analyzed the data in the PACE trial with an independent team using the pre-defined and published statistical analysis plan from the PACE Plus trial; the original PACE trial authors had no influence on the aim, methods and conclusions of this study and effectively gave us “carte blanche” to conduct this analysis. In the reproducibility study, paracetamol had no effect on the core outcomes when compared to placebo.

In our second analysis, we investigated the efficacy of paracetamol among participants who complied to treatment. As stated earlier, although it was demonstrated that paracetamol had no overall effect on outcomes of acute LBP when compared to placebo (1), it was unclear if there was a difference between paracetamol and placebo in compli-

ers to the treatment regimen; this may have played a role in the observation that four recent guidelines did not change their recommendation regarding paracetamol for LBP. In **Chapter 6**, we showed that paracetamol was not more effective than placebo for acute LBP, regardless of the definition of compliance or follow-up period, using a complier average causal effects (CACE) analysis.

In **Chapter 7**, we presented our secondary analysis of PACE, in which we looked into the association of reporting adverse events (AEs) and on the one hand, baseline characteristics and on the other hand, outcomes of LBP. Baseline characteristics that were associated with reporting AEs were older age, more days since the onset of pain, increased feelings of depression. The strongest association was found for the use of medicines for a health problem other than LBP (odds ratio 1.42, 95% confidence interval 1.07 – 1.88), suggesting that not all reported AEs were related to taking trial medication. No association was found between reporting AEs and the core outcome domains of LBP at follow-up (56).

These findings should be interpreted in the context of the original (primary) analysis of the PACE trial (1). The fact that the results from the independent inferential reproduction analysis are consistent with the original results of PACE, even though a different approach to the statistical analysis was used, strengthens the conclusions regarding the lack of efficacy of paracetamol for acute LBP. Our second analysis represented only the second time the CACE analysis technique was used in the LBP research field (57). The findings of this study extend the message of the original analysis of PACE and form a strong appeal to clinicians and policymakers to reconsider their endorsement of paracetamol for the treatment of acute LBP. Finally, our findings in the AEs analysis suggested that if LBP-patients decide to take paracetamol anyway and consequently experience AEs, overall this is not associated with less favorable outcomes of LBP. If we combine all these results, the bottom line seems to be that taking paracetamol has very little influence (neither negative nor positive) on the outcomes of acute LBP.

Limitations

The most important limitation of the studies presented in **Chapters 5, 6 and 7** was that existing data regarding the efficacy of paracetamol for acute LBP was used; no new data was collected during these studies. An additional disadvantage of this is that the available data was not intended to conduct a CACE analysis on or to investigate the association between reporting AEs of paracetamol and outcomes of LBP. The accuracy of the CACE analysis could have been improved by including a measurement for the likelihood of compliance in the baseline questionnaire (58). An important limitation of the AEs analysis is there was no verification whether or not reported AEs were related to taking study medicines in PACE.

8.2 IMPLICATIONS FOR CLINICAL PRACTICE

In spite of the fact that the evidence for a lack of efficacy of paracetamol for acute LBP has been strengthened by the studies in this thesis, the most important piece of the puzzle is still missing: results reproduction of the PACE trial. However, irrespective of the efficacy of paracetamol, it seems that GPs may have taken a wrong turn somewhere in the past decades when it comes to the management of LBP, considering the evidence presented in **Chapter 2**. We still tend to focus on pain intensity and the treatment of pain until a pain level of zero is reached, rather than focusing on the influence that LBP has on the daily activities of our patients and the treatment until an acceptable level of functioning is achieved (56, 59-61).

Although the treatment of pain in evidence-based medicine is currently strongly associated with the prescription of medication, we must not forget that there are other therapeutic options in clinicians' toolkits. Treatment options for acute LBP that are feasible, affordable and available today include superficial heat, massage, or exercise, irrespective of their specific efficacy; research investigating placebo-interventions suggests that for patient reported outcomes, almost any intervention is better than no intervention at all (62). Furthermore, even open-label placebo interventions have demonstrated clinically relevant effects on pain, given that they are provided in a positive context (63). Ideally, these suggested non-pharmacological treatments should therefore be wrapped in the best possible 'therapeutic envelope', which is also known as the patient-provider interaction. In a time when it has been shown that most pharmacological treatments have no clinically relevant effects, larger benefits may be expected from maximizing contextual effects than from the development of new drugs.

Instead of a clear and unambiguous recommendation for clinical practice, this thesis provides an ethical dilemma: should clinicians still prescribe paracetamol to patients with acute LBP, now that we know that even in patients who comply with the treatment regimen, it has no effect when compared to placebo? On the one hand, one could argue they should; placebos are associated with effects on patient reported outcomes (64) and one could argue that although paracetamol is definitely not harmless (21), of all the analgesics, it arguably has the most favorable safety profile. If clinicians stop prescribing paracetamol, many patients that require pain medication will be prescribed NSAIDs or even opioids instead. In such a scenario, are we not better off if we just continue to prescribe paracetamol? On the other hand, in conventional medicine, it is not acceptable to prescribe placebo tablets (which have no characteristic effect, but no adverse effects either). If paracetamol is prescribed solely for the purpose of prescribing a placebo, then are we not breaking our own rules? Furthermore, if we know that the effects of an intervention is based on the placebo effect, but we continue to use the intervention anyway, then what is the difference between conventional evidence-based medicine and

what we call alternative medicine (65)? And if we purposely prescribe paracetamol as a placebo, how sure are we that this placebo effect is clinically worthwhile to LBP patients (13, 14)?

8.3 IMPLICATIONS FOR FUTURE RESEARCH

The discontinuation of the PACE Plus trial left a legacy of unanswered research questions. First, the results of the PACE trial should be reproduced. Second, the relative efficacy of paracetamol as compared to that of NSAIDs and other medicaments and non-pharmacological interventions remains unclear. Third, we still have limited and contradictory evidence regarding the magnitude and clinical relevance of the placebo effect in LBP when compared to no treatment (or waiting list controls).

Reproduction of the results of PACE will be challenging in practice, as it requires the collection of new data. Currently, the recruitment of incident cases of acute LBP in Dutch general practice does not seem realistic, given the amount of pressure GPs are already under due to their normal workload. However, we know that the one-year risk of recurrence of acute LBP is 33% (66, 67). An RCT nested in a cohort of prevalent cases of LBP may therefore be much more feasible. Instead of burdening GPs with patient recruitment, cohort participants could be recruited through large population databases, such has the Integrated Primary Care Information (IPCI) database (68), a large database with 1.5 million primary care patient records from the South of the Netherlands. For instance, patients for whom an ICPC-code L03 (non-radiating LBP) was registered in the past year could be approached via post to participate in the cohort, and could subsequently be instructed to contact the research department as soon as they experience a new episode of LBP. The most feasible approach would be to then randomize these participants to regular paracetamol or placebo, thus answering our research question. Another option would be to use a large observational dataset to answer this research question, given that confounding can be adequately assessed and corrected for (which is the main disadvantage of non-randomized studies). In this scenario, the PACE Plus design could be used as a target trial protocol (69).

Although our experience with PACE Plus suggests the likelihood of failure may increase by attempting to answer multiple research questions in one study (in RCTs, do not try to kill two birds with one stone), it would theoretically be possible in a cohort-nested RCT design to simultaneously investigate the second unanswered research question of PACE Plus as well. In this scenario, patients could be randomized to receive non-pharmacological treatment only (which could consist of advice and reassurance only, superficial heat and or/exercises), or to receive a combination of non-pharmacological treatment and medication. In the latter group, patients could be allocated to different treatment options

(such as paracetamol, ibuprofen or placebo) using a second randomization procedure. A downside of this approach is that it is very costly and labor-intensive. An alternative approach to comparing paracetamol to other pharmacological and non-pharmacological interventions would be by conducting a network meta-analysis (70, 71), in which direct and indirect evidence is combined to reconstruct a comparison between interventions that have never been tested head-to-head in an RCT. Protocols have already been developed for the conduct of such network meta-analyses in order to compare the effects and safety of paracetamol, NSAIDs and opioids for chronic LBP (72) and to compare the effects of all noninvasive treatments of LBP (73).

Apart from ambiguous evidence regarding the comparative efficacy of paracetamol and NSAIDs, it is unclear how acceptable these treatments currently are to patients with LBP. NSAIDs in particular have been in the media in a negative context during recent years (74-76). Observational studies have been conducted for physiotherapy and NSAIDs to investigate when the effects of these interventions become worthwhile to LBP patients (13, 14). Given the fact that over the last decade, many new studies been published about both the efficacy and the safety of paracetamol and NSAIDs (12, 21, 77), it is important to update the current knowledge on when these medicines are clinically worthwhile to patients with LBP in order to place their efficacy into context.

The PACE Plus trial would have been the first RCT in the LBP research field to directly compare a combination of advice and blinded placebo tablets to advice only. The only similar published result would be a comparison between open-label placebo and treatment as usual in people with chronic LBP (63). In this study, open label placebo pills were found to have a significant and possibly clinically relevant effect on both pain and disability after 3 weeks of follow-up when compared to treatment as usual (63). However, as this study used open-label placebo pills which were provided in a positive context, it is unclear whether the magnitude of the effects found in this study reflects the placebo effect (in this case: the effect of a placebo intervention (78)) associated with medication given to people with LBP. The reason why knowledge about the effect size associated with a placebo intervention is so important, is because active interventions are compared to these placebo-interventions in clinical trials in order to determine the efficacy of these interventions. If the effect of placebo interventions compared to no treatment (or for instance a waiting list) is not clinically relevant, then this has implications for the interpretation of the results of placebo-controlled trials as well. Currently, the existence and clinical relevance of the effects of placebo interventions is a topic of debate in the LBP research field: on the one hand, it was found in a meta-analysis that the pooled magnitude of placebo effects for pain is very small (3.2 points on a 100-point pain scale) (79) and on the other hand, it was concluded from a systematic review that placebo tablets could have a clinically meaningful effect on pain in people with non-specific LBP (80). However, the search strategies for these studies are now over ten years old, so many new

RCTs comparing placebo interventions to no treatment may have been conducted in the meantime (81). As stated in **Section 8.2**, another important topic in placebo research is the optimization of the patient-provider interaction (82). New research in this area should mainly focus on the development and implementation of specific evidence-based strategies for general practice. By using the doctor as a medicine, we may be able to avoid the pills (83).

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Chapter 9

Summary
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SUMMARY

The aim of this thesis was 1) to describe the similarities and differences between recommendations for pharmacotherapy of low back pain (LBP) from recent clinical practice guidelines; 2) to investigate if the results and inferences from the Paracetamol for Acute Low Back Pain (PACE) trial could be reproduced; 3) to assess the efficacy of paracetamol for acute non-specific LBP in participants of the PACE trial who complied with the treatment regimen; and 4) to investigate if there is an association between reporting adverse events (AEs) and the outcomes of acute LBP.

In **Chapter 2**, a systematic literature review of recommendations for non-invasive pharmacological management of LBP from recent clinical practice guidelines was presented. These guidelines were compared with each other and with the best available evidence on drug efficacy. Eight recent national clinical practice guidelines were included in this review (from Australia, Belgium, Canada, Denmark, The Netherlands, UK and US). Guidelines are universally moving away from pharmacotherapy due to the limited efficacy and the risk of AEs. NSAIDs have replaced paracetamol as the first choice analgesics for LBP in half of the recent guidelines. Opioids are considered to be a last resort in all guidelines, but prescriptions of these medications have been increasing over recent years. Only limited evidence exists for the efficacy of antidepressants and anticonvulsants in chronic LBP. Muscle relaxants are one of the analgesics of first choice in the US, but they are not widely available and thus not widely recommended in most other countries. As pharmacological treatments for LBP only have small to moderate effects at best, while being associated with a risk of AEs, upcoming guideline updates should shift their focus from pain to function and from pharmacotherapy to non-pharmacologic treatment options.

The PACE trial, published by Williams and colleagues in 2014, was the first large randomized controlled trial (RCT) to investigate the efficacy of paracetamol for acute LBP. A study protocol for a new RCT to follow-up on the PACE trial was presented in **Chapter 3**; this new study was called the PACE Plus trial. This trial aimed to assess the effectiveness of paracetamol, diclofenac and placebo for patients with acute LBP over a period of 4 weeks and to assess the additional effectiveness of paracetamol, diclofenac and placebo to advice only over a period of 4 weeks. Patients with acute LBP aged 18-60 years presenting in general practice were included and subsequently randomized into four groups: 1) Advice only (usual care conforming with the clinical guideline of the Dutch College of General Practitioners); 2) Advice and paracetamol; 3) Advice and diclofenac; 4) Advice and placebo. The primary outcome was LBP intensity measured with a 0-10 numerical rating scale. Secondary outcomes included compliance to treatment, physical functioning, perceived recovery, costs, adverse reactions, satisfaction, sleep quality, co-interventions and adequacy of blinding.

Due to insufficient patient recruitment, the PACE Plus trial was prematurely terminated within 6 months after the start of the trial. In **Chapter 4**, the reasons behind the discontinuation of PACE Plus were explored. General Practitioners (GPs) from 36 participating practices received a single-question survey in which they were asked to give the three most important factors that, in their opinion, contributed to failure of patient recruitment. GPs from 33 of the 36 (92%) participating practices sent a response; a total of 81 factors were reported. These factors were categorized into patient factors (26 out of 81 comments, 32%), GP factors (39 out of 81 comments, 48%) and research factors (16 out of 81 comments, 20%). Patient recruitment in the PACE Plus trial may have failed due to inefficient medication distribution, recruitment of incident rather than prevalent cases, a design that was too complicated, adequate self-management of LBP, patient expectations being different from the trial's scope, and lack of time of participating GPs. Substantial differences in design may explain why the preceding PACE trial did manage to successfully complete patient recruitment. Although the PACE Plus trial was terminated as a result of insufficient patient inclusion, the research questions addressed in this trial remain relevant but unanswered.

Three secondary analyses of data collected in the PACE trial were conducted. The inferential reproducibility of the original conclusions of PACE was investigated in **Chapter 5**. An independent research team used the published analysis plan of the PACE Plus trial to re-analyze the PACE trial. The reproduction analyses indicated no effect of treatment on pain intensity and confidence intervals excluded clinically worthwhile effects (coefficient for regular paracetamol versus placebo 0.00 (-0.02 - 0.01, p = 0.85); coefficient for paracetamol as-needed versus placebo 0.00 (-0.02 – 0.01, p = 0.92)). Similar results were obtained for all secondary outcomes (physical functioning, health-related quality of life (HRQoL), sleep quality and time until recovery). This indicated that the conclusions of the PACE trial were inferentially reproducible, even when using a different analytical approach. This reinforced the notion that management of patients with acute LBP should focus on providing advice and reassurance without the addition of paracetamol.

Another secondary analysis was presented in **Chapter 6**. This study aimed to investigate the efficacy of paracetamol in acute LBP among compliers. Using individual participant data from the PACE trial, Complier Average Causal Effects (CACE), Intention-to-treat (ITT) and Per Protocol (PP) estimates were calculated for pain intensity (primary), physical functioning, global rating of symptom change and executive functioning (all secondary) after two weeks of follow-up. Compliance was defined as intake of an average of at least four of the prescribed six tablets of regular paracetamol per day (2660 milligrams in total) during the first two weeks after enrolment. Exploratory analyses using alternative time points and definitions of compliance were conducted. Mean between-group differences in pain intensity on a 0-10 scale using the primary time point and definition of compliance were not clinically relevant (propensity weighted CACE 0.07 (-0.37, 0.50) p = 0.76;

joint modelling CACE 0.23 (-0.16, 0.62) p = 0.24; ITT 0.11 (-0.20, 0.42) p = 0.49; PP 0.29 (-0.07, 0.65) p = 0.12); results for secondary outcomes and for exploratory analyses were similar. The conclusion of this study was that paracetamol is ineffective for acute low back pain, even for patients who comply with treatment.

In the third and final reanalysis of the PACE data, the association between reporting AEs and the outcomes of acute LBP was investigated. The results of this project were presented in **Chapter 7**. Reporting any AE was strongly associated with the use of medicines for a health problem other than LBP (odds ratio (95% CI) 1.42 (1.07-1.88)). Reporting any AE was not associated with less favorable outcomes for LBP intensity, physical functioning, HRQoL or time until recovery (respective coefficients 0.00 (-0.07-0.07), 0.02 (-0.05-0.10),-0.44 (-1.08-0.20),-0.54 (-1.37-0.29) and HR 1.09 (0.94-1.26)). Due to the very low number of serious AEs (death or hospitalization) there was insufficient information to investigate the association between reporting these AEs and baseline characteristics or the association with outcomes of LBP. In the PACE trial, reporting adverse events after using paracetamol or placebo was associated with the use of medicines for other health problems, but not with (unfavorable) outcomes of LBP.

In **Chapter 8**, the findings in this thesis were summarized and discussed in terms of methodological limitations. Moreover, the implications of the findings for clinical practice and for future research were debated.

SAMENVATTING

Het doel van dit proefschrift was 1) om de overeenkomsten en verschillen tussen aanbevelingen voor de medicamenteuze behandeling van lage rugpijn uit recente behandelrichtlijnen te vergelijken; 2) om te onderzoeken of de resultaten en conclusies van de 'Paracetamol for Acute Low Back Pain' (PACE) trial reproduceerbaar zijn; 3) om het effect van paracetamol op de uitkomsten van acute aspecifieke lage rugpijn te onderzoeken onder therapietrouwe deelnemers van de PACE trial; en 4) om te onderzoeken of er een associatie is tussen het rapporteren van bijwerkingen en de uitkomsten van acute lage rugpijn.

In **Hoofdstuk 2** werd een systematisch literatuuronderzoek gepresenteerd naar de aanbevelingen voor de conservatieve farmacologische behandeling van lage rugpijn uit recente behandelrichtlijnen. Deze richtlijnen werden vergeleken met elkaar en met het beste beschikbare bewijs over de effectiviteit van medicijnen. Acht recente nationale behandelrichtlijnen werden geïncludeerd in deze review (uit Australië, België, Canada, Denemarken, Duitsland, Groot Brittannië, Nederland en de Verenigde Staten (VS)). Alle richtlijnen stappen af van het adviseren van medicamenteuze behandeling vanwege de beperkte effectiviteit en het risico op bijwerkingen. Niet-steroïde anti-inflammatoire geneesmiddelen (NSAIDs) hebben paracetamol vervangen als de eerste keus pijnstillers in veel richtlijnen. Opioïden worden in alle richtlijnen beschouwd als een laatste redmiddel, maar desondanks is het aantal voorschriften van deze medicijnen in de laatste jaren sterk gestegen. Er is slechts beperkt bewijs voor de effectiviteit van antidepressiva en anti-epileptica bij de behandeling van chronische lage rugpijn. Spierverslappers zijn een van de medicijnen van eerste keus in de VS, maar zijn niet uitgebreid beschikbaar in de meeste andere landen. Aangezien farmacologische behandelingen van lage rugpijn in het beste geval maar kleine tot gemiddeld grote effecten hebben, terwijl het gebruik ervan wel gepaard gaat met een risico op bijwerkingen, zouden nieuwe versies van behandelrichtlijnen hun focus moeten verleggen van pijn naar functie en van farmacotherapie naar niet-farmacologische behandelopties.

De PACE trial, die werd gepubliceerd door Williams en collega's in 2014, was de eerste grote gerandomiseerde gecontroleerde trial (RCT) die de effectiviteit van paracetamol voor acute lage rugpijn onderzocht. Een onderzoeksprotocol voor een nieuwe RCT als opvolger van PACE werd gepresenteerd in **Hoofdstuk 3**; deze nieuwe studie heette de 'PACE Plus trial'. Deze trial had als doel om de effectiviteit van 4 weken behandeling met paracetamol, diclofenac en placebo voor de behandeling van patiënten met acute lage rugpijn te onderzoeken en om de toegevoegde waarde van paracetamol, diclofenac en placebo te onderzoeken vergeleken met alleen geruststelling. Patiënten met een leeftijd tussen de 18 en 60 jaar die zich in de huisartspraktijk presenteerden met acute lage rugpijn werden geïncludeerd in de studie, en vervolgens gerandomiseerd naar vier behan-

delgroepen: 1) alleen advies (conform de standaardbehandeling uit de NHG-standaard); 2) advies en paracetamol; 3) advies en diclofenac; en 4) advies en placebo. De primaire uitkomstmaat was pijnintensiteit, gemeten met een numerieke schaal (van 0 tot 10). Secundaire uitkomstmaten waren fysiek functioneren, gezondheidsgerelateerde kwaliteit van leven, ervaren herstel, therapietrouw, kosten, bijwerkingen, patiënttevredenheid, slaapkwaliteit, co-interventies en adequaatheid van blindering.

Doordat onvoldoende patiënten geworven konden worden, moest de PACE Plus trial prematuur beëindigd worden binnen zes maanden na de start van het onderzoek. In **Hoofdstuk 4** werden de redenen voor het staken van PACE Plus geëxploreerd. Huisartsen uit 36 deelnemende praktijken ontvingen een vragenlijst die bestond uit slechts één vraag; hierin werden zij gevraagd om de drie redenen te geven die naar hun idee het meest hadden bijgedragen aan het mislukken van de werving van patiënten. Huisartsen van 33 van de 36 deelnemende praktijken (92%) stuurden een antwoord; in totaal werden 81 factoren gerapporteerd. Deze factoren werden gecategoriseerd naar patiëntfactoren (26 van de 81 factoren, 32%), huisartsfactoren (39 van de 81 factoren, 48%) en onderzoeksfactoren (16 van de 81 factoren, 20%). De werving van patiënten in PACE Plus is mogelijk gefaald door een inefficiënte procedure voor de distributie van studiemedicatie, de werving van incidente cases in plaats van prevalente cases, een te complex onderzoeksdesign, zelfredzaamheid van patiënten met lage rugpijn, andere verwachtingen van patiënten dan deelname aan klinisch onderzoek en tijdgebrek van deelnemende huisartsen. Substantiële verschillen in studiedesign zouden kunnen verklaren waarom de Australische voorloper PACE wel succesvol patiënten kon werven. Hoewel de PACE Plus studie gestaakt is, blijven de onderzoeksvragen van deze studie relevant maar onbeantwoord.

Er werden drie secundaire analyses uitgevoerd van data die in de PACE trial was verzameld. De reproduceerbaarheid van de oorspronkelijke conclusies van PACE werden onderzocht in **Hoofdstuk 5**. Een onafhankelijk onderzoeksteam maakte gebruik van het analyseplan van de PACE Plus trial om de PACE trial opnieuw te analyseren. Deze reproductie analyses toonden aan dat er geen effect was van behandeling met paracetamol op pijnintensiteit en de betrouwbaarheidsintervallen sloten klinisch relevante effecten uit (coëfficiënt voor reguliere paracetamol versus placebo 0.00 (-0.02 – 0.01, p = 0.92)). Vergelijkbare resultaten werden gevonden voor alle secundaire uitkomsten (fysiek functioneren, gezondheidsgerelateerde kwaliteit van leven, slaapkwaliteit en tijd tot herstel). Dit wees erop dat de conclusies van de PACE trial reproduceerbaar zijn, zelfs als een andere statistische benadering gebruikt wordt. Dit versterkt het idee dat de behandeling van patiënten met acute lage rugpijn zich zou moeten richten op het verstrekken van advies en geruststelling aan patiënten, zonder de toevoeging van paracetamol.

Een andere secundaire analyse werd gepresenteerd in **Hoofdstuk 6**. Deze studie had als doel om het effect van paracetamol op de uitkomsten van acute lage rugpijn

te onderzoeken bij deelnemers van de PACE trial die zich hielden aan het geadviseerde medicatieschema. Met behulp van individuele deelnemersdata van de PACE trial werden Complier Average Causal Effect (CACE), Intention-to-treat (ITT) en Per Protocol (PP) analyses uitgevoerd voor pijnintensiteit (primaire uitkomstmaat) en fysiek en dagelijks functioneren en ervaren verandering van symptomen (secundaire uitkomsten) na twee weken follow-up. Therapietrouw was gedefinieerd als het innemen van gemiddeld minstens vier van de voorgeschreven zes tabletten reguliere paracetamol per dag (een totaal van 2660 milligram) gedurende de eerste twee weken na randomisatie. Tevens werden verkennende analyses met alternatieve tijdspunten en definities voor therapietrouw uitgevoerd. De gemiddelde verschillen tussen de groepen in pijnintensiteit op een schaal van 0 tot 10 waren niet klinisch relevant op het primaire tijdspunt en bij de primaire definitie van therapietrouw (propensity-gewogen CACE 0.07 (-0.37, 0.50) p = 0.76; joint modelling CACE 0.23 (-0.16, 0.62) p = 0.24; ITT 0.11 (-0.20, 0.42) p = 0.49; PP 0.29 (-0.07, 0.65) p = 0.12); resultaten voor secundaire uitkomsten en voor verkennende analyses waren vergelijkbaar. De conclusie van deze studie was dat paracetamol ineffectief is voor acute lage rugpijn, zelfs voor therapietrouwe patiënten.

In de derde en laatste heranalyse van de PACE data werd de associatie tussen het rapporteren van bijwerkingen en de uitkomsten van acute lage rugpijn onderzocht. De resultaten van dit project werden gepresenteerd in **Hoofdstuk 7**. Het rapporteren van bijwerkingen was sterk geassocieerd met het gebruik van medicijnen voor andere gezondheidsproblemen dan rugpijn (odds ratio (95% betrouwbaarheidsinterval) 1.42 (1.07-1.88)). Er was geen associatie tussen het rapporteren van bijwerkingen en de uitkomsten pijnintensiteit, fysiek functioneren, gezondheidsgerelateerde kwaliteit van leven of tijd tot herstel (respectievelijke coëfficiënten 0.00 (-0.07-0.07), 0.02 (-0.05-0.10), -0.44 (-1.08-0.20),-0.54 (-1.37-0.29) en hazard ratio 1.09 (0.94-1.26)). Vanwege een zeer klein aantal ernstige bijwerkingen (met hospitalisatie als gevolg) was er onvoldoende informatie beschikbaar om de associatie tussen het rapporteren van deze ernstige bijwerkingen en baseline karakteristieken of tussen het rapporteren van deze bijwerkingen en de uitkomsten van rugpijn te onderzoeken. In de PACE trial was het rapporteren van bijwerkingen na inname van paracetamol of placebo dus geassocieerd met het gebruik van medicijnen voor andere gezondheidsproblemen, maar niet met (ongunstige) uitkomsten van lage rugpijn.

In **Hoofdstuk 8** werden de bevindingen van dit proefschrift samengevat en bediscussieerd in het kader van methodologische beperkingen. Tevens werden de implicaties van deze bevindingen voor de klinische praktijk en voor toekomstig onderzoek besproken.

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om te spelen met de cover band!), Vulfpeck – Running Away, Smile – Doing All Right (Janneke, bedankt voor de tip om naar Bohemian Rhapsody te gaan!), Tom Misch – NPR Tiny Desk Concert (dit stond op repeat tijdens het schrijven van mijn General Introduction & Discussion). Een playlist behorende bij dit proefschrift is te vinden op https://www.youtube.com/playlist?list=PLnt1q8UpE1LmZh1CbQIpkJd9sOVg6St8a.

Een AIOTHO traject vraagt niet alleen flexibiliteit van de promovendus, maar ook van zijn praktijkopleiders! Brigitte, Jolanda, Joost, Michelle, Ronald, Lisette, Cindey en René, heel erg bedankt voor jullie begrip en voor het creëren van de benodigde ruimte om dit project tot een goed einde te brengen!

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CURRICULUM VITAE

Marco Schreijenberg is geboren op 10 juni 1989 in Vlissingen. Hij is de zoon van Kees Schreijenberg en Marjolijn Pundke. Hij groeide samen met zijn jongere zussen Lisette en Elvira op in Biggekerke, een klein dorpje in de buurt van het Zeeuwse Middelburg.

Na het behalen van het Gymnasium diploma in 2007 aan Stedelijke Scholengemeenschap Nehalennia in Middelburg, verhuisde Marco naar Rotterdam om de studie Geneeskunde te gaan volgen aan de Erasmus Universiteit. Tijdens zijn geneeskundestudie volgde hij tevens de onderzoeksmaster ***Molecular Medicine***; beide studies rondde hij in 2014 met goed gevolg af. Na kort gewerkt te hebben als wachtarts in de acute psychiatrie bij Bavo Europoort in Capelle aan den IJssel, begon hij in maart 2015 met de huisartsopleiding bij Huisartsenpraktijk De Tjasker in Papendrecht.

Een jaar later werd zijn opleidingstraject omgezet naar een AIOTHO-traject (arts in opleiding tot huisarts en onderzoeker), waarna hij startte als promovendus op de afdeling Huisartsgeneeskunde van het Erasmus MC. Hij werkte aanvankelijk onder begeleiding van co-promotor Pim Luijsterburg en prof. Bart Koes aan een gerandomiseerde gecontroleerde studie die de effectiviteit van paracetamol, diclofenac en placebo voor acute aspecifieke lage rugpijn onderzocht. Na voortijdige beëindiging van deze studie deed Marco onderzoek met eerder verzamelde Australische data, onder begeleiding van Chris Lin en prof. Chris Maher van de ***University of Sydney***. Bij de afronding van zijn promotietraject werd hij begeleid door co-promotor Alessandro Chiarotto. Tijdens zijn promotie gaf hij onderwijs aan geneeskundestudenten in de bachelor- en masterfases en aan huisartsen in opleiding; tevens was hij van 2016 tot en met 2019 betrokken bij de organisatie van activiteiten voor de afdeling Huisartsgeneeskunde als lid van de sfeercommissie. In 2019 behaalde Marco een ***Master of Science in Clinical Epidemiology*** aan het ***Netherlands Institute for Health Sciences*** (NIHES).

Vanaf september 2019 werkt Marco in het kader van het laatste jaar van de huisartsopleiding bij Huisartsenpraktijk Veere. Samen met zijn vriendin Annemieke verhuisde hij in 2019 terug naar Middelburg.

PHD PORTFOLIO

Erasmus MC Department: General Practice
PhD Period: March 2016 – September 2019
Promotors: Prof. dr. B.W. Koes and Prof. dr. C.G. Maher
Co-promotor:dr. A. Chiarotto

	Year	Workload (ECTS)
Courses/training		
Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2016-2019	70
BROK Course	2016	1
Scientific Integrity	2016	0.3
EndNote & Pubmed Courses, Erasmus MC, Rotterdam	2016	-
Placebo Course, South Denmark University, Odense, Denmark	2016	2
BKO (Basiskwalificatie Onderwijs) – Blended learning	2017	0.5
CACE-analysis Online Course	2018	-
Professional education		
Vocational training for general practitioner, Erasmus MC, Rotterdam	2015- present	
Oral presentations		
NHG Wetenschapsdag, VuMC, Amsterdam, 1 presentation	2018	1
SBPR meeting, Groningen, 1 presentation	2018	1
NHG Wetenschapsdag, Nijmegen, 1 presentation	2019	1
IFBNP, Québec City, Canada, 2 presentations	2019	1
World Congress Low Back Pain, Antwerp, Belgium, 1 presentation	2019	1
Poster presentations		
SBPR meeting, Groningen, 1 poster	2018	1
NHG Wetenschapsdag, Nijmegen, 1 poster	2019	1
IFBNP, Québec City, Canada, 2 posters	2019	1
Participation (inter)national conferences		
NHG Wetenschapsdag, AMC, Amsterdam	2016	0.3
IFBNP, Buxton, England	2016	1
Teaching		
Clinical reasoning for bachelor and master students	2016 – 2019	3.5
Scientific meetings for GP trainees, Erasmus MC, Rotterdam	2016 – 2019	0.5
Development and teaching of scientific program for GP trainees	2016	2.5
Supervising student session 'Critical Reading'	2019	1
Total		**90.6**

LIST OF PUBLICATIONS

This thesis

Schreijenberg M, Luijsterburg PA, Van Trier YD, Rizopoulos D, Koopmanschap MA, Voogt L, Maher CG, Koes BW. Efficacy of paracetamol, diclofenac and advice for acute low back pain in general practice: design of a randomized controlled trial (PACE Plus). BMC Musculoskelet Disord; 2017, 18(1): 56

Schreijenberg M, Luijsterburg PAJ, Van Trier YDM, Rizopoulos D, Koopmanschap MA, Voogt L, Maher CG, Koes BW. Discontinuation of the PACE Plus trial: problems in patient recruitment in general practice. BMC Musculoskelet Disord; 2018, 19(1): 146

Schreijenberg M, Koes BW, Lin CC. Guideline recommendations on the pharmacological management of non-specific low back pain in primary care - is there a need to change?. Expert Rev Clin Pharmacol; 2019 Feb;12(2):145-157

Schreijenberg M, Lin CC, McLachlan AJ, Williams CM, Kamper SJ, Koes BW, Maher CG, Billot L. Paracetamol is ineffective for acute low back pain even for patients who comply with treatment: Complier Average Causal Effect Analysis of a Randomized Controlled Trial. PAIN 2019 (accepted)

Other publications

Schreijenberg M, Behandeling van acute aspecifieke lagerugpijn. Huisarts Wet; 2017; 60(2):90