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

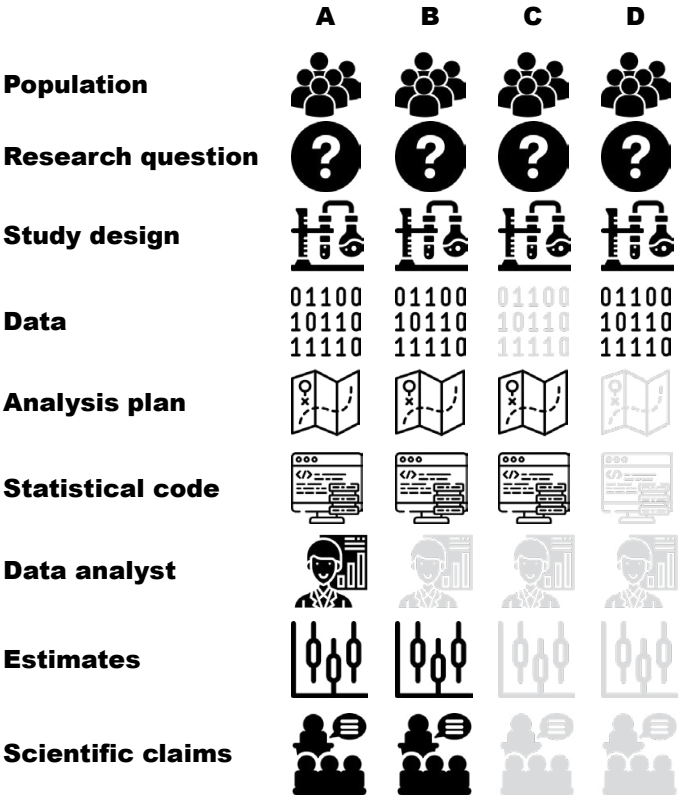

Figure 1: Different types of reproducibility in research according to Goodman's lexicon (58). Column A represents an original study. Columns B, C and D represent reproduction studies, with changes as compared to the original study represented in grey. Column A represents a methods reproduction study. 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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