University of Southern Queensland

INVESTIGATING THE USE OF ORAL PARACETAMOL AND TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) - DICLOFENAC AS A COMBINATION THERAPY FOR MILD TO MODERATE OSTEOARTHRITIS (OA) PAIN: AN EVIDENCE-BASED ASSESSMENT USING DATA MINING AND THE APPLICATION OF MACHINE LEARNING (ML)

A Thesis Submitted by

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ABSTRACT

Osteoarthritis (OA) is a major cause of chronic pain and disability in older adults and currently affects more than 500 million people worldwide. However, pain management in OA continues to remain suboptimal. The use of combination therapy of oral acetaminophen (APAP) and topical diclofenac (DIC), exhibiting complementary mechanisms of action, is an attractive strategy to achieve effective pain relief. However, there is limited information on the use of this combination for OA pain management. This study uses modified Delphi methodology to gather the perspectives of expert healthcare professionals (HCPs) towards the use of APAP either as monotherapy or in combination with topical NSAIDs in three different geographies, including Australia, Malaysia, and Sweden. The research shows that while oral APAP remains the gold standard treatment for the HCPs, there is limited prescription uptake for its combination with topical NSAIDs due to a lack of strong scientific evidence on their efficacy. In the absence of evidence on the combination in OA pain, the study uses a model-based meta-analysis (MBMA), a robust statistical technique, to extrapolate the combination effect from published studies conducted in acute pain setting. The MBMA indicates greater pain reduction and opioid sparing effect for the combination versus APAP monotherapy. Given the overlap in the pathophysiology of acute and chronic pain, similar beneficial effects from the use of combination can be expected on extrapolation to OA pain. Additionally, while topical DIC is considered well-tolerated due to its low systemic exposure, concerns of liver toxicity with APAP at standardised doses remain. Therefore, a separate MBMA is implemented to investigate the association between APAP and risk of hepatotoxicity. The MBMA demonstrates short-term (8-16 weeks) APAP use at standard analgesic doses (≤4000 mg/day) to be associated with a very low risk of clinically meaningful liver injury when compared with placebo. The findings in the study contribute to bridging the evidence gap in the literature on the efficacy and tolerability of combination of oral APAP and topical DIC in the management of mild to moderate OA pain.

CERTIFICATION OF THESIS

I Vidhu Sethi declare that the Thesis entitled *Investigating the use of oral paracetamol and topical non-steroidal anti-inflammatory drug (NSAID) - diclofenac as a combination therapy for mild to moderate osteoarthritis (OA) pain: An evidence-based assessment using data mining and the application of machine learning (ML)* is not more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references, and footnotes. The thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work.

Date: 15 June 2023

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STATEMENT OF CONTRIBUTION

I, Vidhu Sethi, made the majority (more than 50%) contribution to the conduct of the research and authorship of the papers (published and submitted) in this thesis.

Published paper:

1. Sethi V, Van der Laan L, Gupta S, Piros KC. Perspectives of Healthcare Professionals Towards Combination Use of Oral Paracetamol and Topical Non-Steroidal Inflammatory Drugs in Managing Mild-to-Moderate Pain for Osteoarthritis in a Clinical Setting: An Exploratory Study. Journal of Pain Res. 2022 Aug 6;15:2263-2272.

Vidhu Sethi contributed 60% to this paper. Collectively [Luke Van der Laan, Sanjeev Gupta, and K Cornelius Piros] contributed the remainder.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAOS	American Academy Of Orthopedic Surgeons
AEs	Adverse Events
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
APAP	Acetaminophen
CI	Confidence Interval
CNS	Central Nervous System
COX	Cyclo-Oxygenase
CV	Cardiovascular
CVD	Cardiovascular Disease
DIC	Diclofenac
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases
EULAR	European Alliance of Associations for Rheumatology
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GI	Gastrointestinal
GP	General Practitioner
HCP	Healthcare Professional
LR	Literature Review
MBMA	Model-Based Meta-Analysis
MOA	Mechanism Of Action
NICE	National Institute for Health and Care Excellence
NRS	Numerical Rating Scales
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OSE	Opioid Sparing Effect
OTC	Over The Counter
PCA	Patient-Controlled Analgesia
RACGP	Royal Australian College of General Practitioners
RCT	Randomized Controlled Trial
RR	Relative Risk
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WHO	World Health Organisation
WOMAC	Western Ontario and McMaster Universities Arthritis Index
YLDs	Years Lived with Disability

CHAPTER 1: INTRODUCTION

This chapter provides an outline to the background to the study and the research motivation by defining the problem statements, research gaps, research objective and its significance to the field. The chapter concludes with a framework outlining the contents of the remaining chapters of the thesis.

1.1 Background

Osteoarthritis (OA) is the most common degenerative joint disorder of the diarthrodial joints, affecting both the small joints (e.g., those in the hand and foot) and large joints (e.g., knee and hip joints). The progressive degeneration of tissues, such as cartilage, bone, and muscle, within and around the synovial joints results in symptoms that include pain, stiffness, swelling, tenderness, and occasionally locking the joint which restricts mobility, triggers functional disability and severely affects the quality of life of patients (Martel-Pelletier et al., 2016; Mobasheri and Batt, 2016).

OA affects approximately 7% of the global population, which is more than 500 million people worldwide (Global Burden of Disease Collaborative Network, 2020a). In 2019, OA was the 15th leading cause of years lived with disability (YLDs) globally and accounted for 2% of the total global YLDs. It is estimated that the number of persons affected by OA increased by 48 percent from 1990 to 2019 (Global Burden of Disease Collaborative Network, 2020b). It is a leading cause of disability, especially in populations ≥ 45 years and affects approximately 18% of women and 10% of men over the age of 60 years globally (Nelson, 2018). The burden of OA is expected to rise due to increased life expectancies and ageing of the global population and the obesity epidemic (Safiri et al., 2020). The societal costs of OA currently amount to 0.25–0.50% of the GDP for most developed countries (Puig-Junoy and Ruiz Zamora, 2015).

Pain is the hallmark symptom of OA and the main reason for affected individuals to seek medical care (Neogi, 2013). Pain from arthritis is one of the key barriers to maintaining physical activity which leads to a cyclic pattern of deconditioning and additional muscle weakening, resulting in the reduction of muscular support and shock absorption around the joint and contributing to

increased pain (Macera et al., 2017). In addition, since OA pain results in reduced physical activity in the affected individuals, there is a significant decrease in the patients' ability to self-manage other conditions, such as diabetes and hypertension, which in turn are associated with increased all-cause mortality (Piva et al., 2015). Moreover, the presence of the above comorbidities further restricts the use of existing OA therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs) in these populations (Cooper et al., 2019).

In the absence of effective disease-modifying medical treatments, the treatment focus for OA is to reduce pain, improve the function of the affected joints and increase quality of life. Current management strategies recommended by clinical practice guidelines for OA can be divided into three categories: non-pharmacological (including education and self-management, exercise, weight loss, and walking aids and nutraceuticals), pharmacological (including acetaminophen, oral and topical NSAIDs, opioid drugs and intra-articular injections) and surgical modalities (including joint replacement procedure/arthroplasty) (Martel-Pelletier et al., 2016; Mobasheri and Batt, 2016).

1.2 Problem

While guidelines emphasise the use of non-pharmacological interventions for management of OA, pharmacological agents (especially paracetamol and NSAIDs) are widely used as first-line therapies either over-the-counter (OTC) or by prescription despite exhibiting no influence on the disease process (Nowaczyk et al., 2022; Wilson et al., 2015). However, these pharmacological agents suffer from various limitations. Paracetamol (APAP), historically the first-line pain medication for osteoarthritis (Majeed et al., 2018), was recently shown to possess limited efficacy as a single agent for the treatment of osteoarthritis (Bannuru et al., 2010). Oral NSAIDs, the most common and frequently prescribed pharmacological agents for the treatment of OA, are associated with significant toxicity (including renal, gastrointestinal and cardiovascular complications) on long-term use, especially among the elderly population who are the most affected with this debilitating condition (Cooper et al., 2019; Wehling, 2014). Opioids, although lacking the end-

organ toxicity associated with NSAIDs, exhibit considerable and frequent adverse effects including nausea, vomiting, dizziness, constipation, sleepiness, tiredness, and headache, which outweigh their benefits in pain relief. In addition, physical or psychological dependence is another potential risk of opioids, especially in long-term use (Fuggle et al., 2019; Griessinger et al., 2003).

Therefore, in an effort to enhance patient safety and minimise potential side effects, clinicians undertreat pain which results in a substantial proportion of patients continuing to experience discomfort (van Laar et al., 2012). A recent study showed that there is a significant unmet need for effective treatments with more than half of patients with OA experiencing inadequate pain relief despite using symptomatic analgesics (Conaghan et al., 2015). Inadequate management of pain continues to have a considerable negative impact on quality of life of patients and their ability to function both physically and mentally (Sinatra, 2010).

In considering the high economic costs and the suffering associated with OA pain, it is important to evaluate and identify effective and well-tolerated analgesic therapies to limit the negative consequences of undermanaged OA pain. Therefore, the aim of the current investigation is to evaluate the efficacy of combination therapy of oral acetaminophen and topical diclofenac, as an alternative to oral NSAIDs or opioids, that may provide a meaningful pain relief option in OA clinical practice.

1.3 Main thesis of the study

Mounting evidence suggests OA pain is a complex phenomenon integrating sensory, affective, and cognitive processes and encompass multiple types of pain transmission pathways (e.g., inflammatory and non-inflammatory) at both peripheral (joints) and central (spinal and supraspinal) levels of the nervous system (Perrot, 2015; Salaffi et al., 2014). Considering the multi-mechanistic nature of chronic pain indication such as OA, it is expected that no single therapy will provide adequate pain relief while demonstrating optimal risk-benefit ratio in the long-term and successful treatment approaches may require targeting several pathways at the same time (Raffa et al., 2003; van Laar et al., 2012; Varrassi et al., 2010).

Following this logic, the use of rational combinations of analgesic drugs that act via different mechanisms offers a viable approach to analgesia that can provide more effective pain relief at reduced individual doses while also minimizing side effects (Raffa, 2006; van Laar et al., 2012). The use of a combination of analgesics has shown increasing promise in clinical practice and is also recommended by major clinical practice guidelines for management of pain including World Health Organization and the American College of Rheumatology (Paladini and Varrassi, 2020).

Paracetamol and topical diclofenac exhibit complementary modes of action and are therefore promising candidates to be used in combination analgesia. The mechanism of action for APAP is not completely understood; however, prevailing evidence strongly suggests APAP to act mainly through the CNS rather than the periphery (Mauger et al., 2010; Raffa, 2001). Topical diclofenac is an NSAID that alters peripheral pain transmission pathways by providing analgesia to the skin overlying the painful area (Brewer et al., 2010; Shah and Mehta, 2012). The addition of topical diclofenac to oral APAP could also be a useful strategy to address the limitations of APAP monotherapy, which has recently been shown to have limited efficacy as a single agent in the treatment of OA (Bannuru et al., 2010) and can be suitable for patients averse to oral NSAIDs due to comorbidities (Cooper et al., 2019). In addition, several clinical practice guidelines on the management of OA allow the use of topical NSAIDs concomitantly with APAP (Bruyère et al., 2014; Geenen et al., 2018; NICE, 2014). Moreover, the combination is generally perceived to be efficacious and well-tolerated since most trials in chronic pain allow APAP as a rescue therapy (Courtney and Doherty, 2002; Stewart et al., 2018). Furthermore, topical NSAIDs are generally considered as a safe treatment in the management of OA due to their low systemic exposure (Honvo et al., 2019b). In contrast, the safety concerns of overdose and/or long-term use of acetaminophen have been frequently raised, especially its associated risk of liver toxicity (Roberts et al., 2016).

Optimizing the use of this combination treatment may delay the progression to the use of systemic NSAIDs and opioids which exhibit low benefit-to-risk ratio. Moreover, the combination treatment can provide clinicians an effective first-line option for management of mild to moderate OA pain with a minimal

risk of systemic toxicity or drug-drug interactions. Therefore, we propose as the main thesis of the study that there is no change in the treatment behaviours and perspectives of healthcare professionals (HCPs) on the benefits and risks of oral APAP either as monotherapy or in combination with topical NSAIDs for OA pain management despite recent changes in the recommendations in clinical practice guidelines for OA. In addition, we propose that the combination of oral APAP and topical diclofenac exhibits greater efficacy than either APAP or topical diclofenac alone in the management of OA pain and that there is no significant risk of liver toxicity with APAP when used at standard analgesic dosages in OA pain management.

1.4 Research gaps

Several studies show that APAP monotherapy remains a common treatment option prescribed by clinicians for managing pain in OA patients. However, there is limited evidence related to the clinical practice behaviours of HCPs towards the use of APAP as monotherapy and in combination with topical NSAIDs in managing OA pain after the recent updates in the OA clinical guidelines. These guidelines downgraded oral APAP from first-line treatment to conditionally recommended in mild to moderate OA pain. In addition, there is a need to assess the influence of recent updates in guidelines on their real-world clinical practice behaviours of HCPs for the management of mild to moderate OA.

In addition, it is surprising that there is a lack of previous efficacy analyses on the combination of oral APAP and topical diclofenac in this costly therapeutic area. Furthermore, there is scarcity of good quality clinical evidence assessing the liver safety of oral APAP. The limited clinical evidence on the combination treatment of APAP and topical diclofenac prohibits HCPs from making informed treatment decisions and recommending this combination to patients in clinical practice with a high degree of confidence. Moreover, this also leads to difficulty in decision-making for professional organizations in drafting evidence-based recommendations for the management of OA disease. For example, all the latest clinical practice guidelines in OA cite limitations in recommending treatment options due to the lack of well-synthesized evidence (Bruyère et al., 2014; Geenen et al., 2018). This

uncertainty has resulted in the need for methodologically robust studies on the efficacy and safety of combination therapy as a viable alternative in the management of OA pain.

Therefore, the research gaps in the field of OA pain management are:

1. There is no recent evidence on the treatment behaviours and perspectives of expert HCPs on the benefits and risks of oral APAP as monotherapy and in combination with topical NSAIDs for OA pain management.
2. There are no previous efficacy analyses on the combination of oral APAP and topical diclofenac versus APAP and DIC monotherapies in the management of mild to moderate OA pain.
3. There are no recent analyses assessing the liver safety of oral APAP as a treatment for OA pain.

1.5 Research questions

There are several crucial questions that guide this research. These questions are:

1. What are the current treatment behaviours and perspectives of expert HCPs on the benefits and risks of APAP as monotherapy or in combination with topical NSAIDs for OA pain management considering the recent changes/updates in the clinical practice guideline recommendations?
2. How effective is the combination treatment of oral APAP and topical diclofenac when compared with APAP and DIC monotherapies in mild to moderate OA pain?
3. What is the risk of liver toxicity associated with oral APAP, especially when used in OA pain management?

1.6 Research objectives

To address the research questions, this thesis has the following objectives:
Objective 1: To determine the treatment behaviours and perspectives of HCPs on the benefits and risks of oral APAP either as monotherapy or in combination with topical NSAIDs for OA pain management considering the

recent changes/updates in the recommendations to clinical practice guidelines.
This objective will be achieved through the following:

- Designing and conducting an exploratory qualitative study using Delphi methodology to gather and understand the treatment behaviours and perspectives of expert HCPs (orthopaedic specialists, general practitioners, and senior pharmacists) from three diverse geographies including Australia, Malaysia, and Sweden.

Objective 2: To assess the effects of combination treatment of oral APAP and topical DIC and compare its performance relative to APAP and topical DIC monotherapy in mild to moderate OA pain using published clinical evidence identified through literature searches and advanced predictive modelling and simulation techniques.

This objective will be achieved through the following approach:

- Conducting literature reviews exploring existing clinical evidence on the combination of APAP and topical DIC in pain
- Implementing a model-based meta-analysis (MBMA) that compares the efficacy of APAP + DIC combination to APAP and topical DIC monotherapy

Objective 3: To investigate the association between the use of oral APAP and the risk of hepatotoxicity, particularly in OA management, using summary-level data from RCTs identified through literature searches.

This objective will be achieved through the following approach:

- Conducting literature review to identify existing clinical evidence investigating acetaminophen associated liver toxicity, preferably in OA pain.
- Implementing an MBMA to quantify the relationship between oral APAP use and the likelihood of liver abnormality defined by deviation from the upper limit of normal (ULN) in levels of liver enzymes (alanine aminotransferase or aspartate aminotransferase).

1.7 Significance of research

The output of this thesis will contribute to bridging the evidence gap in the literature on the efficacy and tolerability of combination of oral APAP and topical diclofenac in the management of mild to moderate OA pain. Our research will provide insights into the potential mechanisms of interaction as well as the pharmacokinetic and pharmacodynamic relationships between the two analgesics and will generate evidence to support their combination regimen in OA pain management. The research may improve evidence-based clinical practice and help in formulating rational treatment algorithms for OA and will be helpful to a range of stakeholders including individual patients, clinicians, policy makers and other health care funders. The research may open the door for a valuable treatment option for the ever-increasing aging population suffering from OA, especially who exhibit CV and GI comorbidities and hence are restricted to move to stronger analgesics such as oral NSAIDs and opioids.

1.8 Conclusion

This chapter presented a summary of the research gaps in the associated literature, research objectives and main thesis of the study. Chapter 2 presents a detailed review of relevant literature to provide the rationale of the study and outlines the research methodology and structure of the thesis. Chapter 3 describes the study conducted to investigate the receptiveness and current clinical practice behaviours of different types of HCPs towards use of APAP monotherapy and combined therapy of APAP and topical NSAIDs in the management of mild to moderate OA pain. Chapter 4 presents the modelling study on the efficacy and safety of APAP and topical DIC combination in mild to moderate OA pain. Finally, chapter 5 discusses how the findings have contributed towards addressing the research questions, the contributions of the research for current practice and the relevant field of knowledge, the limitations of the study and lines of enquiry for further research, followed by the study's conclusion. Chapter 6 contains the researcher's critical reflections on her doctoral research journey.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter aims to present a detailed review of relevant literature related to osteoarthritis disease and the pain associated with it. It then discusses the pharmacological options currently used in the symptomatic management of OA pain and their limitations. Subsequently, it discusses the rationale of analgesic drug combinations in the treatment of pain before specifically focusing on drug combination use in OA pain. It directs the reader to the research gap and provides an understanding of the research objectives in the context of the research questions. The chapter concludes by outlining the rationale for the research methodology and structure of the thesis.

2.2 Osteoarthritis

Osteoarthritis (OA) is a chronic disease characterised by degradation and loss of articular cartilage, subchondral bone remodeling, inflammation of the synovial membrane and structural alterations of the joint capsule, ligaments, and associated muscles (Mobasheri and Batt, 2016). OA is the most common degenerative joint disorder of the diarthrodial joints, affecting both the small joints (e.g., those in the hand and foot) and large joints (e.g., knee and hip joints). The progressive degeneration of tissues, such as cartilage, bone, and muscle, within and around the synovial joints results in symptoms that include pain, stiffness, swelling, tenderness, and occasionally locking in the joint that restricts mobility, triggers functional disability and severely affects the quality of life of patients (Martel-Pelletier et al., 2016; Mobasheri and Batt, 2016).

2.2.1 Risk factors

Several risk factors have been identified for the development and progression of OA which can be divided into two broad types: those acting at the level of individual susceptibility (person-level) and those altering the biomechanical stability of individual joints (joint-level). While the major person-level risk factors include increased age, female sex, genetic factors and obesity, the chief joint-level factors comprise of joint injury or trauma, repetitive joint use through occupation or leisure and joint malalignment. The

risk factors for OA are also classified based on the individual's ability to address them through lifestyle changes, as modifiable (obesity, trauma and avoiding occupational injuries) and non-modifiable (age, genetics and gender) (Johnson et al., 2012; Neogi, 2013).

2.2.2 Epidemiology and burden

According to the 2019 Global Burden of Disease study, OA affects approximately 7% of the global population, which is more than 500 million people worldwide (Global Burden of Disease Collaborative Network, 2020a). In 2019, OA was the 15th leading cause of years lived with disability (YLDs) globally and accounted for 2% of the total global YLDs. It has been estimated that the number of persons affected by OA increased by 48 percent from 1990 to 2019 (Global Burden of Disease Collaborative Network, 2020b). It is a leading cause of disability, especially in the population ≥ 45 years and affects approximately 18% of women and 10% of men ≥ 60 years globally (Nelson, 2018). Although osteoarthritis occurs in people of all ages, symptoms of osteoarthritis typically begin after 45 years of age and progress slowly, with the disease most commonly present in people aged 60 years and over and in women. Moreover, the prevalence of knee OA is increasing exponentially due to the rapidly aging global population and the obesity epidemic (Safiri et al., 2020).

Since OA is a relatively common condition, it has substantial implications for the individuals, families, and health care systems as well as wider socioeconomic costs. While OA exhibits considerable negative effects on physical function, sleep and psychological health at the individual level, it also significantly causes considerable societal costs in terms of reduced quality of life, diminished employment capacity, early retirement and increased healthcare costs (Hawker, 2019). Societal costs of OA currently amount to 0.25–0.50% of the GDP for most developed countries (Puig-Junoy and Ruiz Zamora, 2015). The economic burden on individual patients is also substantial in every country that it has been estimated. In 2003, a study in the United States estimated the total costs attributable to arthritis and other rheumatic conditions as approximately $128 billion, which amounted to 1.2% of the gross domestic product. While direct costs (i.e., medical expenditures) amounted to $80.8 billion, indirect costs (i.e., lost earnings) were $47 billion.

In 2009, another US study estimated costs attributable to hospital expenditures of total knee and hip joint replacements respectively, to be $28.5 billion and $13.7 billion. In addition, OA patients have higher out of pocket expenses for health-related expenditures when compared with age and gender matched populations with the average direct costs of OA per patient estimated to be approximately $2,600 per year. Furthermore, indirect costs due to lost productivity are estimated to cost from $3.4 to $13 billion/year (March et al., 2016).

OA is also associated with considerable comorbidity. According to a recent systematic review, patients with OA exhibited a pooled prevalence for overall cardiovascular disease pathology of 38.4% and were almost three times as likely to have heart failure (relative risk, RR: 2.80) or almost twice as likely to have ischemic heart disease (RR: 1.78) when compared with matched non-OA controls (Hall et al., 2016). In addition, since OA pain results in reduced physical activity in the affected individuals, there is a significant decrease in the patients ability to self-manage other conditions, such as diabetes and hypertension, which in turn are associated with increased all-cause mortality (Piva et al., 2015).

Moreover, the presence of the above comorbidities further restricts the use of existing OA therapies such as NSAIDs in these populations (Cooper et al., 2019). Overall, individuals with OA exhibit greater all-cause mortality (standardised mortality ratio: 1.55) when compared with the control population. Furthermore, the greater the restriction in walking ability, the higher the risk of death (p-value for trend <0.001), driven largely by cardiovascular disease. OA triggered chronic pain and joint deformity results in limitation of movement and an increased risk of falling which compromises the affected individual’s independence and promotes the development of mental disorders in patients (Nüesch et al., 2011). In 2016, a recent systematic review and meta-analysis demonstrated that ~20% of patients with OA experience symptoms of depression and anxiety (Stubbs et al., 2016).

2.2.3 Pathophysiology

OA is a degenerative joint disease that involves the cartilage and its surrounding tissues including ligaments, menisci, synovium, and joint capsule. The major hallmarks of clinical OA include damage and loss of articular cartilage, alterations in the underlying subchondral bone and formation of cysts and osteophytes and thickening of the joint capsule. The articular cartilage maintains a balance between degenerative and synthesising processes, including the maintenance of collagen and proteoglycans to preserve its integrity. When mature articular cartilage is damaged, it exhibits a poor ability for repair as it is devoid of nerves and blood vessels. Cartilage damage and associated impaired function results in abnormal joint mechanics and triggers the deterioration of other joint tissues. Loss of cartilage and joint disruption is linked to attempts at repair with new bone formation and the development of subchondral sclerosis and osteophytes(Martel-Pelletier et al., 2016; Mobasheri and Batt, 2016).

The progression of OA is generally divided into three main stages: Stage 1 involves the proteolytic breakdown of cartilage matrix. Stage 2 is characterised by fibrillation and erosion of the cartilage surface and subsequent release of breakdown products into the synovial fluid. In stage 3, synovial cells ingest breakdown products through phagocytosis and secrete proteases and proinflammatory cytokines such as interleukin-1β (IL-1β) and tissue necrosis factor-alpha (TNF-α) and trigger synovial inflammation and pain (Martel-Pelletier et al., 2016; Mobasheri and Batt, 2016).

2.2.4 Pain in osteoarthritis results from multiple pathways

Pain is the principal symptom of OA and the major reason for the affected individuals to seek medical care. Pain from arthritis is one of the key barriers to maintaining physical activity and can be considered a key factor in the onset of frailty in the elderly (Neogi, 2013). Mounting evidence suggests that pain associated with OA often originates from multiple sources such as the synovial membrane, joint capsule, periarticular ligaments or muscle, periosteum, and subchondral bone and involves multiple types (e.g., inflammatory, and non-inflammatory) and multiple pain transmission pathways. In addition, it is now widely recognised that OA pain is a complex

phenomenon integrating sensory, affective, and cognitive processes and encompassing a variety of abnormal cellular mechanisms at both peripheral (joints) and central (spinal and supraspinal) levels of the nervous system (Perrot, 2015; Salaffi et al., 2014).

2.3 Overview of treatment approaches for osteoarthritis pain

Although several therapeutic options are available for the management of OA, none of them can arrest or reverse the progression of the disease (Hermann et al., 2018). In the absence of effective disease-modifying medical treatments, the treatment focus for OA is to reduce pain, improve function of the affected joints and increase quality of life. Several evidence--based guidelines from advanced organizations and societies exist for the management of OA. There is a consensus across the guidelines on the recommended management strategies for OA, which can be divided into three categories - non-pharmacological, pharmacological and surgical modalities(Martel-Pelletier et al., 2016).

Non-pharmacological interventions are mostly recommended as first-line and include education and self-management, exercise, weight loss, walking aids and nutraceuticals. Pharmacological strategies most often recommended in the guidelines for pain and inflammation management include acetaminophen, oral and topical nonsteroidal anti-inflammatory drugs (NSAIDs), opioid drugs and intra-articular injections. Surgery including joint replacement procedure /arthroplasty is reserved only for advanced, severe OA when conservative therapy is ineffective. Although it is effective in reducing pain and improving joint function, it is not recommended in young patients due to the finite lifespan (usually 10–15 years) of artificial implants. Moreover, the long-term results of arthroplasty show considerable variation among individuals (Martel-Pelletier et al., 2016).

2.4 Current pharmacological options for osteoarthritis pain and their limitations

Even though all guidelines emphasise the use of non-pharmacological interventions for the management of OA, pharmacological agents (especially paracetamol and NSAIDs) are widely used as first-line therapies even though they do not influence the disease process (Akazawa et al., 2019; Fallach et

al., 2021; Wilson et al., 2015). These symptomatic interventions are considered at the early stages of OA. The major drugs used for management of OA-related pain are:

Paracetamol: Paracetamol or acetaminophen (APAP) is one of the most used analgesic and antipyretic medications globally, that is listed in the World Health Organization's List of Essential Medicines (Conaghan et al., 2019; Zhang et al., 2016). APAP has been shown to act centrally via the descending serotonergic pathways with minimal influence on peripheral pathways (Mauger et al., 2010; Raffa, 2001). The use of APAP in OA is supported by a vast body of clinical literature and is also well-established in clinical practice. Paracetamol was historically the first-line pain medication for osteoarthritis (Majeed et al., 2018). However, recent systematic reviews and meta-analysis showed APAP to exhibit modest efficacy when compared with placebo group along with safety concerns and concluded that APAP has limited use as a single agent for the treatment of osteoarthritis (Bannuru et al., 2010; Leopoldino et al., 2019; Machado et al., 2015).

NSAIDs: NSAIDs are one of the most common classes of drugs used for the treatment of chronic pain associated with OA. NSAIDs work by inhibiting COX enzymes, which are involved in the synthesis of prostaglandins peripherally (Cooper et al., 2019). NSAIDs can be classified into two main types:

- *Oral NSAIDs*: Oral NSAIDs are one of the most widely used and universally recommended drugs by guidelines for the management of pain in osteoarthritis. However, they are associated with significant toxicity (in particular, gastrointestinal, and cardiovascular complications), especially among the elderly population who are the most affected with this debilitating condition. Therefore, the use of oral NSAIDs is preferably restricted to short-term use (as needed) at the smallest dose possible (Cooper et al., 2019).
- *Topical NSAIDs*: Topical NSAIDs have also been used extensively for OA in individuals with contraindications or lack of efficacy from oral NSAIDs (Rannou et al., 2016)]. Topical NSAIDs target local, peripheral mechanisms of pain and inflammation by acting on peripheral COX

inhibition in the skin and soft tissue (Brewer et al., 2010; Shah and Mehta, 2012). A meta-analysis published in 2018 showed topical NSAIDs to be effective for pain relief in OA, with corrected mean effect sizes of 0·30 for pain relief and 0·35 for function when compared with placebo (Zeng et al., 2018). In clinical studies, topical NSAIDs demonstrated comparable efficacy to oral NSAIDs with fewer adverse events. The most common adverse events of topical NSAIDs were local site reactions. Mounting evidence indicates that topical NSAIDs have a moderate effect on relief of osteoarthritic pain, comparable to that of oral NSAIDs, but have better safety profiles than oral NSAIDs as systemic drug levels are much lower (Rannou et al., 2016; Yakushin et al., 2021). This has resulted in several international and national clinical practice guidelines to position these agents as either a first-line option or adjunct to oral medications (paracetamol/acetaminophen, selective and nonselective NSAIDs, opioids) for the management of osteoarthritic pain of the knee and hand (Bruyère et al., 2014; Geenen et al., 2018; NICE, 2014).

Opioid analgesics: Opioids are generally considered the treatment of choice for moderate to severe pain and are recommended for patients who are unresponsive or contraindicated to traditional analgesics such as NSAIDs and acetaminophen. However, opioids exhibit considerable and frequent adverse effects including nausea, vomiting, dizziness, constipation, sleepiness, tiredness, and headaches, which may outweigh the benefits in pain relief. Opioid abuse is another potential risk of using these drugs. In addition, opioids should be avoided as there is no medical evidence for their efficacy on a long-term basis (Fuggle et al., 2019; Griessinger et al., 2003). A recent systematic review and meta-analysis including over 9,000 subjects with hip and knee OA showed that opioids provided minimal relief of OA symptoms and even less improvement in function. Moreover, stronger opioids exhibited consistently inferior efficacy and lower safety when compared with weak/intermediate opioids (Osani et al., 2021).

As a consequence of the unacceptable side effects associated with the above OA drugs, clinicians undertreat pain in an effort to enhance patient safety and minimise potential side effects which results in a substantial

proportion of patients continuing to experience pain despite the availability of effective treatment options (van Laar et al., 2012). An observational study of real-world therapies for OA revealed that more than half of patients with knee OA reported inadequate pain relief defined as moderate to severe pain after taking physician-prescribed treatment for at least 14 days. Moreover, NSAIDs (60% of patients), followed by paracetamol (44%) and opioid-containing medications (27%) were the most prescribed analgesic medications in the study (Conaghan et al., 2015). Inadequate management of pain continues to have a considerable negative impact on quality of life and the ability to function both physically and mentally (Sinatra, 2010). Therefore, there exists a significant need for effective, well-tolerated analgesic therapies to limit the negative consequences of undermanaged OA pain.

2.5 Usefulness of analgesic drugs combinations in the treatment of pain

A growing body of evidence suggests that when the pathophysiology of a medical condition is multi-modal, i.e., related to multiple physiological causes or mediated by multiple pathways, the optimal strategy can be to use a combination of drugs that contribute via different mechanisms to the therapeutic goal (Raffa et al., 2003).

Considering the multi-mechanistic nature of chronic pain indication such as OA it is expected that no single therapy provides adequate pain relief while demonstrating optimal risk-benefit ratio in the long-term and successful treatment approaches may require targeting several pathways at the same time. Here, the use of rational multi-modal or combinations of analgesic drugs that act via different mechanisms offer a viable approach to analgesia that can provide more effective pain relief at reduced individual doses while also minimising side effects (Altman, 2004; Raffa et al., 2003).

The use of multimodal therapy involving a combination of analgesics has shown increasing promise in clinical practice and is also recommended by major clinical practice guidelines for management of pain including the World Health Organization and the American College of Rheumatology (Paladini and Varrassi, 2020). In clinical practice, drug combinations are frequently used to manage OA pain, and several guidelines on OA management allow

the use of topical NSAIDs concomitantly with APAP (Bruyère et al., 2014; Geenen et al., 2018; NICE, 2014).

APAP is a simple analgesic that has remained one of the most steadfast options for the management of OA pain for decades. APAP has broad tolerability and is considered to be a safer treatment choice than NSAIDs in people at increased risk of NSAID-related adverse effects, e.g. older patients, patients with cardiovascular or renal co-morbidities or diabetes, or patients with a previous history of gastrointestinal symptoms or NSAID hypersensitivity (Conaghan et al., 2019). However, the major adverse effect associated with paracetamol is liver damage due to overdose and it should not be prescribed to patients with liver disease. The definitive mechanism of action for APAP remains unclear; however, prevailing evidence strongly suggests APAP acts mainly through the CNS rather than the periphery. The use of APAP in OA is well-supported by a vast body of clinical literature and is also well-established in clinical practice (Mauger et al., 2010; Raffa, 2001). Recent publications have demonstrated APAP monotherapy provides minimal short-term benefits comparable to placebo, in individuals with OA (Bannuru et al., 2010; Leopoldino et al., 2019; Machado et al., 2015). This resulted in several clinical practice guidelines downgrading their recommendations for paracetamol from the position of first-choice analgesic to conditionally recommended in patients with OA (Bannuru et al., 2019). However, despite the above downgrade in APAP recommendation, recent evidence from clinical practices continue to show that APAP remains the preferred drug for early-stage OA patients with mild to moderate pain (Freo et al., 2021).

A growing body of evidence suggests that peripheral transmission pain pathways may be altered by the local application of analgesia to the skin overlying the painful area. Since there is strong evidence supporting topical NSAIDs having comparable efficacy and superior safety profile to oral NAIDs formulations, they are increasingly recommended in international guidelines as first-line analgesic therapy or adjuvant treatment to APAP monotherapy, before the use of oral NSAIDs, particularly in patients who experience OA pain localised to joints that are closer to the surface, such as the hands and knees (Brewer et al., 2010; Shah and Mehta, 2012). Furthermore, several

recent systematic reviews and meta-analysis have suggested topical diclofenac, amongst other topical NSAIDs, to provide great levels of pain relief, with topical diclofenac solution equivalent in efficacy to oral NSAID therapy in knee and hand osteoarthritis (da Costa et al., 2021; Zeng et al., 2021; Zeng et al., 2018).

Therefore, the addition of topical diclofenac to oral APAP as a combination therapy could be a promising strategy to address the limitations of APAP monotherapy in the treatment of mild to moderate OA pain as both APAP and diclofenac have a complementary mode of action. Both these pharmacological interventions have been shown to be effective in reducing pain and improving function whilst demonstrating high tolerability over short- and long-term use. Combining paracetamol with topical NSAIDs such as diclofenac may be appropriate in patients averse to oral NSAIDs due to comorbidities. In addition, the combination is generally perceived to be efficacious and well-tolerated as more than half of the studies investigating the effect of topical NSAIDs in chronic pain allowed APAP as rescue therapy. Optimising the use of this combination treatment may delay the progression to the use of systemic NSAIDs and opioids which exhibit low benefit-risk ratio. Moreover, the combination therapy can provide clinicians an effective option for management of mild to moderate OA pain with a minimal risk of systemic toxicity or drug-drug interactions.

2.6 Analgesic drug combinations used in osteoarthritis pain

A review of existing literature reveal a limited number of studies which have investigated the effect of combining analgesics, especially NSAIDs and paracetamol, in osteoarthritis therapy.

Murphy, Donald, and Layes Molla compared the analgesic efficacy of a combination of fenoprofen (200 mg) and paracetamol (500 mg) with dihydrocodeine tartrate (30 mg) in two groups of 75 patients suffering from a wide variety of presenting conditions including osteoarthritis, spondylitis and lumbago. The study revealed the combination to exhibit significantly greater analgesia than dihydrocodeine tartrate with a much lower incidence of side effects (Murphy et al., 1978). Similarly, Seideman, Samuelson, and Neander conducted a double-blind clinical study of 18 patients with osteoarthritis of the

hip to investigate the effect of 3 monotherapy doses of naproxen (0.5, 1.0, and 1.5 g daily) and 2 doses of naproxen in combination with paracetamol (0.5 g + 4 g daily and 1.0 g + 4 g daily). The research group showed that treatment with naproxen and paracetamol was more effective than treatment with higher naproxen doses alone. In addition, the effect of the highest naproxen dose was not better than the effect of the lower naproxen dose (1.0 g daily) combined with paracetamol (Seideman et al., 1993). Doherty et al. showed that the use of two combination tablets of ibuprofen/paracetamol, at non-prescription doses, resulted in significant improvements in pain relief, function and patient quality of life when compared with paracetamol monotherapy in patients with knee pain/osteoarthritis for both short and long-term use (Doherty et al., 2011). Furthermore, Pareek et al. demonstrated aceclofenac-paracetamol combination to exhibit significantly superior efficacy to aceclofenac monotherapy with respect to the patients' and investigators' overall efficacy assessments ($p = 0.035$ and $p = 0.009$ respectively) in patients with osteoarthritis (OA) flare-up (Pareek et al., 2009). Pareek, Chandurkar, Ambade, Chandanwale, and Bartakke in 2010 showed etodolac-paracetamol to be significantly more effective in the treatment of OA flare-up than etodolac alone (Pareek et al., 2010).

In addition, studies have also shown the combination of paracetamol and opioids to provide significantly greater analgesia than nonselective NSAID or COX-2 inhibitors therapy alone. Emkey et al. evaluated the effect of adding tramadol (37.5 mg)/acetaminophen (325 mg) to therapy with a COX-2 inhibitor in 307 patients with OA whose pain was not adequately controlled by the COX-2 inhibitor (either rofecoxib or celecoxib). The study revealed significant improvements in visual analog scale scores for pain relief among patients taking combination tramadol/acetaminophen/COX2 inhibitor when compared with those taking placebo plus COX-2 inhibitors ($p = 0.002$). The treatment group also showed significantly improved WOMAC OA Index physical function ($p = 0.049$) and the Medical Outcome Study Short Form-36 role-physical measures ($p = 0.010$) (Emkey et al., 2004). Silverfield and co-workers (2002) and Rosenthal and co-workers (2004) showed that tramadol plus acetaminophen was an effective adjunct to nonselective NSAID or COX-2 inhibitors therapy for patients with poorly controlled OA pain (Silverfield et

al., 2002) (Rosenthal et al., 2004). Additionally, Vlok and van Vuren demonstrated the combination analgesic containing ibuprofen 200 mg, paracetamol 250 mg and codeine phosphate 10 mg per tablet to provide significantly better pain relief than ibuprofen 200 mg alone ($p < 0.05$) while exhibiting comparable safety (Vlok and van Vuren, 1987).

2.7 Combination of APAP and topical NSAIDs in osteoarthritis pain

Topical NSAIDs and paracetamol (APAP) are frequently used for osteoarthritis (OA) pain. In real-world settings, the combination treatment is commonly used with more than one-quarter of patients using topical NSAIDs in addition to oral non-opioid analgesics such as APAP (Jackson et al., 2017). In addition, several key clinical practice guidelines on OA management - EULAR, NICE, and ESCEO - allow concomitant use of topical NSAIDs with oral APAP (Bruyère et al., 2014; Geenen et al., 2018; NICE, 2014).

However, there is limited amount of literature available on the combination of oral paracetamol and topical NSAIDS despite APAP being used as the rescue medication of choice in OA analgesic trials (Courtney and Doherty, 2002; Stewart et al., 2018). Our literature review identified only one randomised controlled trial (RCT) of 4-weeks duration that evaluated the efficacy and safety of combination treatment with APAP and a topical NSAID (ketoprofen plaster) in 43 patients with knee OA. The study revealed the combination of APAP/topical ketoprofen to exhibit significantly greater efficacy in pain reduction ($p = 0.03$) and physician's global assessments ($p = 0.01$) when compared with APAP or placebo (Yoo et al., 1996).

CHAPTER 3: METHODOLOGY

3.1 Introduction

The thesis aims to address the apparent gap in the literature associated with: (a) perspectives and the clinical practice behaviours of expert HCPs on the benefits and risks of APAP as monotherapy or in combination with topical NSAIDs for OA pain management (b) efficacy and safety of the combination of oral APAP and topical DIC in mild to moderate OA pain. To respond to the research questions, the study is necessarily exploratory in nature. While the aim of the study is to address the gap in the literature, the aim of the research methodology is to investigate the phenomenon and provide an empirical basis for future studies.

The study adopts a pragmatism paradigm as a lens to view the phenomenon. Pragmatism is problem-centered and concerned with real-world practice (Creswell and Creswell, 2017). In the case of this study and in view of the gap in knowledge, the research focuses on ‘what works’ as it arises out of (a) the actions, situations, and consequences of OA treatment practice, and (b) the efficacy of APAP/topical NSAIDs combination therapy as an indicator of effectiveness. As such the research adopts an exploratory approach that seeks to present a tentative indication of what may be a solution to the research problem. Findings would therefore necessitate further confirmatory studies.

3.2 Research design

Pragmatism assumes that rather than the research methods being the most important consideration, the problem is the most important and is thus indicative of what methods are most appropriate in order to adequately respond to the research questions. Pragmatism is problem-focused and usually requires a mixed methods (qualitative and quantitative data) research design (Creswell and Creswell, 2017).

The literature reveals that efficacy studies related to the combination of APAP/topical NSAIDs in the treatment of OA are scarce without contemporary insight to inform practice. Similarly, with recent reports showing that APAP monotherapy exhibits modest efficacy and hepatotoxicity

related side-effects, no recent studies of practitioner responses in treatment scenarios are apparent.

Pragmatism suggests that a plurality of research methods is necessary to adequately respond to research questions (Allemang et al., 2022). For this study, it was deemed that both practice insights (qualitative) and treatment efficacy results (quantitative) were necessary to form a holistic view of OA treatment options, specifically APAP/topical NSAIDs combination therapy.

The study therefore adopted an exploratory sequential mixed methods research design commonly associated with the pragmatism approach (Creswell and Creswell, 2017). The research design consists of two-phases. Phase one (qualitative) used a modified Delphi method approach to investigate practice behaviours (study 1). Phase two (quantitative) used a secondary data modelling method to investigate efficacy (study 2a) and safety (study 2b) of the combination therapy. The research design is shown in the figure 3.1.

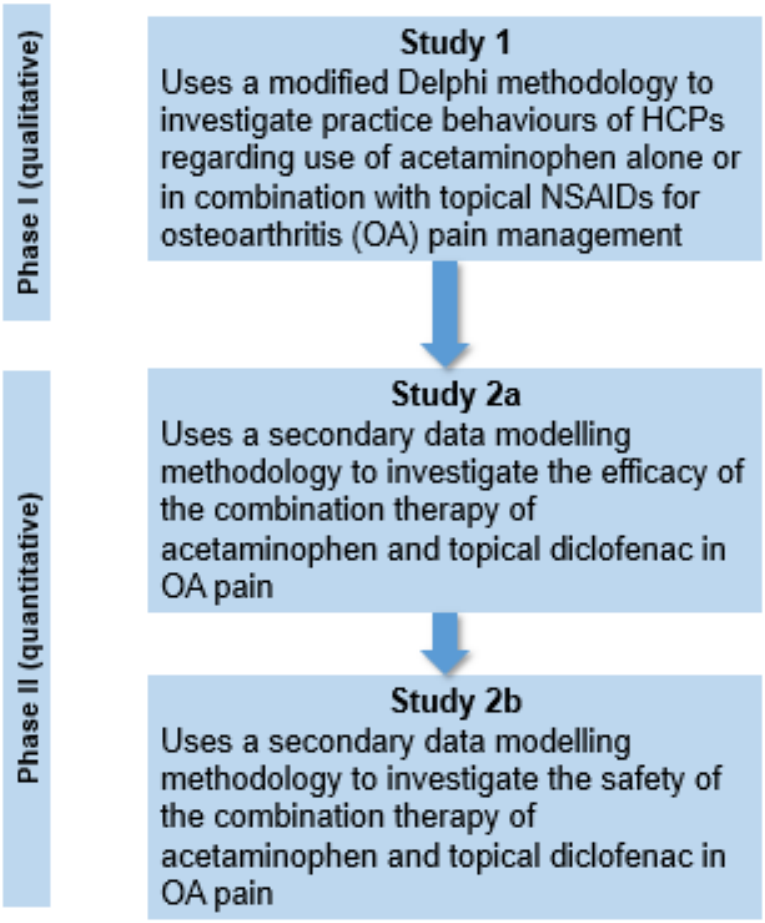


Figure 3.1: Research design

3.3 Delphi methodology

The Delphi method is an accepted scientific, structured, and systematic process to gather informed consensus on a topic that does not have clear evidence information using a series of questionnaires interspersed with controlled feedback including group statistical responses (Green et al., 1999). The method (also called the Delphi technique or Delphi process) was developed as a forecasting tool for military action in the 1950s and subsequently became a popular method for business forecasting before gaining further acceptance in the scientific community in the 1980s (Taylor, 2020). Its popularity arises from the fact that a large number of individuals across diverse locations and areas of expertise can be included anonymously, thus avoiding domination of the consensus process by one or a few experts and allows free expression of opinions (Boulkedid et al., 2011). The presence of anonymity amongst the panel members avoids individual dominance resulting from strong verbalisation, track records or professional

dominance while also permitting panelists to alter their opinion based on the arguments presented by the other panel members without admitting it publicly (Veugelers et al., 2020). In healthcare, the Delphi process is primarily used to achieve consensus in the development of guidelines or treatment protocols in situations where there is inadequate or conflicting evidence available. The Delphi method involves panel selection, development of content surveys, and iterative rounds of anonymous responses to gain consensus. The respondents receive feedback after each round in the form of a statistical representation of the overall group's response. Here, the aim of conducting multiple iterations is to reduce the range of responses and gain expert consensus (Taylor, 2020).

Presently there are no formal, universally agreed guidelines on the use of the Delphi method nor does any standardization of methodology exist. Therefore, flexibility exists in the design and format of the method depending on the research problem (Keeney et al., 2006). There are at least ten commonly used types of Delphi designs. The classical design is used to forecast and gather opinion by involving an open qualitative first round to allow panelists to record responses, the modified design, generally involving fewer rounds, provides panelists with pre-selected items, drawn from various sources, within which they are asked to consider their responses. The decision design is used to inform immediate decision-making, whereas the policy design serves to guide policy development by allowing participants to share divergent opinions. Additionally, other designs include real-time, involving tabulation of results after each round using computer technology, e-Delphi, involving administration of Delphi via email or online survey; technological, involving use of hand-held keypads allowing responses to be recorded and generation of instant feedback; online design, Delphi performed using any online instrument such as a chat room, or forum; argument, wherein participants are purposely selected to represent opposite sides of an issue; and disaggregative policy, wherein participants are requested to speculate on future scenarios (Hasson et al., 2011).

Therefore, considering the lack of a robust body of supporting clinical evidence on combination of APAP and topical NSAIDs, the consensus forging Delphi method is well-suited to filling this void by relying on the

knowledge and experience of experts, who actively treat patients with osteoarthritis, and gathering their real-world clinical practice behaviours and perspectives.

3.4 Artificial intelligence-based machine learning methods

Artificial intelligence (AI) refers to machine-based data processing to achieve objectives that typically require human cognitive function. In the modern age, AI has mined vast amounts of data and demonstrated the potential to identify and categorise complex patterns and new representations of data that were beyond human capabilities. Machine learning (ML) is a subdiscipline of AI and fundamentally involves use of algorithms to parse data, learn from it with an aim decide or a prediction about the future state of any new data sets. ML extends the range of traditional statistics because of its ability to identify nonlinear relationships and high-order interactions between multiple variables that may be challenging using conventional statistical methods (Feeny et al., 2020; Vamathevan et al., 2019).

ML comprises chiefly of three approaches which include supervised, unsupervised, and reinforcement learning. While supervised learning training a model based on known input and output data relationships to predict future outputs for new input data, unsupervised learning does not require any training steps and involves identification of hidden or intrinsic patterns in the input data before using these to cluster data in meaningful ways. In contrast, reinforcement learning involves training the machine about the correct and false responses (Mousavi et al., 2022; Vamathevan et al., 2019).

In the pharmaceutical industry, much of the rationale for the use of ML technologies is driven by business needs to lower overall attrition and costs. In the field of rational drug discovery, ML tools, such as quantitative structure–activity relationship (QSAR) modeling for virtual screening, were traditionally used to identify potential biological active molecules from millions of candidate compounds quickly and in a cost-effective manner. However, ML has nowadays advanced into deep learning methods, which exhibit greater power and efficiency to deal with the massive amounts of data generated from modern drug discovery approaches in this era of ‘big’ data (Zhang et al., 2017).

ML algorithms are currently used at all stages of drug discovery and development, including clinical trials, to identify novel therapeutic targets, generate stronger evidence for target– disease associations and increase understanding of disease mechanisms, improve small-molecule compound design and optimization, develop new biomarkers for disease prognosis, progression and drug efficacy, improve analysis of biometric and other data from patient monitoring and wearable devices, digitally enhance pathology imaging and extract high-content information from images at all levels of resolution (Vamathevan et al., 2019). Therefore, given the above benefits, ML algorithms are well-suited to identify hidden correlations among the data and to improve the predictive efficiency of the models developed in the study.

3.5 Model-based meta-analysis

Meta-analysis is a well-established statistical technique in evidence-based medicine that involves collecting and combining results from several individual clinical studies with an aim to integrate the findings and provide a pooled estimate of those studies that offers powerful and important outcomes. Generally, there are three types of meta-analysis: (i) pairwise meta-analysis (PW-MA), (ii) network meta-analysis (NMA), and (iii) model-based meta-analysis (MBMA). While a PMA is limited to comparisons of two treatments at a time employing treatment arms directly evaluated in head-to-head trials, NMA extends the principles of PMA to allow the evaluation of more than two treatments simultaneously by permitting direct comparisons based on data from RCTs and indirect comparisons of treatments, which were not assessed in the same clinical trial, using a common comparator treatment, such as placebo or standard-of-care (SOC). However, NMA also exhibits some limitations. Firstly, it does not consider the structural relationships of dose response. Secondly, it is difficult to integrate multiple time courses and placebo responses using NMA. Lastly, it may be subjected to bias due to design differences in the combined studies (Alhaj-Suliman et al., 2020; Chan et al., 2022).

In this direction, MBMA has emerged as a robust quantitative approach that can leverage published individual- and summary-level data, incorporate longitudinal data and the pharmacologic concept of dose–response relationship and combine and incorporate covariates in the analysis to inform

key drug development decisions, such as the benefit-risk assessment of a treatment under investigation. An MBMA is a meta-analysis that applies pharmacological principles such as effects of treatment, dose, time, and patient population characteristics on the study outcomes (Mandema et al., 2011a; Mould, 2012). In addition, MBMA is widely used in comparing treatments that have never been studied together in one clinical trial. Other benefits of MBMA are: (i) selection of optimal dose and dosing regimen through characterisation of dose-response and efficacy-time course relationships, (ii) response prediction for drug doses that have not been clinically evaluated, (iii) optimized design of clinical trials for future by bridging the data across studies, (iv) comparing new treatments and other emerging drugs with existing drugs, (v) accounting for trial-to-trial covariates (random and fixed effects) and decreasing heterogeneity in the cumulative outcome arising due to combining data from multiple clinical trials (Boucher and Bennetts, 2016; Chan et al., 2022). The above strengths justify the use of MBMA as an appropriate methodological approach in our study.

3.6 Identified research gap and conclusion

Osteoarthritis (OA) is the most common degenerative disease of the joints. Chronic pain is the hallmark symptom of OA that results in significant disability and reduced quality of life in older adults. OA affects more than 500 million people worldwide and was the 15th leading cause of years lived with disability (YLDs) globally, accounting for 2% of the total global YLDs in 2019. Moreover, the burden of OA is expected to rise considering increased life expectancy and ageing of the global population and the obesity epidemic. Several pharmacological agents (especially paracetamol and NSAIDs) are widely used either as OTC or by prescription despite exhibiting no disease-modifying effect. However, these pharmacological agents either exhibit modest efficacy when compared with placebo or pose high risk of serious adverse events especially in the elderly population who are the most affected by this disease. Hence, there is a significant need to evaluate and identify effective and well-tolerated analgesic therapies to limit the negative consequences of undermanaged OA pain which will the decrease the economic cost and personal suffering.

Considering the multi-mechanistic nature of OA pain, the use of rational combinations of analgesic drugs acting via different mechanisms offers a viable approach to analgesia that can provide more effective pain relief at reduced individual doses to minimise side effects. In this direction, combining oral paracetamol and topical diclofenac, which exhibit complementary modes of action, can be a promising strategy to achieve effective analgesia. Although several studies have investigated the effect of combining paracetamol and oral NSAIDs in OA therapy, there is a lack of clinical evidence on the combination of oral APAP and topical NSAIDs in OA. This literature review also describes the utility of Delphi methodology in gathering the perspectives of a panel of experts and generating consensus on a topic. In addition, it also emphasises the usefulness of a model-based meta-analysis (MBMA) approach in generating clinical evidence by comparing and predicting the efficacy and safety of treatments and their doses that have never been studied together in a clinical trial and by extrapolating evidence across disease indications.

This thesis aims to bridge the evidence gap on the combination therapy of oral acetaminophen and topical NSAIDs in OA pain by conducting a study using the Delphi methodology to explore the clinical practice behaviours and perspectives of HCPs on the benefits and risks of oral APAP either as monotherapy or in combination with topical NSAIDs for OA pain management in real-world clinical settings considering the recent downgrade in recommendations on APAP by clinical practice guidelines in OA management. Secondly, it aims to evaluate the effects of combination of oral acetaminophen and topical diclofenac and compare its performance relative to acetaminophen or topical diclofenac monotherapy in mild to moderate OA pain using an MBMA. Finally, the thesis aims to study the association between APAP use and the risk of hepatotoxicity, particularly in OA pain management, by implementing an MBMA on published summary-level data from RCTs identified through literature search.

3.7 Structure of the thesis

The thesis component of the study is presented as a thesis by publication. A thesis by publication is defined as “A Thesis where some chapters are in the form of research papers published in, or submitted to, peer-reviewed

journals” (USQPolicy, 2016) . After introducing the topic, describing the background, and stating the research question (Chapter 1), the thesis presents a literature review. Chapter 3 presents a brief summary of the study methodology and research design. Chapter 4 and Chapter 5 of the thesis present the results of the research methods as published and as relevant to the broader study. These chapters present the publications associated with the phases of the study as follows:

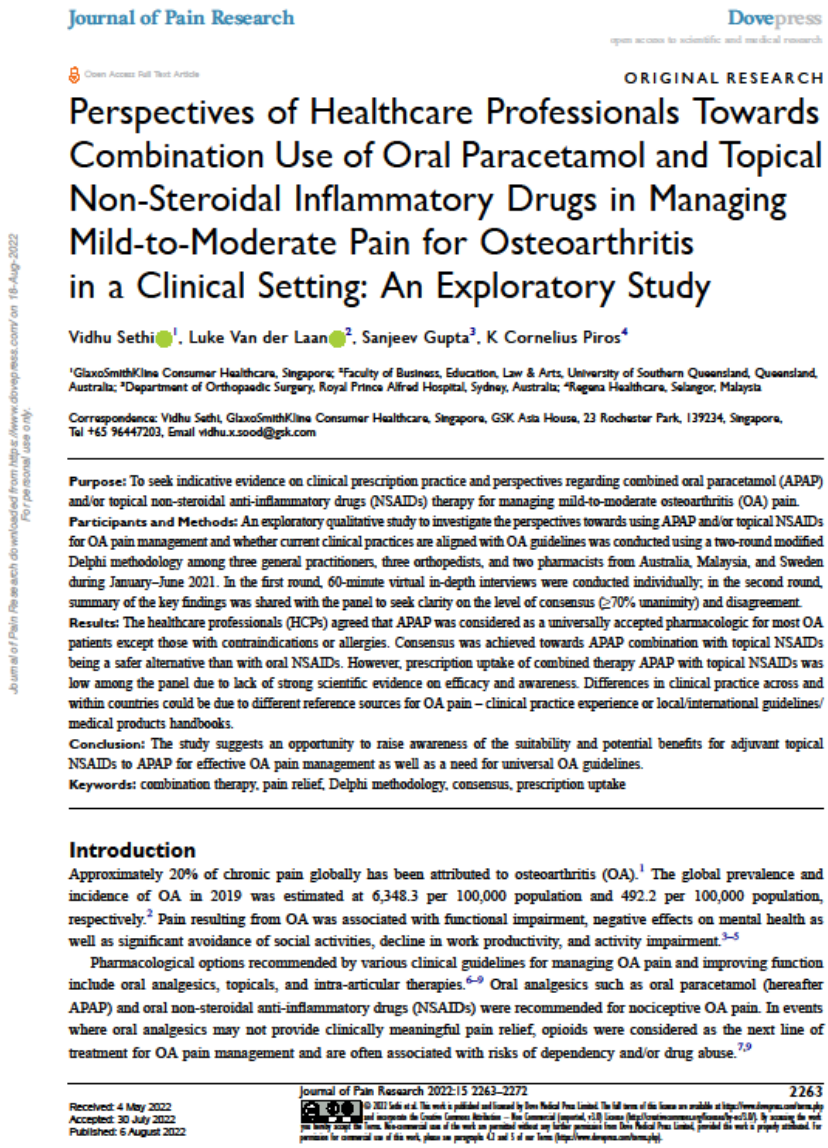
- Chapter 4: Delphi study to gather the perspectives of healthcare professionals towards combination use of oral paracetamol and topical non-steroidal inflammatory drugs in managing mild to moderate OA pain.
- Chapter 5a: Model-based meta-analysis to assess the efficacy of combination therapy of oral paracetamol and topical diclofenac in mild to moderate OA pain.
- Chapter 5b: Model-based assessment of the liver safety of combination therapy of oral paracetamol and topical diclofenac in mild to moderate OA pain.

CHAPTER 4: PERSPECTIVES OF HEALTHCARE PROFESSIONALS TOWARDS COMBINATION USE OF ORAL PARACETAMOL AND TOPICAL NON-STEROIDAL INFLAMMATORY DRUGS

4.1 Introduction

This paper was developed based on the results of the first phase of the research design (qualitative study) and sought to gather the perspectives of the healthcare professionals (HCPs) towards use of oral paracetamol (APAP) in combination with topical non-steroidal inflammatory drugs (NSAIDs) or as monotherapy in managing mild to moderate OA pain. The study was conducted with an aim to gather the evidence on the usage of a combination of APAP and topical NSAIDs, a new potential treatment option, in the real-world settings and identify the barriers which hindered their uptake and the facilitators to increase their uptake. The study also aimed to investigate the receptiveness of the HCPs towards usage of APAP monotherapy in clinical settings considering the recent downgrading by OA clinical practice guidelines.

4.2 Published paper



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ORIGINAL RESEARCH

Perspectives of Healthcare Professionals Towards Combination Use of Oral Paracetamol and Topical Non-Steroidal Inflammatory Drugs in Managing Mild-to-Moderate Pain for Osteoarthritis in a Clinical Setting: An Exploratory Study

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Purpose: To seek indicative evidence on clinical prescription practice and perspectives regarding combined oral paracetamol (APAP) and/or topical non-steroidal anti-inflammatory drugs (NSAIDs) therapy for managing mild-to-moderate osteoarthritis (OA) pain.

Participants and Methods: An exploratory qualitative study to investigate the perspectives towards using APAP and/or topical NSAIDs for OA pain management and whether current clinical practices are aligned with OA guidelines was conducted using a two-round modified Delphi methodology among three general practitioners, three orthopedists, and two pharmacists from Australia, Malaysia, and Sweden during January–June 2021. In the first round, 60-minute virtual in-depth interviews were conducted individually; in the second round, summary of the key findings was shared with the panel to seek clarity on the level of consensus (≥70% unanimity) and disagreement.

Results: The healthcare professionals (HCPs) agreed that APAP was considered as a universally accepted pharmacologic for most OA patients except those with contraindications or allergies. Consensus was achieved towards APAP combination with topical NSAIDs being a safer alternative than with oral NSAIDs. However, prescription uptake of combined therapy APAP with topical NSAIDs was low among the panel due to lack of strong scientific evidence on efficacy and awareness. Differences in clinical practice across and within countries could be due to different reference sources for OA pain – clinical practice experience or local/international guidelines/ medical products handbooks.

Conclusion: The study suggests an opportunity to raise awareness of the suitability and potential benefits for adjuvant topical NSAIDs to APAP for effective OA pain management as well as a need for universal OA guidelines.

Keywords: combination therapy, pain relief, Delphi methodology, consensus, prescription uptake

Introduction

Approximately 20% of chronic pain globally has been attributed to osteoarthritis (OA).[1] The global prevalence and incidence of OA in 2019 was estimated at 6,348.3 per 100,000 population and 492.2 per 100,000 population, respectively.[2] Pain resulting from OA was associated with functional impairment, negative effects on mental health as well as significant avoidance of social activities, decline in work productivity, and activity impairment.[3–5]

Pharmacological options recommended by various clinical guidelines for managing OA pain and improving function include oral analgesics, topicals, and intra-articular therapies.[6–9] Oral analgesics such as oral paracetamol (hereafter APAP) and oral non-steroidal anti-inflammatory drugs (NSAIDs) were recommended for nociceptive OA pain. In events where oral analgesics may not provide clinically meaningful pain relief, opioids were considered as the next line of treatment for OA pain management and are often associated with risks of dependency and/or drug abuse.[7,9]

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Sethi V, Van der Laan L, Gupta S, Piros KC. Perspectives of Healthcare Professionals Towards Combination Use of Oral Paracetamol and Topical Non-Steroidal Inflammatory Drugs in Managing Mild-to-Moderate Pain for Osteoarthritis in a Clinical Setting: An Exploratory Study. Journal of Pain Res. 2022 Aug 6;15:2263-2272. doi: 10.2147/JPR.S373382.

Additional publications /poster presentations:

Sethi V, Van der Laan L, Gupta S, Piros KC. Combined Use of Paracetamol and Topical NSAIDs in Managing Mild-to-Moderate Osteoarthritis Pain in Clinical Setting in Australia, Malaysia and Sweden. Poster presented at Australian Pain Society conference, 2022

Background

Osteoarthritis (OA) is a common and progressive joint disease whose global prevalence was estimated at more than at 6,348.3 per 100,000 population in 2019 (Global Burden of Disease Collaborative Network, 2020b). Moreover, OA has been shown to contribute to approximately 20% of chronic pain globally (Perrot, 2016). Pain resulting from OA causes substantial functional impairment, negatively affects mental health, and also leads to marked disruption in social activities and a decline in work productivity (Dibonaventura et al., 2011; Hawker, 2019; Nakata et al., 2018). Several pharmacological options, recommended by various clinical practice guidelines, are available for managing OA pain and improving function including oral analgesics, topical analgesics, and intra-articular therapies (American Academy of Orthopaedic Surgeons, 2021; Bannuru et al., 2019; NICE, 2014; Primorac et al., 2021). Traditionally oral analgesics, such as paracetamol (hereafter APAP) and non-steroidal anti-inflammatory drugs (NSAIDs), were used for nociceptive OA pain, whereas opioids were considered as the next line of treatment when oral analgesics failed to provide clinically meaningful pain relief. However, opioids are often associated with risks of dependency and/or drug abuse (Bannuru et al., 2019; Primorac et al., 2021).

In recent years, few publications have shown APAP to exhibit small clinical effect sizes comparable to placebo which led to discussions on its suitability as a first-line analgesic in OA and prompted several OA guidelines to change their recommendations for APAP monotherapy from first-line pharmacologic to recommending additional adjuvant options e.g., topical/oral NSAIDs, or intra-articular injections of corticosteroids or hyaluronic acid (Balmaceda, 2014; Primorac et al., 2021). Moreover, growing clinical evidence on the efficacy of topical NSAIDs has led to their approval as a first-line analgesic therapy or adjuvant treatment to APAP monotherapy for effective OA pain management (Balmaceda, 2014; Freo et al., 2021). The clinical practice

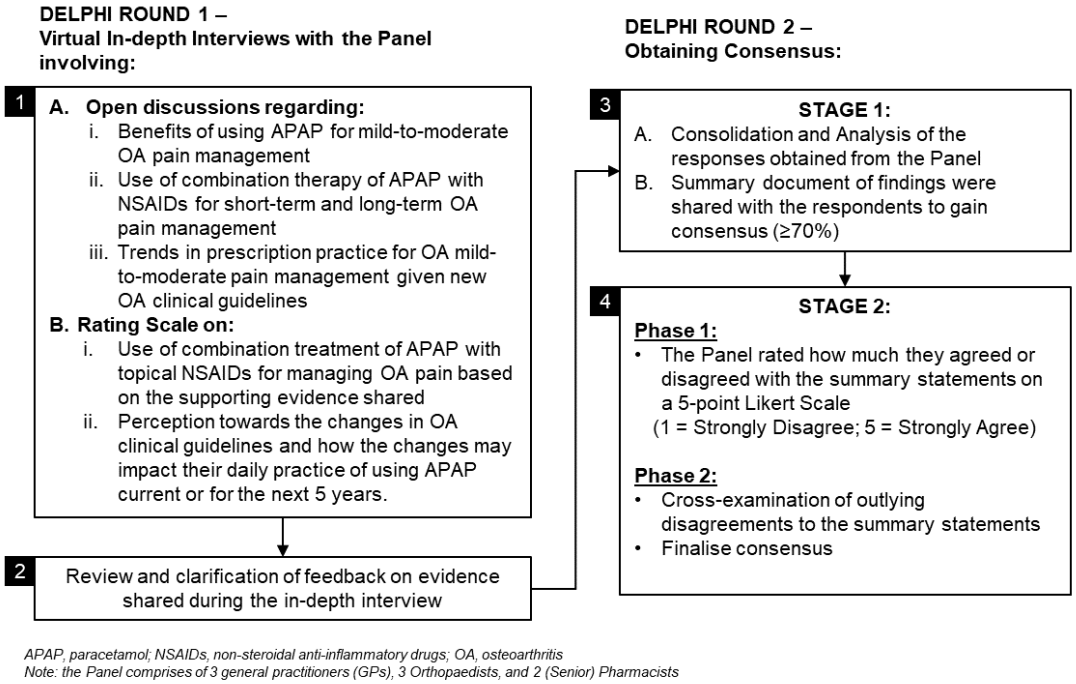
guidelines by the National Institute for Health and Care Excellence (NICE)(NICE, 2014) as well as Ministry of Health, Malaysia (MOHM) (Malaysia Health Technology Assessment Section (MaHTAS), 2013) now recommend topical NSAIDs for use with APAP ahead of oral NSAIDs for mild to moderate OA pain management.

While previous studies reported APAP monotherapy as a common prescription by clinicians for managing pain in OA patients (Jawad, 2005), there is limited information available related to the recent clinical practice of clinicians in managing OA pain since the latest updates in guidelines. Therefore, this study aimed to explore and gather the perspectives and clinical practices of a panel consisting of different types of healthcare professionals (HCPs) – general practitioners (GPs), orthopedists, and pharmacists - towards APAP as monotherapy and in combination with topical NSAIDs from three diverse geographies including Australia, Malaysia, and Sweden using the Delphi methodology. In addition, it aimed to assess the impact of recent updates in guidelines on their practice behaviours for the management of mild to moderate OA. Furthermore, the study aims to gather indicative evidence on the effectiveness of combination therapy of APAP and topical NSAIDs in relieving OA pain from the clinical practice behaviours and perspectives of the HCPs.

Methodology

This exploratory qualitative study, conducted between January and June 2021, adopted the Delphi method wherein HCPs were invited based on their experience and/or expertise to independently rate given enquiries to establish consensus. The Delphi methodology was deemed suitable as it provides panel members equal voice, anonymity from other panel members and the ability to revise their opinions in light of other responses, without the pressure to maintain previously expressed opinions (van den Heuvel et al., 2005). The method seeks a level of consensus regarding the responses of panel members as evidence of clinical practice behaviours and perspectives while allowing for the exploration of non-consensual responses and reasons for disagreement.

In this study, the practice perspectives towards the use of APAP and/or topical NSAIDs in OA pain management were gathered from a panel of HCPs using a modified Delphi technique comprising of two rounds (Figure 4.1). All the HCPs were blinded to the study sponsor and to each other. The first round involved 60-minute virtual in-depth interviews with individual HCPs, wherein scientific evidence on the use of APAP plus topical ketoprofen (combination therapy) for pain reduction (Yoo et al., 1996) and few recently updated OA treatment guidelines addressing concomitant and/or sequential use of APAP with topical NSAIDs, was shared with the panel members (Bannuru et al., 2019; Bruyère et al., 2014; Kolasinski et al., 2020; The Royal Australian College of General Practitioners, 2018).



APAP, paracetamol; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis
Note: the Panel comprises of 3 general practitioners (GPs), 3 Orthopaedists, and 2 (Senior) Pharmacists

Figure 4.1. Study design.

Items discussed during the open interviews in the first round of Delphi method explored HCPs perspectives towards (i) current clinical practices for managing mild to moderate OA pain; (ii) combination use of APAP with NSAIDs (oral and topical; over short- and long-term use); (iii) clinical guidelines (NICE, European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [ESCEO], and

European Alliance of Associations for Rheumatology [EULAR]) regarding use of APAP for OA pain management; and (iv) awareness of recent updates in OA clinical guidelines (NICE, Osteoarthritis Research Society International [OARSI], RACGP, American College of Rheumatology [ACR]) and the potential impact of the guideline changes on their future clinical practice as well as their perspectives on the impact of the scientific evidence supporting the interview items.

Subsequently, the key findings emerging from the first round were summarized and shared with the panel members in the second round to gather additional clarity. In addition, the extent of consensus and disagreement towards key statements derived from the findings were then sought from the panel members along with their clarifications. Consensus was determined using a quantitative 5-point Likert Scale (1= “strongly disagree” and 5= “strongly agree”) and was considered achieved when there was ≥70% unanimity within the panel. Outlying disagreements were assessed to gain a better understanding of the reasons for continued disagreement at the second phase of round two.

Eligibility criteria

Inclusion criteria for GPs and orthopaedists comprised of ≥10 years of clinical experience and spending ≥60% of their time in direct patient care. The preliminary screening criteria for eligible HCPs included having experience in treating mild to moderate OA or joint pain, having attended conferences or having membership of medical societies, e.g. pain societies, and having relevant publications in the area of pain management in peer-reviewed journals. Additional inclusion criteria for GPs and orthopaedists involved consultation of ≥30 patients with mild to moderate OA pain per month and treatment of ≥30% and ≥10% patients with APAP and combination treatment (including APAP with topical NSAIDs), respectively.

Pharmacists having ≥10 years of experience as senior pharmacist, permanent employment, and spending ≥5 hours daily in direct patient contact were invited to participate in the study. Additional inclusion criteria involved monthly interactions with ≥30 patients with mild to moderate OA pain and dispensing ≥30% and ≥10% APAP and combination treatments (including

APAP with topical NSAIDs), respectively. The profiles of the HCPs are detailed in Table 4.1.

Table 4.1. Clinical experience, patient load and prescription practice of general practitioners (GPs), orthopedists, and (senior) pharmacists in Australia, Malaysia, and Sweden.

	GPs			**Orthopedists**			**Pharmacists**	
	Australia (n=1)	**Malaysia (n=2)**		**Australia (n=1)**	**Malaysia (n=1)**	**Sweden (n=1)**	**Australia (n=1)**	**Sweden (n=1)**
Years of Practice	25	15	11	11	6	30	10	10
Number of OA patients seen per month	450	60	75	100	40	35	250	100
Number of OA patients suffering from mild to moderate pain	150	30	35	50	35	30	150	70
% of OA patients treated with:								
[a]*Oral APAP*	70%	30%	30%	50%	40%	100%	50%	80%
[a]*Oral NSAIDs*	20%	40%	30%	25%	50%	80%	25%	20%
[a]*Topical NSAIDs*	30%	10%	20%	0%	80%	0%	15%	30%
[a]*Others*	30%	Tab Colla: 10% Gluejoint: 10%	20%	50%	-	Oxycodone: 5%	10%	30%
% of OA patients treated with:								
[b]*Monotherapy*	20%	20%	20%	0%	0%	5%	60%	40%
[c]*Combination therapy*	30%	50%	80%	100%	100%	95%	30%	50%

Notes: [a]Indicated therapeutics were not differentiated between prescriptions initiated by the HCP and those requested by the patients at the time of medical consultation. [b]Monotherapy refers to the single use of either therapeutic option indicated in [a]. [c]Combination therapy refers to the combination use of any therapeutic option indicated in [a]. Abbreviations: APAP, paracetamol; GPs, general practitioners; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis

Results

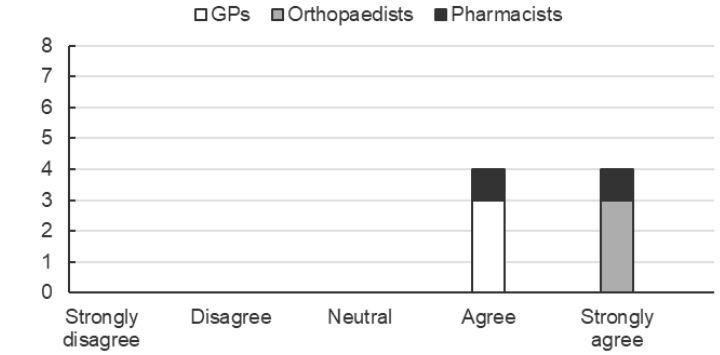
Prescription pattern for the pharmacologic treatment

The usage of the pharmacologic modalities for the management of mild to moderate pain in OA patients varied widely across different types of HCPs (as shown in Table 4.1). GPs treated 30-70% of their patients with APAP, 10-20% with topical NSAIDs, and 30-80% with combination therapy. Orthopaedists prescribed APAP in 40-100% and combination treatment in 95-100% of the patients while topical NSAIDs were prescribed by only one orthopaedist to 80% of the patients. The pharmacists dispensed APAP, topical NSAIDs and combination therapy to 50-80%, 15-30% and 30-50% of their patients, respectively.

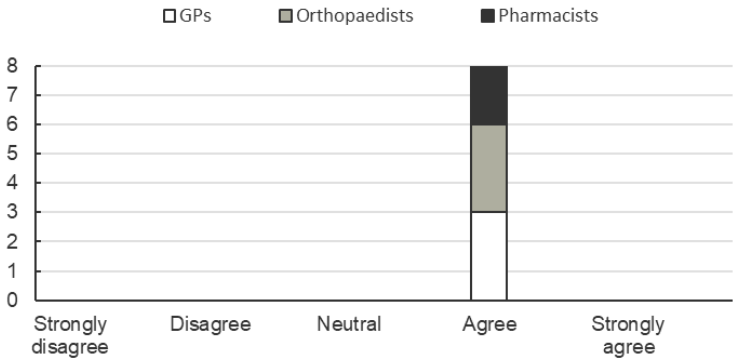
Paracetamol in the management mild-to-moderate OA pain

All panel members agreed or strongly agreed that APAP was the universally accepted pharmacologic option for majority of OA patients, except in the case of patients contra-indicated to APAP due to liver abnormalities or allergies (Figure 4.2A, Supplementary Table S4.1). There was considerable difference across the three countries for the duration for which APAP was prescribed for OA pain management (Supplementary Table S4.1).

A. Consensus based on the feedback that APAP is:
(i) Considered universal treatment option for mild-to-moderate OA pain, (ii) recommended across all patient profiles, (iii) with considerations needed for patients with history of liver disease/dysfunction and allergies.



B. Consensus based on the feedback towards OA treatment choices:
(i) Where the overall aim was to relieve pain, and approaches for (ii) younger patients focused on recovery or preventing further damage, while (iii) other treatments e.g., surgery or supportive therapy instead of long-term medications were recommended for older patients



C. Consensus based on the feedback regarding OA guidelines:
(i) Different HCPs in each country referenced different sources of clinical guidelines, (ii) with no known changes in guideline recommendations especially for the use APAP for OA pain recommended across all patient profiles, and (iii) any changes in guideline recommendations over the next 3-to-5 years were perceived to have minimal impact on their prescription practice.

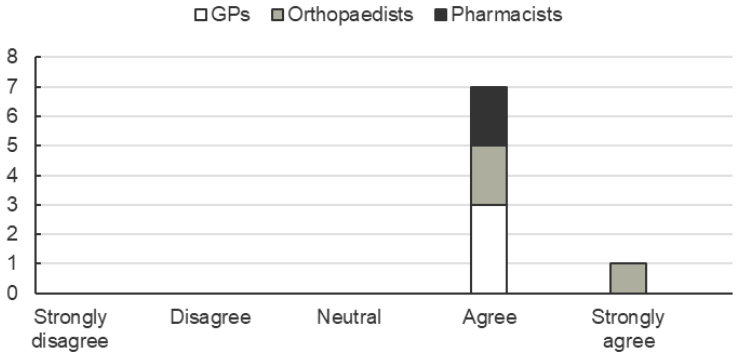


Figure 4.2. Consensus of the key findings pertaining to paracetamol (APAP), treatment choices, osteoarthritis (OA) guidelines among the panel of general practitioners (GPs) (n=3), orthopaedists (n=3), and pharmacists (n=2). Proportion of panel members level of agreement or disagreement towards the feedback on (A) the relevance of APAP monotherapy for patients with mild to moderate OA pain, (B) relevance and aim of different OA treatment options, and (C) awareness of OA guidelines and guideline updates.

Treatment choice for the management of mild to moderate OA pain

All the HCPs from the three countries agreed that the general objective of OA treatment was to relieve pain across all age groups. However, there was marked differences in the approach used to relieve pain in younger and older (aged >60 years) OA patients (Figure 4.2B). Therapeutic regimens for younger patients frequently comprised of non-pharmacological strategies such as physiotherapy or exercise to trigger recovery or prevent further joint deterioration. In contrast, patients of advanced age or those with comorbidities were often prescribed other supportive management options such as surgery while avoiding long-term prescription of medication such as oral NSAIDs (Figure 4.2A, Supplementary Table S4.2).

In addition, in cases of inadequate pain relief with APAP monotherapy, all the HCPs responded positively to the use of oral NSAIDs as an adjuvant to APAP due to their higher efficacy in relieving OA pain than APAP. However, the combination therapy needed to be prescribed with caution in patients with prior gastrointestinal (GI) or liver dysfunction issues, on co-medications or of older age (≥65 years) (Supplementary Table S4.2).

Impact of osteoarthritis guidelines on prescription practice towards use of APAP

HCPs were generally unaware of the recent changes in the OA guideline recommendations especially towards the use of APAP. In addition, all of them agreed/strongly agreed that any changes in recommendations in the next 3 to 5 years would have minimal impact on their prescription practice towards the use of APAP (100% consensus) (Figure 4.2C, Supplementary Table S4.3).

Combination therapy of paracetamol with topical NSAIDs for mild to moderate osteoarthritic pain

The panel (87.5% consensus) agreed/strongly agreed that combination APAP therapy with topical NSAIDs was a safer alternative for managing mild to moderate OA pain when compared with oral NSAIDs (Figure 4.3A). Only one panel member disagreed on the safety profile of topical NSAIDs due to observation of patients presenting with adverse events such as skin blistering upon long-term use of topical NSAIDs (Supplementary Table S4.4).

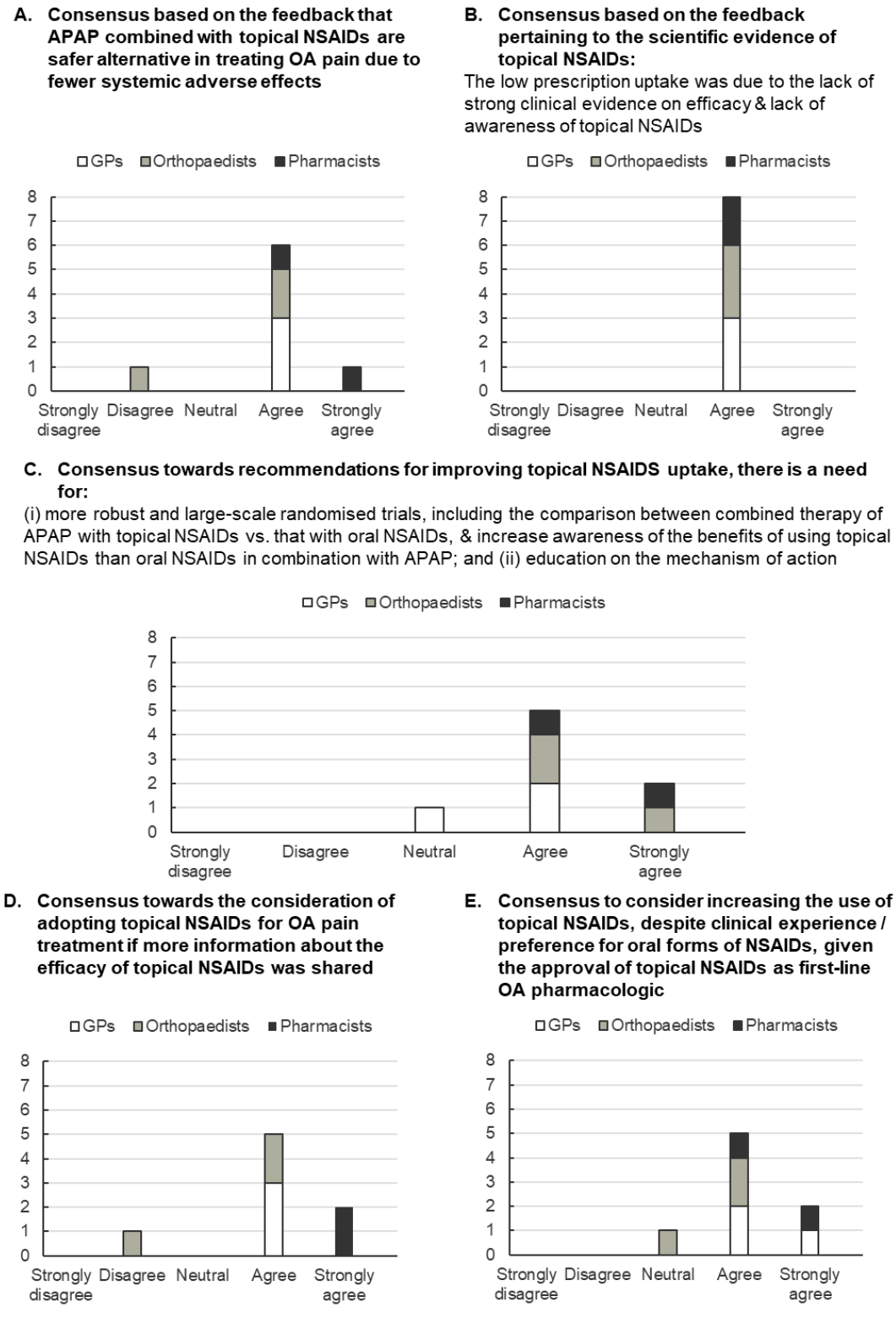


Figure 4.3. Consensus of the key findings pertaining to use of topical non-steroidal anti-inflammatory drugs (NSAIDs) as an adjuvant therapy with paracetamol (APAP) among the panel of general practitioners (GPs) (n=3), orthopaedists (n=3), and pharmacists (n=2). Proportion of panel members level of agreement or disagreement towards feedback on (A) combined APAP therapy and topical NSAIDs as safer alternatives in OA management, (B) availability of strong scientific evidence on combined therapy of APAP

with topical NSAIDs versus APAP with oral NSAIDs predisposed low prescription uptake of APAP combination therapy with topical NSAIDs efficacy, (C) recommendations for improving topical NSAIDs, (D) considerations to adopting topical NSAIDs for OA pain if more information was available, and (E) considerations to increasing use of topical NSAIDs based on clinical guidelines regardless of clinical experience and preference.

However, all panel members exhibited a lack of confidence in the use of combination of APAP and topical NSAIDs and attributed its low prescription uptake to lack of strong scientific evidence on the efficacy of combined therapy of APAP and topical NSAIDs when compared with the combination of APAP and oral NSAIDs (Figure 4.3B). The lack of awareness of the benefits and mechanism of action of topical NSAIDs emerged as another significant reason behind their low prescription rate among the HCPs (Figure 4.3C and D). Moreover, a panel member with a neutral stance suggested conducting additional randomised clinical trials, by independent investigators and without any interference from the manufacturing companies, to generate reliable scientific evidence on the combination of oral APAP and topical NSAIDs (Supplementary Table S4.4).

Most HCPs (87.5%), despite their preference for oral NSAIDs, agreed to consider increasing the prescription rate of topical NSAIDs in the management of OA pain considering the latest recommendations on the use of topical NSAIDs as a first-line agent from major OA guidelines (Figure 4.3E). However, one orthopaedist, who disagreed with the other panel members on the above, revealed reconsidering prescribing topical NSAIDs once more robust and convincing scientific evidence is available demonstrating the efficacy of topical NSAIDs in the management of OA pain (Supplementary Table S4.4).

Discussion

The present study used the Delphi methodology to explore the perspectives of different categories of HCPs, considering the recent updates in the clinical practice guidelines for OA, towards the use of combination therapy of APAP and topical NSAIDs in the management of mild to moderate OA pain.

Growing evidence on the small effect size of APAP for relief of OA pain in clinical trials is likely attributable to the high placebo effect (Zhang, 2019).

Despite initial reports suggesting APAP monotherapy to be associated with inadequate clinically meaningful pain relief in all patients with OA, APAP continues to remain universally accepted by HCPs in real-life settings for the management of mild to moderate OA pain (Freo et al., 2021). The findings from our study aligned with the above observation as all panel members supported APAP use while exercising caution in patients with liver or GI comorbidities. Amongst all the HCPs, the prescribing rate for combination treatment was highest among orthopaedists (95%-100%), followed by GPs (30%-80%) and pharmacists (30-50%). This could be explained when considering severity of OA symptoms, where patients having more severe OA pain consulting orthopaedists when compared with those consulting GPs or pharmacists (Musila et al., 2011). This is an interesting incongruity wherein real-life practice suggests a strong use of combination therapy in spite of a minimal supporting scientific evidence.

While all the panel members were receptive to the use of combination therapy of APAP with NSAIDs, the majority preferred oral NSAIDs to topical NSAIDs. The low uptake of topical NSAIDs among the panel members in this study was attributed chiefly to the lack of awareness of scientific evidence showing the efficacy of topical NSAIDs. In addition, the existing evidence comparing the efficacy of oral NSAIDs with topical NSAIDs was deemed insufficient and the panel members suggested the need to conduct additional large-scale clinical studies comparing the efficacy of NSAIDs delivered via oral and subcutaneous route for OA pain relief.

Several recent publications showed topical NSAIDs to have comparable efficacy and safety against other pharmacologic agents (Argoff and Gloth, 2011; Klinge and Sawyer, 2013; Rannou et al., 2016; Zeng et al., 2021) which supported the European and US-based OA clinical practice guidelines to consider topical NSAIDs as first-line agents (Balmaceda, 2014; NICE, 2014). Remarkably, the panel members were unaware of changes in guideline recommendations for managing OA pain, which could be explained by the presence of different OA guidelines with differing therapeutic recommendations being followed within the respective countries. For instance, two different guidelines were referenced in Malaysia - the American Academy of Orthopedic Surgeons (AAOS) and the MOHM OA guidelines.

While the AAOS guideline recommended APAP monotherapy for pain relief and improved function in knee OA when it is not contraindicated (American Academy of Orthopaedic Surgeons, 2021), the guideline by MOHM recommended adjuvant use of topical NSAIDs with APAP (Malaysia Health Technology Assessment Section (MaHTAS), 2013). This is indicative of a need to standardise clinical practice guidelines for managing OA pain.

Another reason for the low prescription uptake of topical NSAIDs among the panel HCPs in this study, apart from the lack of awareness, could be the lesser understanding of how the application of NSAIDs topically could effectively relieve OA pain. Topical NSAIDs mediate anti-nociception and anti-inflammation by inhibiting cyclooxygenase enzymes (COX-1 and COX-2), and blocking the conversion of arachidonic acid to prostaglandin H2, the precursor of prostaglandins, prostacyclin, and thromboxanes which trigger inflammatory pain (Altman, 2004). This is complementary to APAP's analgesic activity that is mediated primarily through activation of serotogenic pathways that result in increase in the pain threshold (Anderson, 2008).

In addition, several studies have shown topical NSAIDs to exhibit equivalent efficacy to oral NSAIDs in rheumatic diseases, (Klinge and Sawyer, 2013; NICE, 2014; Rannou et al., 2016; Zeng et al., 2021) while showing fewer risks of GI-related adverse effects than oral NSAIDs as they are absorbed into local tissues with minimal systemic exposure (Klinge and Sawyer, 2013). The pharmacological effect delivered by combining analgesics and anti-inflammatory exhibiting minimal GI side effects could serve as a viable option that fulfills the treatment needs of managing pain and inflammation associated with OA (Altman, 2004) and thus emphasises the need to educate HCPs on the suitability of the different forms of topical agents.

The findings from the study also suggest an opportunity to increase awareness of the suitability and potential benefit of adding topical NSAIDs to oral APAP therapy in the management of mild to moderate OA pain. This can be achieved by educating HCPs on the mechanism of action of the combined use of topical NSAIDs with APAP and aligning OA clinical practice guidelines across different clinical practices and specialties.

The major strength of this study is that it is based on the Delphi technique exploring an aggregation of perspectives and current clinical prescription practices towards the use of pharmacologic treatments such as APAP with or without adjuvant topical NSAIDs from a panel of diverse HCPs from three different countries. This ensures that the ratings of each individual panel member remained unaffected by dominant members in the panel and, therefore, are more likely to be unbiased.

A key limitation of this study is the small sample size for each HCP type across the three countries. While a diverse panel of experts allows for a broader perspective of current clinical practice towards using pharmacologic treatments, the small sample of experts may limit the applicability of the results. However, since this is an exploratory study, the findings could only serve as a framework for further research into this line of enquiry with larger sample size of each HCP type.

Considering the scarcity of research on treatment practices for mild to moderate OA pain, the study has identified themes describing behaviour in clinical practice for future research. Moreover, additional studies with a larger HCPs sample size are warranted in this direction to provide suggestions or recommendations necessary to initiate potential changes in clinical practice.

Summary & conclusion

This chapter presented the study conducted to investigate the receptiveness and current clinical practice behaviours of different types of HCPs from three diverse geographies towards use of APAP monotherapy and combined therapy of APAP and topical NSAIDs in the management of mild to moderate OA pain. It included a summary of the relevant literature, results, discussion, and implication of findings. The study was published in the Journal of Pain in 2022. The study showed that oral paracetamol remains the gold standard treatment for the HCPs in the management of mild to moderate OA pain in real-world clinical settings despite scientific evidence showing high placebo effect to be associated with APAP. Our study demonstrated limited uptake of topical NSAIDs by HCPs for OA pain and attributed that to a lack of awareness of scientific evidence supporting the efficacy of topical NSAIDs as well as understanding of their mechanism of action. This is despite the fact

that several recently updated OA clinical practice guidelines now recommend using topical NSAIDs in combination with APAP.

Therefore, the findings provide several indications which justify the need to increase awareness of the suitability and potential benefits of using topical NSAIDs as an adjuvant to oral APAP therapy for effectively managing mild to moderate OA pain. Further investigations involving a larger sample size of HCPs are needed to validate the findings from this study and provide more robust evidence on the efficacy of combination therapy of APAP with topical NSAIDs.

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Supplementary tables and figures

Supplementary Table S4.1. Key perspectives of the Panel towards the use of APAP for mild to moderate OA pain.

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
Using APAP for mild to moderate OA pain management		
(i) APAP is considered to be a universal/gold standard/regular treatment option for mild to moderate OA pain management since it alleviates patients' symptoms	*"The gold standard is to reduce their pain. So far it's working." – Malaysia, GP* *"Regular and compliance is important." – Sweden, Orthopaedist*	NA
(ii) APAP is recommended across all patient profiles for mild to moderate OA pain management	*"It's universal and irrespective of what other medications they're on." – Australia, Orthopaedist*	
(iii) Considerations are needed when recommending to patients with a history of liver disease and any liver dysfunction or allergic to APAP	*"the only ones I wouldn't give to are people who are who have evidence of liver disease because of potential for toxicity." – Australia, GP* *"Allergies." – Malaysia, Orthopedic specialist & GP*	
(iv) there were differences in the prescription patterns (time frame)	*Australia:* *"...for a couple of weeks." – Sr. Pharmacist* *"It can be indefinite." – Orthopaedist* *Malaysia:* *"1 month" - Both GPs* *"3 weeks of stock…" - Orthopaedist* *Sweden:* *"prescription for several month, it can for years…" - Pharmacist* *"...3 to 12 months." - Orthopaedist*	NA

Abbreviations: APAP, paracetamol; GPs; general practitioner; NA, not available

Supplementary Table S4.2. Key perspectives of the Panel's treatment choice for mild-to-moderate OA pain management.

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
Treatment choice for mild to moderate OA pain management		
(i) Overall aim for treatment choice was to relieve OA pain across all age groups		NA
(ii) Approaches for younger patients were focused on recovery or preventing further damage by prescribing physiotherapy or exercise	*"Older patients may have complications or diabetes etc. Rehab may be difficult for them. But for younger patients they may do some exercise." – Malaysia, Expert GP* *"If it is a younger patient the likelihood is less for a surgery." – Sweden, Orthopaedist*	
(iii) Approaches for older patients (aged >60 years) tend to avoid long-term medication with preference for other treatments like surgery and other supportive therapy	*"have...concerns about other medication interactions, potential issues with blood pressure, stomach upsets/reflux etc. (in older patients)" – Australia, Pharmacist*	
(iv) Majority of HCPs had a positive perception of using combination therapy of APAP with NSAIDs for mild to moderate OA pain management since it would provide better pain management.	*"They can work together to provide greater efficacy." – Australia, GP* *"It works better in combination (multimodal)." – Malaysia, Orthopaedist* *"Combined with NSAIDS, a small dose of (APAP) can enhance the effects." – Malaysia, GPs* *"The benefit is a stronger pain management." – Sweden, Pharmacist*	NA
(v) Caution of using APAP with oral NSAIDs is needed for patients with GI issues, comedications, prior liver dysfunction or older age	*"NSAID...in patients over the age of 65, due to decreased renal function or kidney issues…(need to) watch against interactions and other blood pressure medications." – Australia, Pharmacist* *"Need for Monthly liver functions test, especially for those elderly people." – Malaysia, Orthopaedist*	*NA*

Abbreviations: APAP, paracetamol; GPs; general practitioner; NA, not available

Supplementary Table S4.3. Key perspectives towards using APAP in prescription practice for OA pain management based on OA guidelines updates.

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
Impact on prescription practice towards using APAP for OA pain management based on OA guidelines updates		
(i) Different HCPs in each country had different prescription practices as different sources were referenced for managing mild to moderate pain in OA patients		NA
(ii) Clinical practice, local/international guidelines or medical product handbooks were referenced	*Australia:* *"few resources...one of them is...called eMIMs which I think is pretty much worldwide now. There's a big book that we use in all pharmacies in Australia called the AMH, Australian Medicines Handbook" – Pharmacist* *"Have OCP (Osteoarthritis Care Programme) clinic in hospital" - Orthopaedist* *"We all have an idea of what is safe, what isn't safe, what to use when, etc. And it's nice to see these guidelines and confirm what we have thought and what we are doing" – GP* *Malaysia:* *"Follow the OA management from MOH" – GP* *"Not that important. Experience is more important." – GP* *"Prefer the AAOS." –Orthopaedist* *Sweden:* *"Local guidelines." – GP* *"'Kloka Listan' where the recommended first line medicine are listed. And the pharmacies also follow "Kloka Listan" for OTC medicines, additional they follow "Swedish Medical Products Agency" and "1177 Vårdguiden"." – Pharmacist*	
(iii) To the best of the HCPs' knowledge, there have been no change in guideline recommendations especially for the use APAP for OA pain	*"No, not heard anything about moderate/mild OA." – Australia, Pharmacist* *"Not noticed anything specifically." – Australia, Orthopaedist* *"No changes. Attention is not on PCM." – Malaysia, Orthopaedist* *"It has been the same for 7-10 years." – Sweden, Pharmacist* *"Not when it comes to OA patients, same last 10 years." – Sweden, Orthopaedist*	NA

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
(iv) Any changes in guideline recommendations over the next 3-to-5 years were perceived to have minimal impact on their prescription practice	*Australia: Belief that the daily practice is in line with the guidelines. Also based on experience APAP is considered a safe option.* *Malaysia: Guidelines highlight the need to be careful of high dosages, which is a part of the daily practice.* *Sweden: Although open to any changes in the guidelines in the future, the notion is the current treatment algorithm works fine.*	

APAP, paracetamol; GPs; general practitioner; NA, not available

Supplementary Table S4.4. Key perspectives towards the use of combination therapy of APAP with topical NSAIDs for mild to moderate OA pain management.

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
Use of Combination therapy of APAP with Topical NSAIDs for mild to moderate OA pain management based on the evidence shared [14]		

Key Perspectives	Supporting Verbatim statements	Reason of Disagreement
(i) GPs and Senior Pharmacists considered APAP adjuvant with topical NSAIDs to be an acceptable & safe combination for mild to moderate OA pain management due to lesser systemic reactions and side effects like gastric issues or liver toxicity	*"In the context of other alternative treatments, this combination is quite safe." – Australia, GP* *"Start with single dose, topical NSAIDS, mild-mod start (APAP), give any kind of topical application. Study is good because (APAP) itself can relieve the pain. – Malaysia, GP*	NA
(ii) However, there is a low prescription uptake with Topical NSAIDs:		
(a) Reasons for low uptake included the lack of strong clinical evidence on efficacy	*"Not convincing, evidence is less than 50 patients. Not a good sample size." – Malaysia, Orthopaedist* *"The data is still quite weak. The study had 44 patients and only 31 completed it. We have 200,000 people who present to Orth Surg every year with OA. If you can only do a study with 31 people, that's frightfully poor. That's a very weak study and has very little validity." – Australia, Orthopaedist*	
(b) Lack of awareness of topical NSAIDs	*"In the last 2-3 years the pharmacies have ... (Ketoprofen)... in ... gel, which is seldom prescribed." – Sweden, Pharmacist*	
(iii) There is a need for more robust and large-scale randomised trials, including that comparing combined therapy of APAP with topical NSAIDs vs. that with oral NSAIDs, and to increase the awareness toward the benefits of using topical NSAIDs than oral NSAIDs in combination with APAP.	*"Need for study which compares preoral with sub-cutaneous. Studies from practitioners would provide more robustness to the evidence." - Sweden*	*(i) An independent (not from the manufacturing company) large scale trial had to be conducted to add credibility to the evidence*
(iv) HCPs further recommend a need to educate on the mechanism of action	*"need to educate more on mechanism of action of using patches in the combination treatment. Also...regarding different routes of application such as patches given the common topical NSAIDs used are gels or creams. - Australia*	
Future use of topical NSAIDs for combination therapy of OA		

Key Perspectives	**Supporting Verbatim statements**	**Reason of Disagreement**
(i) APAP combined with Topical NSAIDs are safer alternative in treating OA pain due to fewer systemic adverse effects	*NA*	*(i) Adverse events were previously observed in patients who had used topical NSAID gels for long-term.* *(ii) Not convinced on the mechanism of action of the topical NSAID gel.*
(ii) Will consider adopting topical NSAIDs for OA pain treatment if more information about the efficacy of topical NSAIDs was shared	*NA*	*(i) Perception that there is no evidence of efficacy for using topical NSAIDs for OA treatment*
(iii) Given the approval and use of topical NSAIDs as the first-line agents in OA treatment guidelines, due consideration to increase the use of topical NSAIDs in the treatment of OA pain, despite clinical experience/preference for using oral forms of NSAIDs	*NA*	*(i) Insufficient convincing data in terms of efficacy for topical NSAIDs, however, the HCP will reconsider if additional convincing data in terms of efficacy is provided.*

APAP, paracetamol; GPs; general practitioner; NA, not available

4.3 Links and implications

The study showed that all the HCPs still considered oral APAP as the gold standard for the management of mild to moderate OA pain in real-world clinical settings despite scientific evidence suggesting high placebo effect associated with APAP. Moreover, all the HCPs demonstrated a lack of confidence in the use of combination of APAP and topical NSAIDs and attributed its low prescription uptake to a lack of strong scientific evidence on their efficacy.

The findings of this study suggest that APAP is still considered efficacious by HCPs in the management of mild to moderate OA pain despite the recent downgrade by clinical guidelines. In addition, findings suggest a need to identify clinical evidence on the efficacy of the combination of oral APAP and topical NSAIDs to increase its uptake by the HCPs in the clinical settings. The absence of scientific evidence on the efficacy of combined therapy of APAP and topical NSAIDs as highlighted above stimulated the second phase of the research, which involved searching for evidence on the combination treatment in OA pain. Therefore, we designed our second phase of the research with an aim to identify clinical evidence on the effectiveness and tolerability of the combination treatment in OA pain.

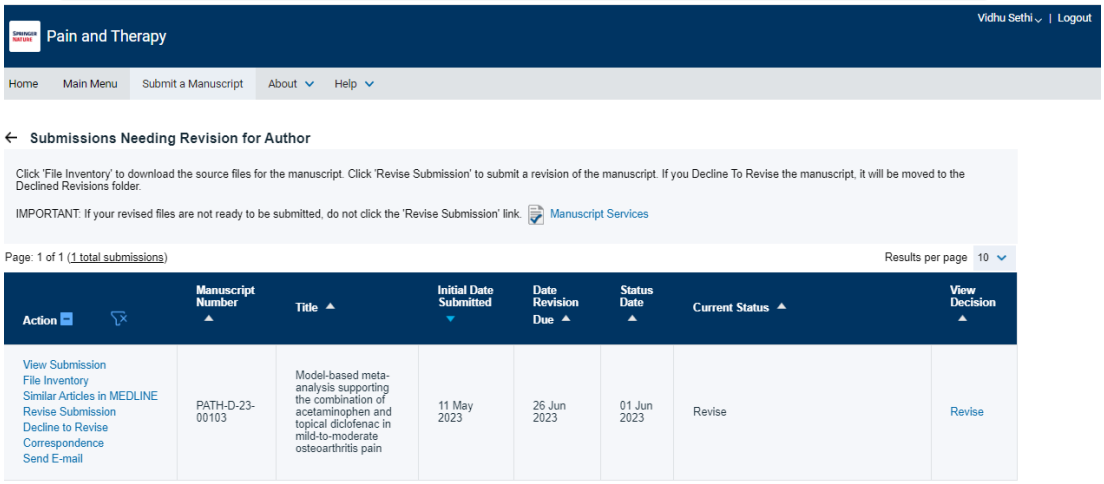
CHAPTER 5A: MODEL-BASED META-ANALYSIS TO ASSESS THE EFFICACY OF COMBINATION THERAPY OF ORAL PARACETAMOL AND TOPICAL DICLOFENAC IN MILD TO MODERATE OSTEOARTHRITIS PAIN

5A.1 Introduction

The results of the phase I of the research design highlighted a need to identify clinical evidence on the combination of oral acetaminophen (APAP) and topical non-steroidal inflammatory drugs (NSAIDs) to improve their prescription and uptake by the HCPs for the management of mild to moderate OA pain. The present quantitative study is part of the phase II of the research design. It was developed based on the findings of the phase I of the research and aimed to identify clinical evidence on the combination of APAP and topical diclofenac, an NSAID, in mild to moderate OA pain. Our literature search found no clinical studies on the combination of APAP and topical or oral DIC in OA pain. Since a growing body of evidence shows overlap in the pain signaling pathways between chronic OA pain and acute pain and given that analgesic and anti-inflammatory mechanisms of the two drugs (i.e., APAP and topical DIC) are similar in both acute and chronic pain setting, we decided to extrapolate the effect of combination of APAP and DIC using a model-based meta-analysis, a regression-based statistical technique, from clinical studies conducted in acute pain setting using pain score reduction and opioid sparing effect as clinical endpoints.

5A.2 Submitted paper

Sethi V, Qin L, Cox E, Trocóniz IF, Della Pasqua O. Model-based meta-analysis supporting the combination of acetaminophen and topical diclofenac in mild to moderate osteoarthritis pain . Submitted to the journal “Pain and Therapy” on 11 May 2023. Under revision as on 12 June 2023



Pain and Therapy

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Action	Manuscript Number	Title	Initial Date Submitted	Date Revision Due	Status Date	Current Status	View Decision
View Submission File Inventory Similar Articles in MEDLINE Revise Submission Decline to Revise Correspondence Send E-mail	PATH-D-23-00103	Model-based meta-analysis supporting the combination of acetaminophen and topical diclofenac in mild-to-moderate osteoarthritis pain	11 May 2023	26 Jun 2023	01 Jun 2023	Revise	Revise

Additional publications /poster presentations:

Sethi V, Qin L, Cox E, Trocóniz IF, Della Pasqua O. Assessment of the efficacy of combination of oral acetaminophen and topical diclofenac in osteoarthritis pain: Insights from a model-based meta-analysis. Abstract accepted for poster presentation at EULAR 2023 (Sood et al., 2023)

Kilchberg, 11 March 2023

European Congress of Rheumatology EULAR 2023

Milan, Italy – 31 May - 3 June 2023

Dear Vidhu Sood,

Thank you for having submitted an abstract for **EULAR 2023** to be held on-site on 31 May – 3 June 2023.

On behalf of the EULAR Congress Committee, we have the great pleasure to inform you that the following abstract has been accepted for a **Poster View presentation** at EULAR 2023.

Submission N°: **242**
Title: **Assessment of the efficacy of combination of oral acetaminophen and topical diclofenac in osteoarthritis pain: Insights from a model-based meta-analysis**

Background

Osteoarthritis (OA) is a major cause of chronic pain and disability in older adults and currently affects more than 500 million people worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). In the absence of curative therapy, symptomatic drugs comprise the backbone

of pain management in OA. However, acetaminophen provides inadequate relief and oral non-steroidal anti-inflammatory drugs (NSAIDs) exhibit significant gastrointestinal (GI) and cardiovascular (CV) toxicity which prohibit their long-term use in the elderly (Bannuru et al., 2010; Cooper et al., 2019). Although opioids can be an effective alternative in patients experiencing insufficient pain relief with other analgesics, concerns have been raised about the risk of side effects, addiction, and overdose deaths (Deveza et al., 2018). This leads to inadequate management of pain which continues to have a considerable negative impact on the quality of life of OA patients and their ability to function both physically and mentally (Sinatra, 2010; van Laar et al., 2012).

Growing evidence suggests that when the pathophysiology of a medical condition is mediated by multiple pathways such as in OA pain, it is not surprising that no single therapy provides adequate pain relief while exhibiting favorable risk-benefit ratio in the long term. In this direction, the use of rational combinations of analgesic drugs that act through a different mechanism of action (MOA) offers a viable approach to achieve more effective pain relief with a better risk-benefit ratio (Altman, 2004; Raffa et al., 2003; Varrassi et al., 2010). The use of combination of analgesics is also recommended by important clinical practice guidelines for pain, such as the World Health Organization and the American College of Rheumatology (Paladini and Varrassi, 2020).

Paracetamol (APAP) and topical diclofenac (DIC) exhibit complementary MOA and are therefore attractive candidates for use in combination analgesia. Although the analgesic MOA of APAP is not fully understood, existing evidence strongly suggests APAP to mediate central analgesic effect via the activation of descending serotonergic pathways while exhibiting minimal influence on peripheral pathways (Anderson, 2008). Topical NSAIDs, including diclofenac, have emerged as useful treatment options for OA population exhibiting contraindications to oral NSAIDs (Honvo et al., 2019b). They mediate their effect primarily by targeting peripheral mechanisms of pain and inflammation by inhibiting peripheral cyclooxygenases in the skin and soft tissue (Shah and Mehta, 2012). Moreover, recent updates in clinical practice guidelines recommend adding topical NSAIDs to APAP for patients

still symptomatic after initial monotherapy (Bruyère et al., 2014; NICE, 2014). Therefore, combining topical diclofenac with oral acetaminophen could be a useful strategy to address the shortcoming of acetaminophen monotherapy, which has recently been shown to have inadequate efficacy as a single agent in the treatment of OA (Bannuru et al., 2010) and can be appropriate for patients exhibiting aversion to oral NSAIDs due to comorbidities (Bruyere et al., 2019; McCarberg and Tenzer, 2013). A plausible pharmacological interaction between these two analgesics might help to address the limited pain control achieved with APAP and delay the progression to systemic NSAIDs and opioids. Moreover, a better pain management regimen would aid in reducing incidences of accidental overdose and related deaths due to oral analgesic use (McCarberg and Tenzer, 2013). Therefore, we hypothesised the combination of oral APAP and topical DIC to show greater efficacy than either monotherapy in the management of OA pain. Whilst abundant clinical evidence is available in the literature on the monotherapies of acetaminophen or topical diclofenac in OA pain, there is a data gap in evidence on their combination use(Bell et al., 2019).

Model-based meta-analysis (MBMA) has emerged as an increasingly important quantitative tool to inform key drug development decisions and address important clinical questions (D'Agate et al., 2021; D'Agate et al., 2020; Mandema et al., 2005). The MBMA is a robust regression-based statistical technique that not only allows direct and indirect comparison of drug treatments, similar to a network meta-analysis, while also allowing assessment of many other key pharmacologic concepts including dose-response, drug interaction covariates analysis, and endpoints bridging. MBMA is increasingly being used in the drug development process across several therapeutic areas to measure overall treatment effect, a drug combination effect, or finding an optimal dose against a comparator drug in a specific disease indication (Chan et al., 2022; Mandema et al., 2005; Mandema et al., 2011a; Mandema et al., 2011b; Maringwa et al., 2021; Witjes et al., 2020). It is one of the new predictive modelling approaches that can be applied in model-informed drug development (MIDD), a concept which has gained recognition across drug regulatory authorities (FDA GUIDANCE, 2018; Madabushi et al., 2022; Marshall et al., 2019).

Growing evidence indicates there is high degree of overlap in acute and chronic pain states with regard to chronology and pathophysiology and that pain is seldom a pure nociceptive or neuropathic phenomenon in clinical practice (Cohen et al., 2021; McCormick et al., 2019). Considering the known gap in clinical evidence on the combination in OA pain (Bell et al., 2019), we have tried to use published summary level outcome data on combination therapy for acute pain indications.

Therefore, the present study aims to compare the effects of APAP and topical DIC combination to APAP or topical DIC monotherapy on pain score reduction and opioid sparing effect using an MBMA.

Methodology

The analysis was conducted according to a pre-defined data analysis plan (DAP) (Figure 5.1)

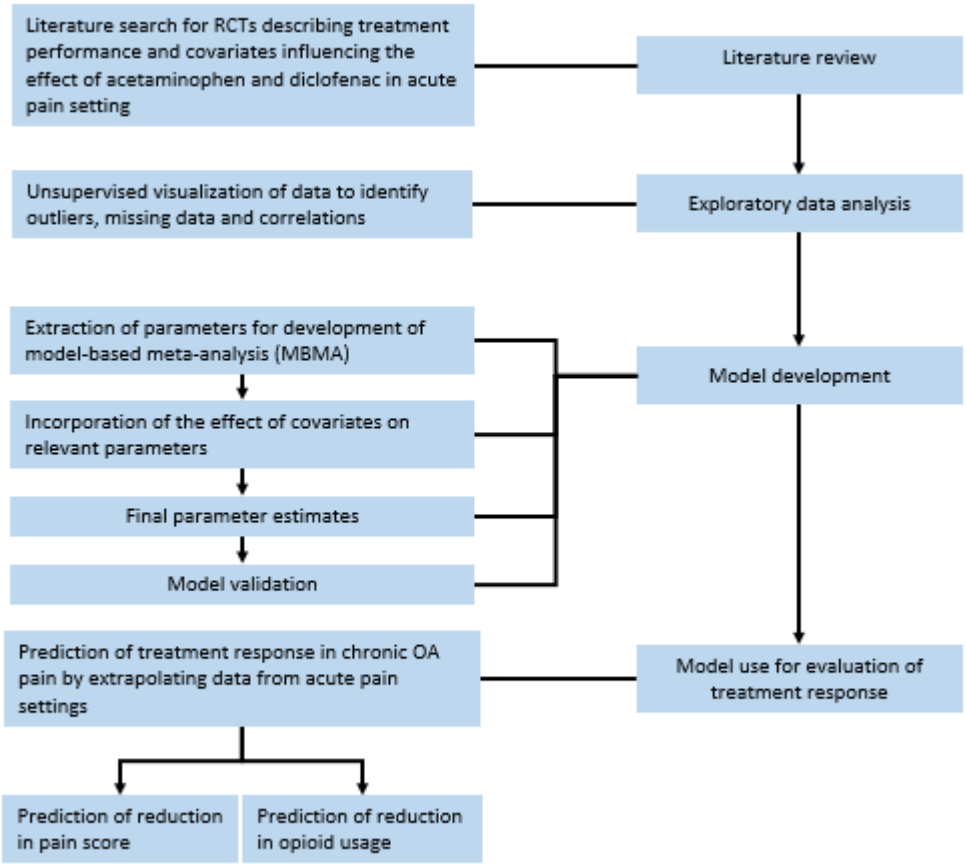

Figure 5.1. Flow diagram depicting the main steps of the analysis from the initial literature review to the predicted treatment effect of the combination therapy of oral acetaminophen and topical diclofenac

Literature review and data extraction

A literature review (LR) was conducted to identify randomised controlled trials (RCTs) investigating the efficacy of the drug combination in acute pain settings. For this LR, MEDLINE database was searched from inception up to December 2021 using key words and medical subject heading terms for ‘paracetamol’, ‘NSAIDs’, ‘diclofenac’ and ‘acute pain’ and their spelling variants. The search strategy is presented in Supplementary Table S5.1. The search was restricted to published RCTs in English language. All published RCTs that evaluated the efficacy of oral APAP along with oral or topical DIC in adults with acute pain were included. The detailed inclusion criteria are presented in Supplementary Table S5.2.

Two independent researchers reviewed all abstracts and selected potentially eligible studies. Full texts of these studies were then retrieved and examined thoroughly for eligibility. All the relevant information from the included studies - such as drug, dose, regimen, sample size etc. - was extracted in a data collection form by one reviewer. A second researcher reviewed the quality of data extraction by conducting random checks.

Clinical Endpoints

The efficacy endpoints were pain score reduction on numerical rating scales (NRS) or visual analogue scale (VAS) and opioid sparing effect (OSE), defined as a reduced opioid dose without loss of analgesic efficacy.

Exploratory Data Analysis

Exploration of the dataset is a critical early step after data collection that provides a better understanding on the total amount of data available using graphical representations and visualisation of potential relationships between response and covariates as well as between covariates and allows detection of outliers and anomalies. The relationships between a set of pre-defined covariates (e.g., baseline) were explored considering potential confounding between the variables that prevent proper understanding of the relationship with treatment effect. The magnitude and variability of the treatment effect across trials was visualised from forest plots that demonstrate the observed change from baseline (mean) and difference from placebo (treatment effect),

and the observed event and % event difference from placebo (treatment effect) in event endpoint (e.g., OSE) for each active arm of each trial.

The relationship between observed treatment effects was further studied by plotting observed treatment effect against covariates. All the included RCTs were used in the development of the model. However, data from only placebo controlled RCTs was used for the purpose of preliminary evaluation of the observed treatment effect.

Model-based meta-analysis

An MBMA was conducted to integrate drug exposure and outcome data for the combination treatments and predict the magnitude of clinical efficacy response including change in opioid sparing effect across acute pain indications. Relevant patient covariates governing differences in drug treatment effects between trials, such as patients and treatments (e.g., baseline pain severity) were also evaluated for inclusion in the model.

Model structure for opioid sparing effect of monotherapy in acute pain

The consumption of opioids (mg) at primary time points was analysed separately using the following MBMA model structure, generally adopted for outcomes that are likely to follow a continuous Gaussian distribution (Mandema et al., 2005; Mandema et al., 2011a; Mandema et al., 2011b; Maringwa et al., 2021; Qin et al., 2021):

$$\Delta Y_{ij,ose} = eo_{i,ose} + f(Drug_{ij}, \boldsymbol{\theta}) + \varepsilon_{ij,ose} \qquad \text{Eq.1}$$

where the consumption of opioids ($\Delta Y_{ij,ose}$) within trial i and arm j is described as a function of (a) placebo response ($eo_{i,ose}$); (b) f(Drug,θ) representing the drug effect (for APAP or DIC) using the fixed-effect model parameter (θ) and $\varepsilon_{ij,ose}$ representing the residual error.

The residual (within-trial) variability, $\varepsilon_{ij,ose}$, was assumed to be normally distributed with a mean of 0 and variance $var(\varepsilon_{ij,ose}) = \frac{\sigma^2{}_{ij}}{N_{ij}}$, which represents the precision associated with each measurement. σ_{ij} is the standard deviation of the outcome in the *i*th trial arm j for the endpoint and *N* is the associated sample size. Note that $\sqrt{var(\varepsilon_{ij.ose})}$ represented the standard

error (SE) of the mean. In this model for between trials variability, the trial-specific placebo response for endpoint ose at primary time in trial i ($eo_{i,ose}$) was described by an unstructured (or non-parametric) model considering the variability to be governed by a substantial number of unexplained factors and thus likely to be highly non-Gaussian in distribution.

Model structure to estimate for opioid sparing effect of combination therapy

The opioid sparing effect of combination of APAP and DIC was assessed assuming an additive effect based on fundamental pharmacology principle for pharmacodynamic response and incorporating an interaction term to account for non-additivity of the two drugs. Combination effect was described using the following model structure:

$$f\left(Drug_{ij}, \boldsymbol{\theta}\right)_{ose} = f(\text{acet}) + f(diclof) + \gamma \cdot f(\text{acet}) \cdot f(diclof) \qquad \text{Eq.2}$$

where f(acetaminophen) and f(diclofenac) represent the effect of each drug as monotherapy, and γ is interaction coefficient. The parameter γ describes non-additivity and represents the type of interaction and quantifies its magnitude. When the estimates of γ are not significantly different from 0, it indicates that the combined effect is the sum of the two individual drug effects and there was no interaction between the two drugs. Negative value of the γ estimate indicates that the improvement in efficacy outcome (opioid sparing effect) is more than the sum of the two individual drug effects. On the other hand, positive value of the γ estimate indicates that the combined efficacy outcome was less than the sum of the two individual drug effects.

Model Evaluation

Candidate models were assessed using maximum likelihood criteria [Akaike Information Criterion (AIC); p-value of <0.05 denoted statistical significance] and graphical diagnostics, with observed response plotted against population and trial-specific predictions to assess the goodness-of-fit plots (e.g., precision, absence of bias). Additionally, forest plots were employed to compare model predicted values for each study arm to their observed values. Moreover, partial residual plots were used as graphical assessments to compare model predicted values with normalised observed values. To

achieve consistency between model predictions and the observed data, residuals from the final model were used to normalise the actual observed values to the model predicted values. A total of 1000 sets of parameter estimates were re-sampled from the variance-covariance matrix of the final MBMA model for computing confidence intervals for simulated outcomes. All analyses and simulations were conducted using generalised least squares regression functions (*gnls*) provided in the *nlme* package in R (version 3.5.3 or higher, 64 bit, running on Windows 10 Professional, SP1).

Results

Exploratory analysis of studies on the effect of the combination of APAP and DIC in acute pain

A total of 11 RCTs studying the effect of systemically administered APAP+DIC combination treatment in acute pain were included for the evaluation of combination effect (**Figure 5.2** and **Table 5.1**).

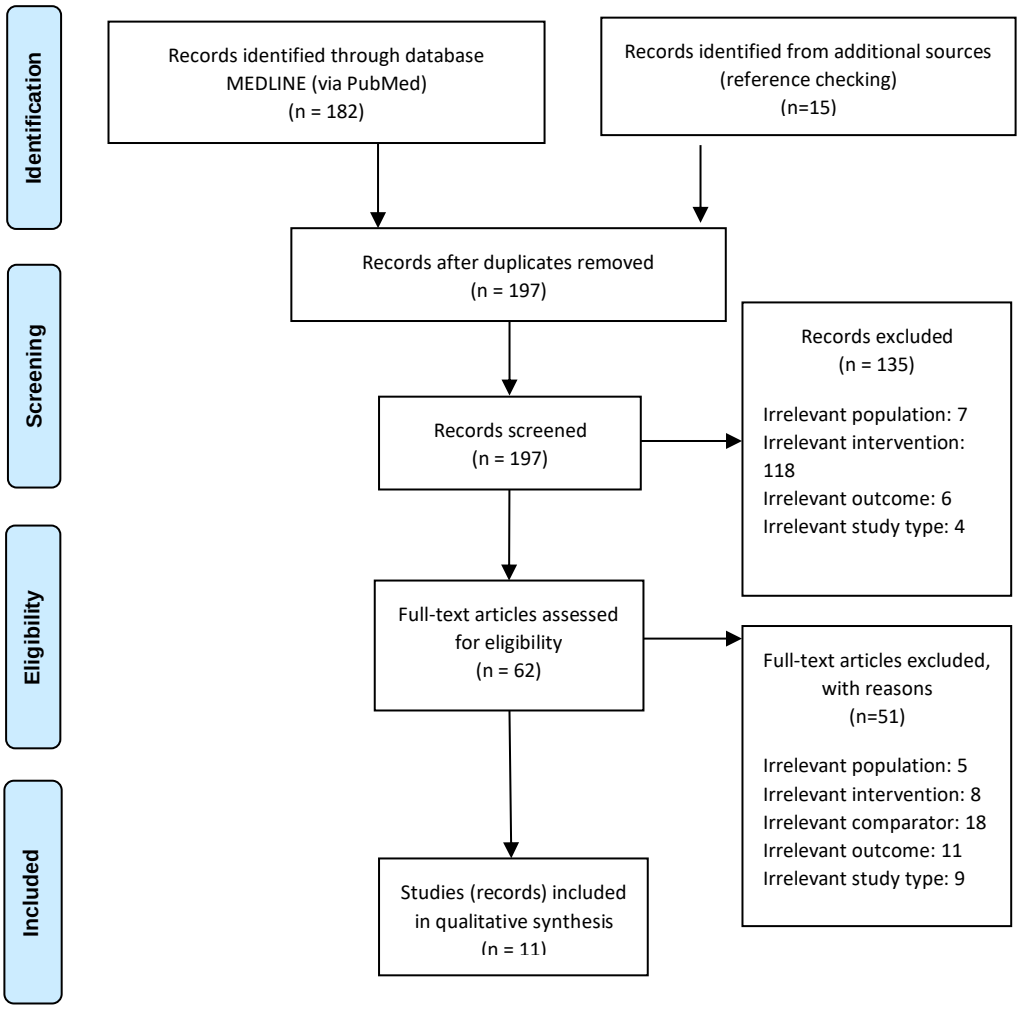

Figure 5.2. Flow chart of the screening and selection process of RCTs on the combination of acetaminophen and diclofenac in acute pain settings

While 7 out of 11 studies demonstrated greater pain reduction with the combination of APAP+DIC when compared with APAP alone, 5 out of 11 studies also showed the combination to have possible beneficial effects when compared with systemic DIC alone (Figure 5.3). However, only two studies reported the combination to exhibit statistically significant efficacy in the management of acute pain when compared with APAP or DIC monotherapy (Breivik et al., 1999; Hannam et al., 2014). The mean reduction in reported pain scores is shown in Supplementary Table S5.3. Due to the variability in the use of pain scales or pain definitions used across studies and misreporting of numeric values, the ratios of observed mean pain score reduction with APAP+DIC vs. APAP or DIC alone were used to demonstrate the extent of the analgesia provided by the combination (Supplementary Table S5.3). While 8 out of 11 studies revealed a change from baseline in the pain outcome scores, 3 studies reported no change from baseline in the pain outcome scores. Of these 3 studies, the first revealed no additional benefit of APAP+DIC when compared with APAP or DIC alone (ratio was set equal to 1). The second study showed no additional benefit of APAP+DIC when compared with DIC alone. However, greater reduction in pain score was found for the combination when compared with APAP alone. The third study demonstrated full additive combination effect and thus the ratio was set equal to 2. Here, the ratio was used as an exploratory tool to visualize the possible magnitude in pain score response and not as an aid to quantify the extent of combination effect. In addition, another significant factor that led to confounding of the magnitude of the combination effect on pain score reduction was the variability in the use of opioids PCA across different trials and their arms. In 7 out of 11 studies, participants were permitted to use opioid analgesics as patient-controlled analgesia (PCA) if inadequate pain relief was experienced. Therefore, in the above clinical studies the ratio of reduction in pain score for the APAP + DIC combination vs APAP/DIC monotherapies were further stratified according to reported use of opioid PCA vs no opioid PCA. For studies reporting use of opioids PCA, the ratio was typically closer to one, especially when compared with DIC alone.

Figure 5.4 depicts the ratio of APAP or DIC to APAP+DIC combination resulting in opioid sparing effect in the 7 studies that allowed the use of opioid PCA. The ratio of APAP monotherapy vs APAP+DIC combination was reported > 1 by six studies and was < 1 for one study (left panel Figure 5.4). The ratio of DIC monotherapy vs APAP+DIC combination was reported > 1 by 6 studies (right panel Figure 5.4). The opioid sparing effect demonstrated a greater likelihood of showing a consistent beneficial effect for the combination when compared with either APAP or DIC monotherapy. Moreover, this outcome has a lesser likelihood of bias in the assessment of the treatment effect as compared to the use of outcomes related to pain score reduction. Here again, the ratio served as an exploratory instrument to visualise the extent of opioid sparing effect exhibited by the combination treatment with no intention to quantify it.

Table 5.1. Characteristics of the studies on the combination of acetaminophen and diclofenac in acute pain

Study	Population	Indication	Endpoint	N	Treatment	ROA	PCA	PCA unit
Matthews RW 1984(Matthews et al., 1984)	Adults	Dental surgery	VAS	27	ace 500 mg; ace 500 mg + dic 50 mg	Oral	ND	NA
Montgomery JE 1996(Montgomery et al., 1996)	Women	Elective gynecological surgery	VAS	59	ace 1500 mg; ace 1500 mg + dic 100 mg; dic 100 mg	Rectal	Morphine	mean mg
Breivik EK 1999(Breivik et al., 1999)	Adults	Oral surgery	VAS	72	ace 1000 mg; ace 1000 mg + dic 100 mg; dic 100 mg	Oral	Codeine/ paracetamol	%
Beck DH 2000(Beck et al., 2000)	Women	Hysterectomy pain	VAS	65	ace 1200 mg; ace 1200 mg + dic 100 mg; ace 2400 mg	Rectal	Morphine	mean mg
Siddik SM 2001(Siddik et al., 2001)	Women	Cesarean pain	VAS at rest	80	ace 2000 mg; ace 2000 mg + dic 100 mg; dic 100 mg; placebo 0 mg	Intravenous; rectal; intravenous/rectal;	Morphine	mean mg
Hiller A 2004(Hiller et al., 2004)	Adults	Tonsillectomy	VAS (0-3)	71	ace 2000 mg; ace 2000 mg + dic 75 mg; dic 75 mg	Iv	Oxycodone	mean mg
Woo WW 2005(Woo et al., 2005)	Adults	Musculoskeletal injury	VAS at rest	229	ace 1000 mg; ace 1000 mg + dic 25 mg; dic 25 mg	Oral	No	NA
Munishankar B 2008(Munishankar et al., 2008)	Women	Caesarean pain	VAS at rest	78	ace 1000 mg; ace 1000 mg + dic 100 mg; dic 100 mg	Oral	Morphine	mean mg
Riad W 2007(Riad and Moussa, 2007)	Children	Postoperation pain	Pain rating scale (0-5) change	108	ace 880 mg; ace 908 mg + dic 22.7 mg; dic 23.7 mg	Rectal	Morphine	mean mg
Hannam JA 2014(Hannam et al., 2014)	Children	Postoperation pain	VAS	496	ace NA mg; ace NA mg + dic NA mg; dic NA mg	Oral/rectal; oral	No	NA
Elzaki WM 2016(Elzaki et al., 2016)	Adults	Post-endodontic pain	NRS	111	ace 1000 mg; ace 1000 mg + dic 50 mg; placebo 0 mg	Oral	Ibuprofen	mean mg

*PCA= Patient-controlled analgesia, ND= No data, NA=Not applicable, ROA: Route of administration, ace=acetaminophen, dic= diclofenac, N=no. of subjects

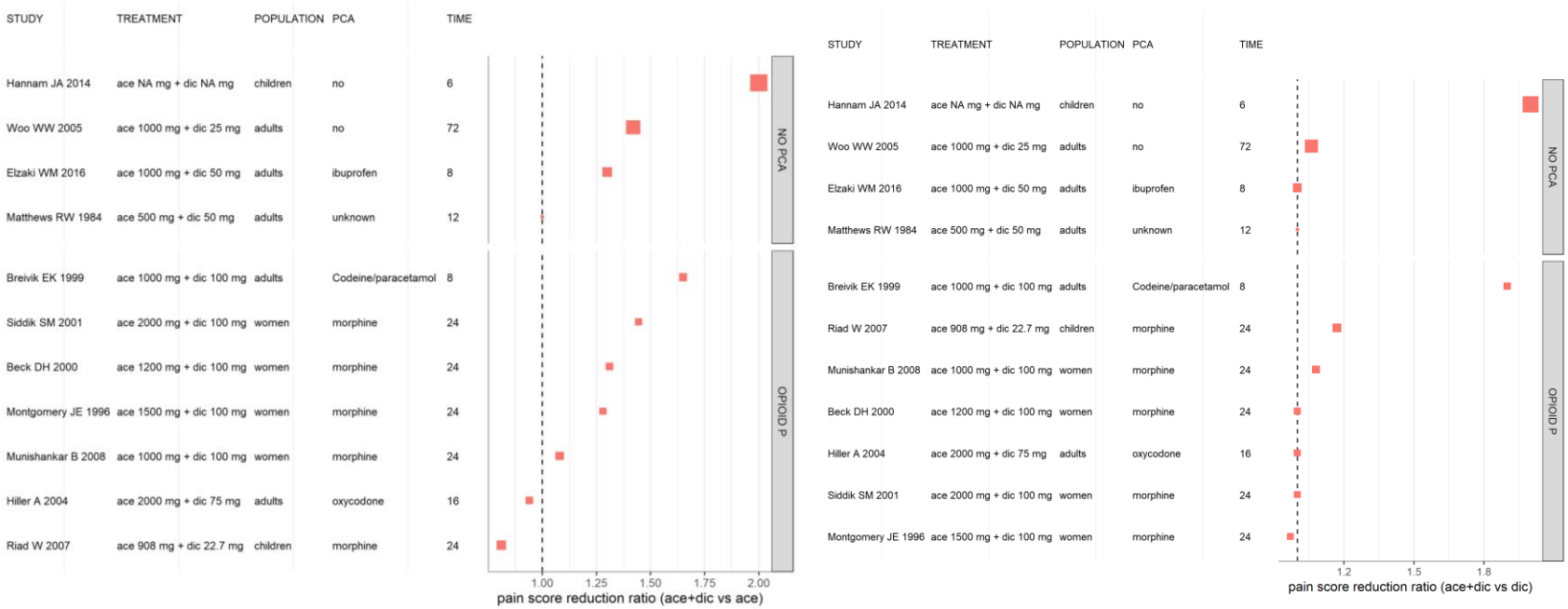

Figure 5.3. The observed ratio of the beneficial effect of systemic APAP+DIC on pain score reduction at 6 to 72 hours, compared to APAP and DIC alone across 11 acute pain studies by use of opioid patient-controlled analgesia (PCA) vs no PCA. The vertical dash line (ratio=1) indicates no beneficial effect of APAP+DIC compared to APAP/DIC alone in the same study. PCA: use of patient-controlled analgesia. The size of symbol represents the sample size in the study arm.

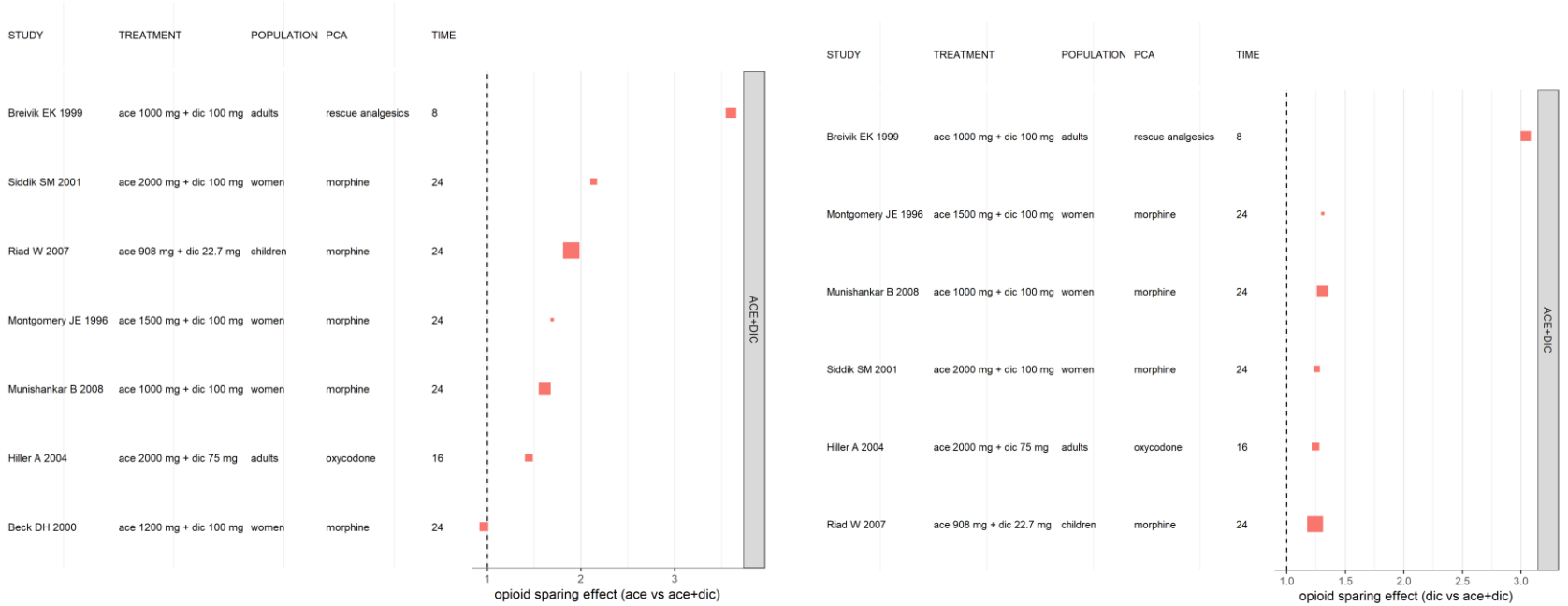

Figure 5.4. The observed ratio of the benefit of systemic APAP+DIC on opioid sparing effect when compared with APAP/DIC alone across seven clinical studies on acute pain by use of opioid patient-controlled analgesia (PCA) vs no PCA between 6 to 72 hours. The vertical dash-line (ratio=1) represents no beneficial effect of APAP+DIC when compared with APAP/DIC alone in the same study. The size of the square symbol represents the sample size in the study arm.

MBMA of opioid sparing effect of APAP+DIC combination treatment in acute pain

The treatment effect for the systemic combination of APAP+DIC was leveraged from 11 RCTs conducted in acute pain indication. Both pain reduction and opioid sparing effects (for studies allowing PCA) were used as clinical endpoints. The pain score definitions, baseline pain score, absolute pain score and change from baseline at time of assessment were heterogeneous across the 11 studies with data missing from few studies (Supplementary Table S5.3). The pain score reduction caused by APAP+DIC combination was not significantly different from either APAP or DIC monotherapy, especially among the seven studies allowing the use of opioids PCA (Figure 5.4). Opioid sparing effect was found to be a better outcome to assess the effect of APAP+DIC combination when compared with either treatment alone (Figure 5.4). Therefore, a parsimonious MBMA model was developed based on five eligible studies reporting mean mg opioid PCA use to quantify the opioid sparing effect of the combination (Supplementary Table S5.4 and Supplementary Figure S5.1). The reported amount (in mg) of opioid PCA used in the 5 included studies is presented in Supplementary Table S5.5.

The model development was performed in a series of stages: APAP and DIC monotherapy data were modelled independently in the first step before the introduction of the combination therapy data in the second step of the analysis. The combined effect of systemic APAP+DIC was described using an interaction term as shown in Equation 2 (in the methodology section). Although addition of the interaction term between APAP and DIC did not result in significant improvement in the model fit, it was included to investigate the magnitude of combination effect due to the two drugs in acute pain. Finally, the model was updated using reported SEs of change in opioid PCA consumption, where the model residual error was measured using SEs representing between-subject variability and the sample size to result in the highest precision associated with each measurement in the model. Supplementary Table S5.6 presents a summary of the key steps involved in model development. The model was able to estimate an interaction

coefficient explaining non-additivity between the two drugs on opioid sparing effect (Table 5.2).

Table 5.2. Parameter estimates from the parsimonious model of opioid sparing effect

Parameter	Parameter description	Estimate	RSE %	Absolute (mg)
e.ace	Drug effect of ACE	-18.9 [-31.4 to -6.43]	29%	-18.9
e.dic	Drug effect of DIC	-28.4 [-40.7 to -16.2]	19%	-28.4
γ*	Interaction between ACE and DIC	0.025 [0.0148 to 0.0353]	18%	
A γ of 0 indicates that the combined effect was the sum of the two individual drug effects. A positive γ indicates that the improvement (increase) was less than the sum of the two individual drug effects, while a negative γ indicates a more than additive effect. ace= Acetaminophen, dic= Diclofenac, RSE = residual standard error				

This positive γ value as additional interaction correction coefficient indicated that the beneficial effect of combination treatment on opioid sparing was less than the sum of the two individual drug effects. Combination treatment showed slightly less use of opioid PCA (in mg) when compared with APAP or DIC alone. Moreover, different acute pain conditions were associated with different levels of opioid PCA, for instance, the opioid PCA use was generally lower for tonsillectomy pain when compared with gynecological surgery induced pain. Due to the limited number of studies for analysis, no further investigation was conducted to differentiate the opioid PCA use based on the type of surgical acute pain.

Model estimated combination or monotherapy effects are presented in Figure 5.5 for each treatment arm in the included studies. The final model showed adequate performance in predicting opioids use across most study arms.

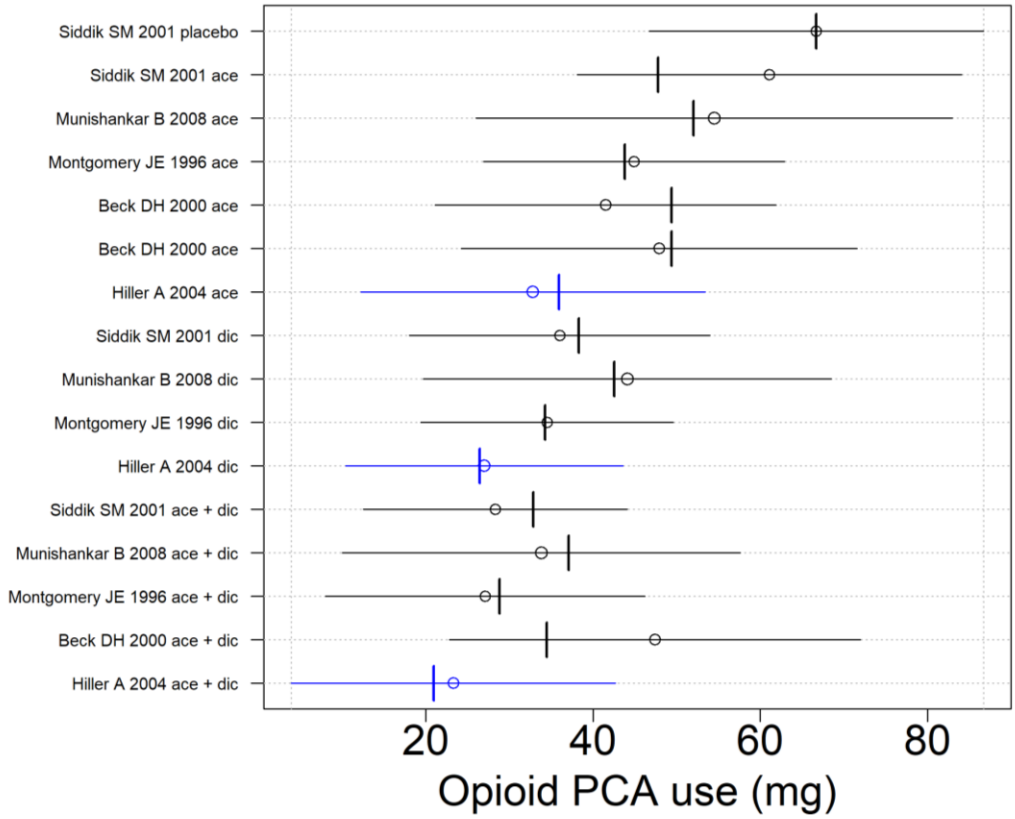

Figure 5.5. Observed (circle) and model-estimated (vertical bar) use of opioid PCA (mg) by included treatment arms. The symbols represent the mean reported response rate in the various trials and treatment arms. Circle size is proportional to sample size of each arm. The horizontal lines present the respective 95% CIs. The vertical tics represent the model-based predictions. Blue: tonsillectomy; Black: gynecological surgery.

Although there was an overlap in the simulated 95% confidence interval (CI) bands, the final simulation showed slight additional benefits of APAP+DIC combination treatment on opioid sparing effects when compared with APAP or diclofenac DIC alone and suggests about 32% less use of opioid than APAP based on point of estimation (Figure 5.6). Additionally, the estimated placebo effect in the model was due mainly to a single placebo control study, which might have contributed to some extent to a bias in estimating the true combination effect.

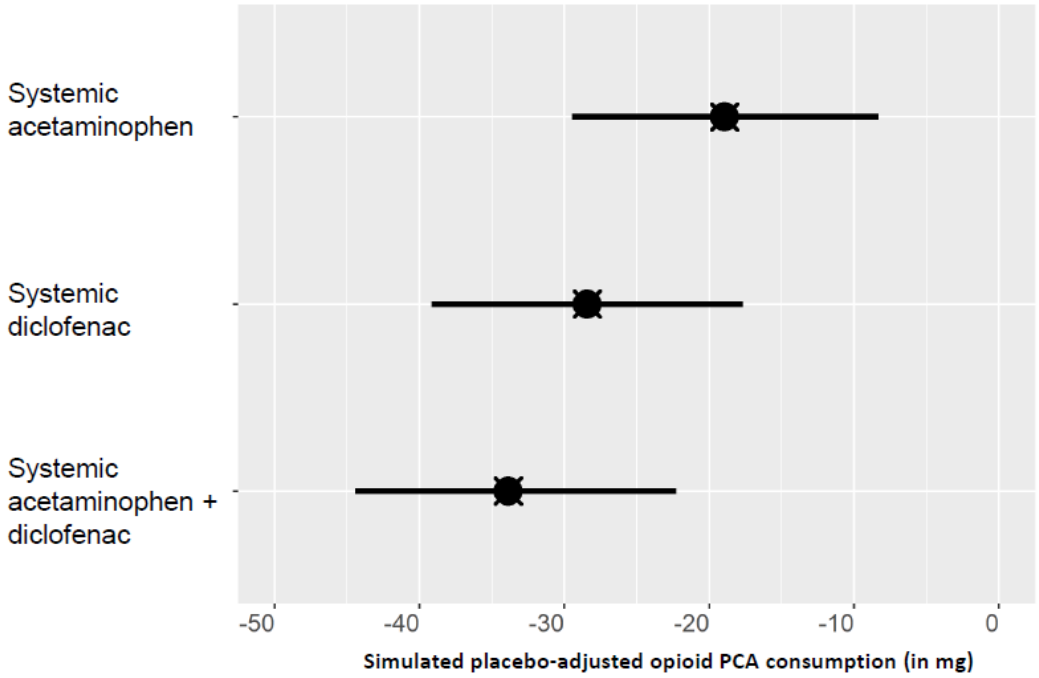

Figure 5.6. Simulated placebo adjusted opioid PCA use (in mg) for monotherapies and combination treatment assuming a typical placebo response (64.7 mg). Symbols indicate maximum likelihood model predictions and error bars present 95% CI of resampling parameter estimates from the final model variance covariance matrix 1,000 times.

Discussion

Chronic OA pain is a multi-mechanistic phenomenon that involves both inflammatory and non-inflammatory pain transmission pathways at both peripheral (joints) and central (spinal and supraspinal) levels of the nervous system (Perrot, 2015; Salaffi et al., 2014). Therefore, it is no surprise that no single analgesic provides adequate pain relief while demonstrating optimal risk-benefit ratio in the long-term and successful approaches may need targeting several pathways at the same time (Raffa et al., 2003; van Laar et al., 2012). Several studies have investigated the effect of combining oral NSAIDs and APAP in OA pain and have shown the combination to provide additional pain relief, thereby leading to dose-sparing of the two monotherapies and thus improved safety (Doherty et al., 2011; Murphy et al., 1978; Pareek et al., 2010; Pareek et al., 2009; Seideman et al., 1993).

The use of a combination of oral APAP and topical DIC can be a promising strategy to achieve optimal analgesia with high tolerability given both the drugs lack the risk of any major serious adverse events in the elderly, the

demographic subset most prone to OA. Additionally, multiple OA guidelines also support the use of topical NSAIDs concomitantly with APAP (Bruyère et al., 2014; Geenen et al., 2018; NICE, 2014). Moreover, the combination is generally considered to be efficacious and well-tolerated as most trials in OA pain allow APAP as rescue therapy (Courtney and Doherty, 2002; Stewart et al., 2018). Whilst the combination treatment is frequently used in real-world settings with more than one quarter of patients using topical NSAIDs with oral non-opioid analgesics such as acetaminophen (Jackson et al., 2017), there is limited literature available on the combination of oral APAP and topical NSAIDs (Bell et al., 2019). Only one RCT of 4 weeks duration was found to evaluate the efficacy and safety of combination treatment comprising of oral APAP and a topical NSAID (ketoprofen plaster) in 43 patients with knee OA and revealed significantly greater pain reduction ($p = 0.03$) and better physician's global assessments ($p = 0.01$) for the combination versus APAP or placebo (Yoo et al., 1996). In addition, a pharmacokinetic-pharmacodynamic study in children with acute postoperative pain evaluated the effect of combining APAP and DIC and demonstrated combination treatment with lower doses of both drugs to provide comparable analgesia to APAP and DIC monotherapies (Hannam et al., 2014).

The first objective of the current study was to assess the efficacy of combination of oral APAP and topical DIC against either monotherapy in OA pain by implementing an MBMA on available published clinical evidence in OA pain. In the absence of RCTs on the combination in OA pain, the combination effect was extrapolated by analyzing RCTs conducted in acute pain settings and using pain score reduction and opioid sparing effect as clinical endpoints. In general, greater pain reduction was reported for the combination, compared to APAP alone, particularly for studies not allowing subjects to use opioids PCA. However, the MBMA of RCTs identified in acute postoperative pain showed beneficial effects in terms of reduction of opioid use (in RCTs allowing PCA) with combination treatments when compared with the sum of individual contributions of the two drugs. The above finding has significant implications given the widespread use of opioids and the serious concerns of the risk of side-effects, addiction and overdoses due to these risks. In addition, opioid use has been shown to be associated with significantly greater structural damage

and faster progression of degenerative changes when compared with controls. Moreover, opioid users also exhibited significantly greater pain, worse symptoms, and lower quality of life than controls, which suggests insufficient pain control by opioids (Bodden et al., 2021). The synergistic activity between APAP and DIC confirms the results of a previous qualitative review of perioperative pain management in children (Wong et al., 2013). Furthermore, similar to the opioid sparing effect described in this paper, the requirement for supplemental (rescue) pain medication has been used as a (joint) endpoint in clinical studies of analgesic drugs effect (Björnsson and Simonsson, 2011).

Although the beneficial effect of the combination in comparison to DIC monotherapy remains inconclusive due to a lack of clinical evidence. However, the combination effect is likely to be comparable to diclofenac alone.

Mounting evidence shows that pain in OA is mediated by both nociceptive and neuropathic pathways that are partially similar to acute pain which is primarily of nociceptive origin (Committee for Medicinal Products for Human Use, 2016; Mease et al., 2011). Therefore, this demonstrated beneficial effect of combination treatment in acute pain settings can be extrapolated to chronic OA pain with high likelihood. The addition of topical DIC to oral APAP could be a potential solution to mitigate safety concerns with acetaminophen by allowing its use at lower dosages and delay the progression to oral NSAIDs and opioids in clinical settings. Our research opens a new therapeutic option for the ever-increasing elderly population suffering from OA, especially those who have cardiovascular and gastrointestinal comorbidities and hence are prohibited to use stronger analgesics such as oral NSAIDs and opioids.

The present study also had some limitations. First, a major limitation of the analysis is the use of summary level data, which was not enough to fully address the research questions involving quantification of exposure response for combination treatment, bridging, and extrapolation across pain indications. However, summary level data might be adequate when the objective of the meta-analysis is to estimate drug effects (Lambert et al., 2002). Second, while our analysis focused specifically on trials having APAP or DIC in one of their treatment arms, inclusion of trials on other NSAIDs could have offered additional insights into the anti-inflammatory effect and helped in understanding whether the observed differences are due to a class effect.

Similarly, it could have confirmed whether the observed placebo response is consistent across studies having similar design and patient populations. Third, the combination effect was predicted by adding treatment effects to the nonparametric placebo response. As there was only one placebo-controlled study to inform placebo responses to the opioid sparing effect in acute pain (Siddik et al., 2001), this may have resulted in some degree of estimation bias. Whilst the inclusion of additional studies in the network could have improved the model precision to some degree, they would not have been sufficient to address the research questions in the current study. Fourth, as the analysis in acute pain was conducted on limited number of studies that had a small sample size, the impact of study-level variation on model precision cannot be ruled out with the power and reliability of the pooled estimates also impacted as suggested by the wide range of simulated CI. In this case, a network meta-analysis assessing a broader range of analgesic doses in adults after major surgery could have offered more precise estimates for the monotherapy effect (e.g., acetaminophen, NSAIDs class) (Martinez et al., 2017). Fifth, the differing levels of severity of acute pain induced by various types of surgeries could have caused large variations in the mean consumption of opioids (e.g., caesarean pain required higher dose of PCA when compared with tonsillectomy), which could not be considered in the current parsimonious model due to a limited number of studies. Additionally, growing research suggest morphine consumption to be dependent to a larger degree on individual pain vulnerability, which is governed by several factors other than the type of surgery (Gerbershagen et al., 2014; Hernandez et al., 2015; Kalkman et al., 2003). Sixth, the clinical differences between acute pain and chronic pain and the inconsistency in the reporting of clinical endpoints across different disease stages precluded implementation of a quantitative MBMA framework based on consistent clinical endpoints to extrapolate the combination effect from acute pain to chronic OA pain. Lastly, the efficacy of the drug regimen is governed to a large extent by compliance with the regimen (Dockerty et al., 2016). However, as there was no compliance related information available in the included

Summary & conclusion

This paper presented the study conducted to investigate the efficacy of the combined therapy of APAP and topical DIC in the management of mild to moderate OA pain. It included a summary of the relevant literature, results, discussion, and implication of findings. This MBMA study demonstrates greater pain reduction and opioid sparing efficacy for the combination of APAP and topical DIC versus APAP alone when treating acute pain. Considering the overlap in pain transmission pathways between acute and chronic OA pain (especially at the earlier stages) and pharmacologically complementary MOAs of the two drugs, the combination may be anticipated to exhibit similar performance on extrapolation to chronic OA pain. Further research based on quantitative systems, pharmacology modeling, and biomarkers is warranted to assess the clinical significance of pharmacodynamic interactions between the drugs and to further optimize the combination regimen. Overall, our research tries to bridge the gap in pharmacological and clinical evidence supporting the use of combination of APAP and topical DIC as a new first-line treatment for mild to moderate OA pain.

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5A.3 Links and implications

The present study used a MBMA to extrapolate the effect of the combination of APAP and topical DIC from acute pain. The MBMA demonstrated greater pain reduction and opioid sparing effect for the combination versus APAP alone when treating acute pain. Considering the overlap in pain transmission pathways between acute and chronic OA pain (especially at the earlier

stages) and pharmacologically complementary MOAs of the two drugs, similar performance may be anticipated with the combination treatment on extrapolation to chronic OA pain.

The findings of this study suggest the combination to possess pain relieving and opioid sparing effect in mild to moderate OA pain. However, the safety of the combination also needs to be confirmed in order to increase its uptake by the HCPs in the clinical settings. Therefore, the next phase of the research was designed with an aim to search and identify clinical evidence on the safety of the combination in OA pain.

CHAPTER 5B: MODEL-BASED ASSESSMENT OF THE LIVER SAFETY OF COMBINATION THERAPY OF ORAL PARACETAMOL AND TOPICAL DICLOFENAC IN MILD TO MODERATE OSTEOARTHRITIS PAIN

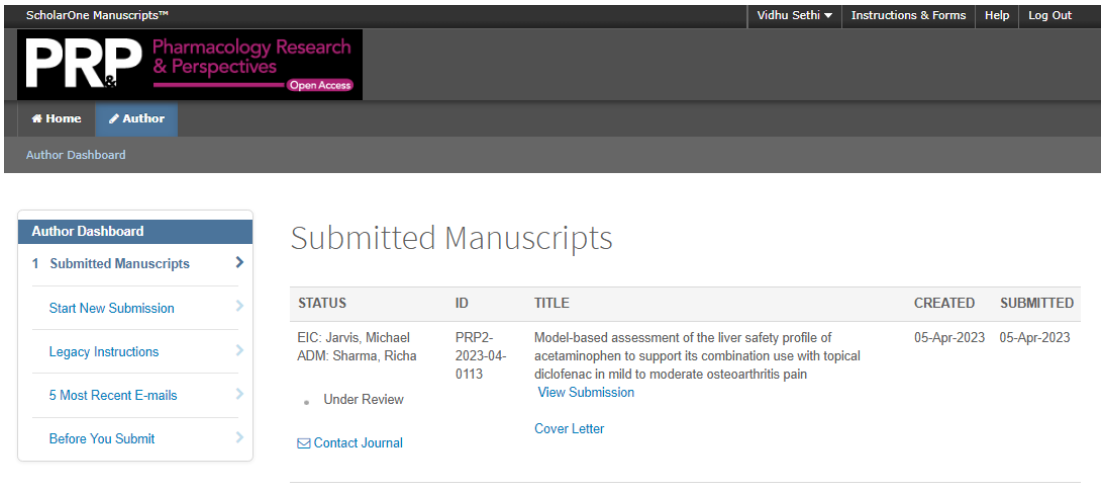
5B.1 Introduction

The results of the first quantitative study of phase II of the research design leveraged clinical evidence on the combination of oral acetaminophen (APAP) and topical diclofenac (DIC) from acute pain and suggested the combination to possess pain relieving and opioid sparing effect in mild to moderate OA pain. The present study is second part of the phase II of the research design and was developed based on the findings of previous study which generated clinical evidence on the efficacy of the combination. Therefore, this study aimed to identify clinical evidence on the safety of the combination of APAP and topical DIC in OA pain. However, there is lack of clinical evidence specifically on the safety of the combination in OA pain. Regarding the combination, topical DIC is considered well-tolerated due to its low systemic exposure. However, concerns of liver toxicity with acetaminophen at standard analgesic doses remain. Thus, the study uses a model-based meta-analysis (a regression-based statistical technique) to investigate the association between use of oral APAP and risk of hepatotoxicity, particularly in OA management by implementing MBMA on published clinical evidence. For this study, a literature review was conducted to identify RCTs reporting liver toxicity on APAP use. Subsequently, an MBMA was implemented to assess the deviation in liver enzymes (alanine aminotransferase or aspartate aminotransferase) from their normal levels and the risk was categorized into three different categories namely mild, moderate, and severe risk of liver abnormality.

5B.2 Submitted paper

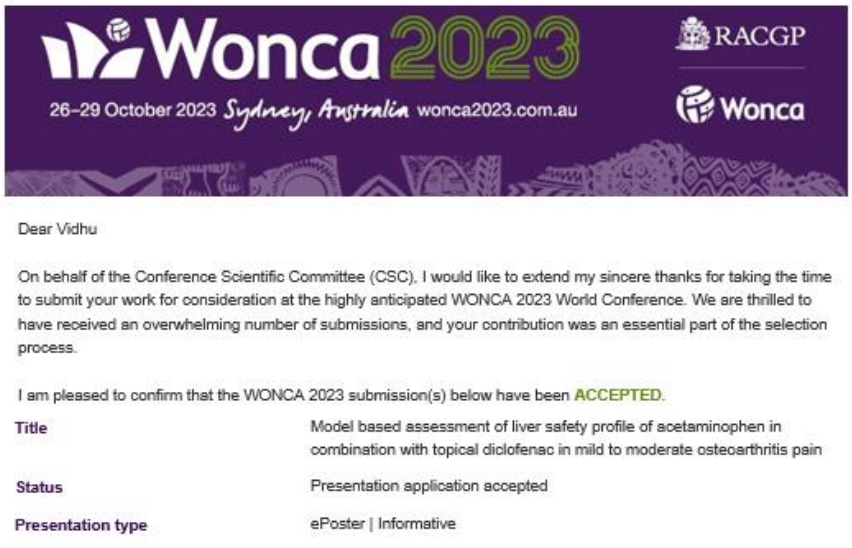
Sethi V, Qin L, Cox E, Trocóniz IF, Van der Laan L, Della Pasqua O. Model-based assessment of the liver safety profile of acetaminophen to support itscombination use with topical diclofenac in mild to moderate osteoarthritis

pain. Submitted to the journal “Pharmacology Research & Perspectives” on 5 April 2023. Under review as on 12 June 2023.



Additional publications /poster presentations:

Sethi V, Qin L, Cox E, Trocóniz IF, Van der Laan L, Della Pasqua O. Model-based assessment of liver safety profile acetaminophen in combination with topical diclofenac in mild to moderate osteoarthritis pain. Abstract accepted for poster presentation at WONCA 2023



Background

The first part of the chapter investigated the efficacy of the combination of APAP and topical DIC in mild to moderate OA pain and showed 32% less opioid use following combination therapy when compared with acetaminophen monotherapy. However, the safety profile of this combination

remains unclear in OA, despite such promising findings. While topical NSAIDs are generally considered to be a safe treatment in the management of OA due to their low systemic exposure (Honvo et al., 2019b), the safety concerns with acetaminophen use have been frequently raised, especially its associated risk of liver toxicity (Roberts et al., 2016).

Therefore, the present study aims to investigate the association between the use of APAP and risk of liver toxicity, particularly in OA management using an MBMA on published data identified through literature searches.

Methodology

Literature search and data extraction

For this study, a literature review (LR) assessing the liver safety of APAP, MEDLINE database was searched from inception to December 2021 using key words and medical subject heading terms for ‘paracetamol’, ‘toxicity’ and ‘liver’ and their spelling variants. The search strategy is presented in Supplementary Table S5.7. The search was restricted to RCTs published in the English language. Studies were eligible for inclusion if they investigated the safety of oral APAP on liver (through hepatic aminotransferases levels) in adult humans with or without any disease and were conducted for a duration of at least 2 weeks (Supplementary Table S5.8).

Two independent researchers reviewed all abstracts and selected potentially eligible studies. Full texts of these studies were then retrieved and examined thoroughly for eligibility. All the relevant information from the included studies such as drug, dose, regimen and sample size was extracted in a data collection form by one reviewer. A second researcher reviewed the quality of data extraction by conducting random checks.

Clinical Endpoints

For assessing APAP liver safety, the risk of liver abnormality was defined by deviation in the upper limit of normal (ULN) in liver enzymes, e.g., alanine transaminase (ALT) or aspartate transaminase (AST) were the primary outcomes. Three threshold categories defined by deviations from the upper limits of normal (ULN) of ALT and/or AST were created: >0-1 ULN (including ">1 ULN" , "0-1 ULN"); >1.5-2 ULN (including ">1.5 ULN", ">2 ULN", "≥2 ULN", ">1-1.5 ULN"); >3 ULN (including ">3 ULN", "ALT/AST >2 ULN,

alkaline phosphatase (ALP)≥718 u/l", ">3 ULN ALT/AST, >1.5 ULN total bilirubin (TB)", "lack of definition; reported as serious AE").

Model-based meta-analysis

An MBMA was conducted to predict the probability of deviating from ULN of ALT/AST in plasma in relation to APAP plasma concentrations.

Model structure to estimate the risk of liver abnormality considering multiplicative effect across thresholds

An MBMA model was implemented to quantify the relationship between drug exposure and the probability of exceeding ULN of ALT and/or AST, which was the most frequently reported liver toxicity definition across studies, at primary time point (time at which the endpoint is reported in the study) of RCTs. To make the best use of all the collated information, a joint response model was implemented to estimate the probability of patients exceeding the three different thresholds k (0-1 ULN, >1.5-2 ULN, >3 ULN of ALT/AST) of liver abnormality events within each treatment arm. The probability of an event was represented as the sum of a non-parametric background or placebo response (eo_i) in trial *i* of threshold k and an event in treatment arm *j* of trial *i* at primary time point of a RCT (as shown in Eq.3):

$$P(event)_{ijk} = eo_{ik} + f\left(Drug_{ij}, Dose_{ij}, \boldsymbol{\theta}\right) \cdot f\left(X_{ij}, \boldsymbol{\beta}\right) \qquad \text{Eq.3}$$

Where $P(event)_{ijk}$ is the likelihood (%) of any given patient exhibiting a liver abnormality event for the k^{th} threshold (0-1 ULN, >1.5-2 ULN, or >3 ULN elevation of ALT/AST) in trial *i* and arm *j* and is described as a function of a (i) placebo effect (eo_{ik}) representing the placebo or background response for k^{th} threshold in trial *i,* and described using a fixed-effect model for each trial representing different thresholds of liver abnormality; (ii) function $f(Drug, Dose, \boldsymbol{\theta}))$ describing the relationship between drug and dose using fixed-effect model parameters (θ_i) and (iii) function $f(X, \beta)$ characterizing the effect of covariates (X) (e.g., threshold) and their multiplicative effect captured using parameter $\boldsymbol{\beta}$.

A threshold specific drug effect was predicted, assuming constant shift across different thresholds, as shown in the following Eq.4:

$$f(threshold, \boldsymbol{\beta}) = \left(1 + \pi_1 * (threshold"">1.5\text{-}2ul"") + \pi_2 * (threshold"">3ul"")\right) \quad \text{Eq.4}$$

where π represent coefficients of drug effects for thresholds demonstrating >1.5-2uln or >3uln relative to threshold for 0-1 uln elevation.

Model structure to estimate the risk of liver abnormality considering additive effect across thresholds

The effect of an additive shift across threshold levels was also accounted for by modifying the Eqs. 3-4 to the following form:

$$P(event)_{ijk} = eo_{ik} + (f\left(Drug_{ij}, Dose_{ij}, \boldsymbol{\theta}\right) + f\left(threshold_{ij}, \boldsymbol{\beta}\right)_{add}) \quad \text{Eq.5}$$

$$f(threshold, \boldsymbol{\beta})_{add} = \left(\pi_{1.add} * (threshold = ">1.5\text{-}2uln") + \pi_{2.add} * (threshold = "> 3uln")\right) \quad \text{Eq. 6}$$

When compared with Eq.3 and Eq.4, the function $f(X_{ij}, \boldsymbol{\beta})_{add}$ in Eq. 5-6 characterises the effect of different threshold levels, parameter β describes the additive effect on the baseline and π_{add} represents the coefficients of drug effects for thresholds representing >1.5-2 ULN or >3 ULN elevation relative to an elevation of 0-1 uln in liver abnormality on an additive scale.

Model structure to estimate the risk of liver abnormality with combination treatment

The effect of oral APAP with another oral drug (e.g., ibuprofen) was investigated as a separate parameter in the model or shared with the overall effect of APAP. The number of patients exhibiting liver abnormality events in the treatment arm *j* of the trial *i* ($N_{event,\, ijk}$) was assumed to follow a binomial distribution with probability of event $P(event)_{ij}$ and sample size N_{ij} as shown in Eq.7:

$$N_{event,\, ijk} \sim binomial\left(N_{ijk},\, P(event)_{ijk}\right) \quad \text{Eq.7}$$

Each observation was weighted based on a variance function for a binary endpoint in treatment arm *j* of study *i* exhibiting probability of event $P(event)_{ijk}$ and sample size $N_{ijk:}$

$$\sigma_{ik}^2 = P(event)_{ijk}(1 - P(event)_{ijk})/N_{ijk} \quad \text{Eq.8}$$

Since the actual probability of the event $P(event)_{ijk}$ was unknown, best estimates obtained from the fitting algorithm were used in the model. The maximum likelihood estimates of the model parameters were achieved assuming a large sample size and normal approximation to the binomial likelihood.

Model Evaluation

Candidate models were assessed using maximum likelihood criteria (Akaike Information Criterion (AIC); p-value of <0.05 denoted statistical significance) and graphical diagnostics, with observed responses plotted against population and trial-specific predictions to assess the goodness-of-fit plots (e.g., precision, absence of bias). Additionally, forest plots were employed to compare model predicted values for each study arm to their observed values. Moreover, partial residual plots were used as a graphical assessment to compare model predicted values with normalised observed values. To achieve consistency between the model prediction and the observed data, residuals from the final model were used to normalise the actual observed values to the model predicted values. A total of 1000 sets of parameter estimates were re-sampled from the variance-covariance matrix of the final MBMA model for computing confidence intervals for simulated outcomes. All analyses and simulations were conducted using generalised least squares regression functions (*gnls*) provided in the *nlme* package in R (version 3.5.3 or higher, 64 bit, running on Windows 10 Professional, SP1).

Results

Exploratory analysis of studies assessing liver safety of APAP

The literature review yielded 160 articles, 102 of which were excluded due to irrelevant interventions or outcomes, were conducted in children, or were non-clinical or observational studies, resulting in 58 articles eligible for full text review. Subsequently, 40 were excluded after full text review yielding 16 studies (18 sources), including 37 treatment arms reporting liver safety data. Lastly, a total of 15 studies were included which reported adverse events related to liver toxicity, defined as elevation in ALT/AST (Figure 5.7).

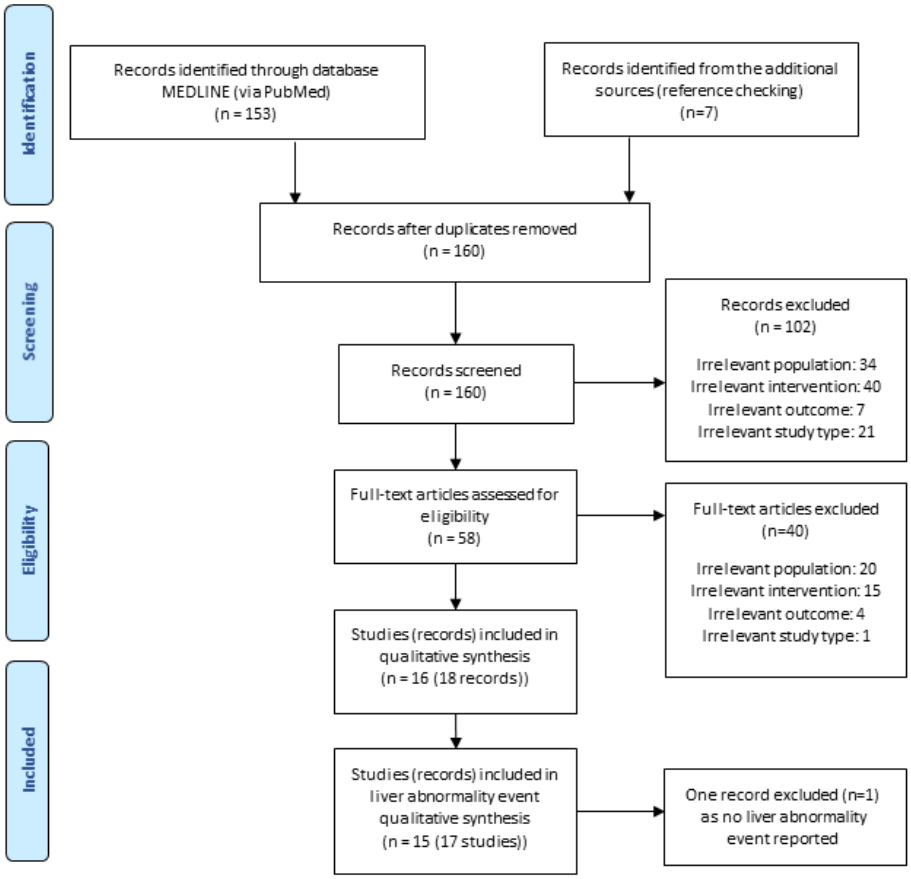


Figure 5.7. Flow chart of the screening and selection process of RCTs on acetaminophen liver safety

Nine of these studies reported absolute values of serum ALT or AST as a biomarker of liver toxicity. Also, 15 of these studies reported the elevation of ALT/AST as an adverse event, defined by the elevation of ALT/AST or liver abnormality (Table 5.3).

Of the 15 included RCTs, eight involved patients with OA pain, four were conducted in healthy subjects and the remaining three involved patients with other conditions such as asthma, glaucoma, chronic pain, and cardiovascular disease (CVD). The total daily dose of APAP was 4000 mg in 11 RCTs, 3000 mg in 3 RCTs and 2000 mg in 3 RCTs when considering some studies had more than one APAP treatment arm. The treatment duration was short (1-4 weeks) in 8 RCTs, intermediate (6-8 weeks) in 2 RCTs and long (12-26 weeks) in 5 RCTs. Moreover, the studies showed considerable variability regarding the criteria defining ALT/AST elevation or liver abnormality. Table 5.4 provides a summary of liver abnormality thresholds reported by various drug treatments in the 15 included studies and also includes treatments other than APAP and

DIC, e.g., ibuprofen, levobunolol and naproxen, to ensure development of a network MBMA analysis (Supplementary Figure S5.2).

Table 5.3. Summary of 15 RCTs included in the final analysis which reported liver safety data

Study	N	Age (in year)	Design	Blinding	Arm	Drug treatment	Endpoint	Definition category	Time (in weeks)	Population
ACTA(Pincus et al., 2001)	454	61.5	Crossover	Double blind	2	Diclofenac+misoprostol, acetaminophen	AST elevation	>0-1 ULN, >1.5-2 ULN, >3 ULN	6	OA hip/knee
Altman RD 2007(Altman et al., 2007)	483	62.2	Parallel	Double blind	3	Acetaminophen, placebo	ALT/AST elevation	>1.5-2 ULN, >3 ULN	12	OA hip/knee
Bradley JD 1991(Bradley et al., 1991)	195	56.5	Parallel	Double blind	3	Acetaminophen, ibuprofen	AST elevation	>0-1 ULN	4	OA knee
Doherty M 2011(Doherty et al., 2011)	892	60.6	Parallel	Double blind	4	Acetaminophen, ibuprofen, ibuprofen+acetaminophen	ALT elevation	>1.5-2 ULN, >3 ULN	13	OA knee
Ganetsky M 2019(Ganetsky et al., 2019)	50	29	Crossover	NA	2	Acetaminophen, acetaminophen+propylene glycol	ALT elevation	>0-1 ULN	2	Healthy volunteers/adults
GUIDE(Herrero-Beaumont et al., 2007)	212	64.2	Parallel	Double blind	2	Placebo, acetaminophen	ALT elevation	>1.5-2 ULN	26	OA knee
Heard K 2014(Heard et al., 2014)	276	33	Parallel	Triple-blind	2	Acetaminophen, placebo	ALT elevation	>0-1 ULN	2.3	Healthy volunteers/adults
Ioannides 2014(Ioannides et al., 2015)	183	39.9	Parallel	Double blind	2	Acetaminophen, placebo	ALT elevation	>1.5-2 ULN, >3 ULN	12	Mild to moderate asthma
Maeda M 2020(Maeda et al., 2020)	242	30	Parallel	Single-blind	2	Acetaminophen, placebo	ALT elevation, liver injury	>0-1 ULN, >1.5-2 ULN, >3 ULN	4	Healthy volunteers/adults
Mohamed N 2013(Mohamed and Meyer, 2013)	18	55	Parallel	Open-label	2	Levobunolol*, acetaminophen	liver injury	>3 ULN	2	Open angle glaucoma
PACES-alpha(Pincus et al., 2004)	638	63.4	Crossover	Double blind	2	Placebo, acetaminophen	liver enzymes elevation	>3 ULN	6	OA hip/knee
Parra D 2007(Parra et al., 2007)	36	70.3	Parallel	Double blind	3	Placebo, acetaminophen	ALT elevation	>1.5-2uln	4	Patients stabilized on warfarin therapy
Prior 2014(Prior et al., 2014)	542	61.7	Parallel	Double blind	2	Acetaminophen, placebo	ALT/AST elevation, ALT/AST/TB elevation	>1.5-2 ULN, >3 ULN	12	OA hip/knee

Study	N	Age (in year)	Design	Blinding	Arm	Drug treatment	Endpoint	Definition category	Time (in weeks)	Population
Temple AR 2006(Temple et al., 2006)	581	59.3	Parallel	Double blind	2	Acetaminophen, naproxen	ALT elevation, ALT/AST elevation	>1.5-2 ULN	4	OA hip/knee
Watkins P 2006(Watkins et al., 2006)	67	33.4	Parallel	Single-blind	2	Placebo, acetaminophen	ALT elevation	>0-1 ULN, >1.5-2 ULN, >3 ULN	2	Healthy volunteers/adults

*Levobunolol was administrated topically; remaining treatments were administrated orally. ALT: alanine transaminase, AST: aspartate transaminase, NA: Not applicable, TB: total bilirubin, OA: osteoarthritis, ULN: upper limit of normal

Table 5.4. Summary of the 15 RCTs included in the systematic literature search for studies investigating the liver safety of APAP showing the three elevation thresholds associated with primary drug treatment.

Drug	Patients	Trials	Arms	Trials (>0-1 uln)	Arms (>0-1 uln)	Trials (>1.5-2 uln)	Arms (>1.5-2 uln)	Trials (>3 uln)	Arms (>3 uln)
APAP	2920	15	20	6	7	10	14	9	12
DIC	227	1	1	1	1	1	1	1	1
Ibuprofen	353	2	3	1	2	1	1	1	1
Levobunolol	9	1	1	0	0	0	0	1	1
Naproxen	291	1	1	0	0	1	1	0	0
Placebo	1069	9	9	3	3	7	7	6	6
Total	**4869**	**15**	**35**	**6**	**13**	**10**	**24**	**9**	**21**

*Levobunolol was administrated topically; other treatments were administrated orally. ULN: upper limit of normal, Arms here mean treatment arms across the trials exhibiting a given ULN elevation

Figure 5.8 depicts the percentage of liver test abnormalities reported for different drugs along with their ULN thresholds. The likelihood of >1.5 ULN elevation in reference range from baseline in the liver enzyme (ALT/AST) was generally lower when compared with the likelihood of < 1.5 ULN elevation. Although the probability of elevation was >0-1 ULN for a majority of the drug treatments, a wide variability was observed in the data across the 15 studies, particularly in the APAP and placebo arms. Moreover, 9 studies reporting the time course of plasma ALT/AST showed a transient rise in liver enzymes - an initial peak, generally 2 weeks after initiation of APAP therapy, which subsequently returned to near-normal levels (Supplementary Figure S5.3 & Supplementary Figure S5.4).

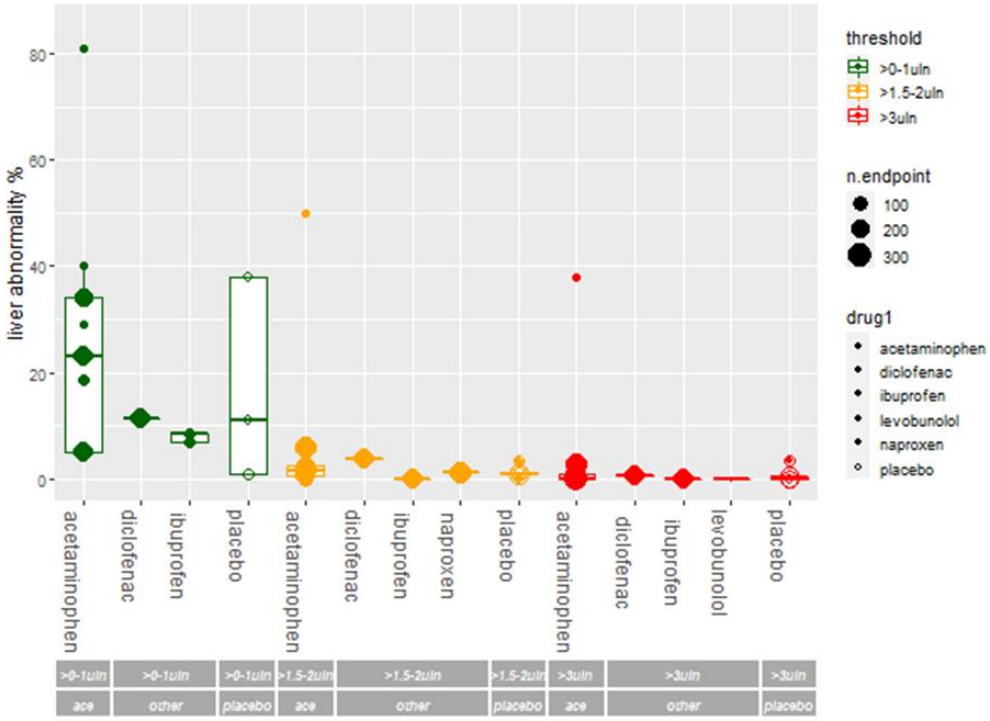


Figure 5.8. Reported liver abnormality event rate at primary time, stratified by three threshold and primary treatments. Box plot presents sample size weighted median. Dot presents each reported liver abnormality by treatment arm and threshold. Symbol size is proportional to the sample size in each treatment arm. Green symbol: >0-1 ULN elevation; yellow symbol: 1.5-2 ULN elevation; red symbol: >3 ULN elevation. ULN: Upper limit of normal, ace: acetaminophen.

MBMA of liver safety of APAP monotherapy

Out of the 15 included RCTs (including 35 treatment arms) assessing the liver safety outcomes with reported event rate of liver abnormality: 6 studies (including 13 treatment arms) reported 0-1 ULN threshold, 10 studies (including 24 treatment arms) reported >1.5-2 ULN threshold and 9 studies (including 21 treatment arms) reported >3 ULN threshold. In addition, 3 studies reported all the three thresholds, 4 studies reported two of the three thresholds and 8 studies reported either one of the three thresholds (Table 5.3).

No dose-response for the effect APAP on liver abnormality was identified from the current model, based on APAP dose range (1500-4000 mg/day) evaluated in the studies. In general, the model demonstrated adequate

performance in predicting the event rates of different thresholds when considering the 95% CI of the observed rate (Figure 5.9). Considering the limited number of studies on other drugs (Table 5.4) and no distinct differences on reported liver abnormality events for drugs other than APAP, the effect of those drugs (DIC, ibuprofen, levobunolol and naproxen) were also estimated with common shared effects on liver safety endpoints.

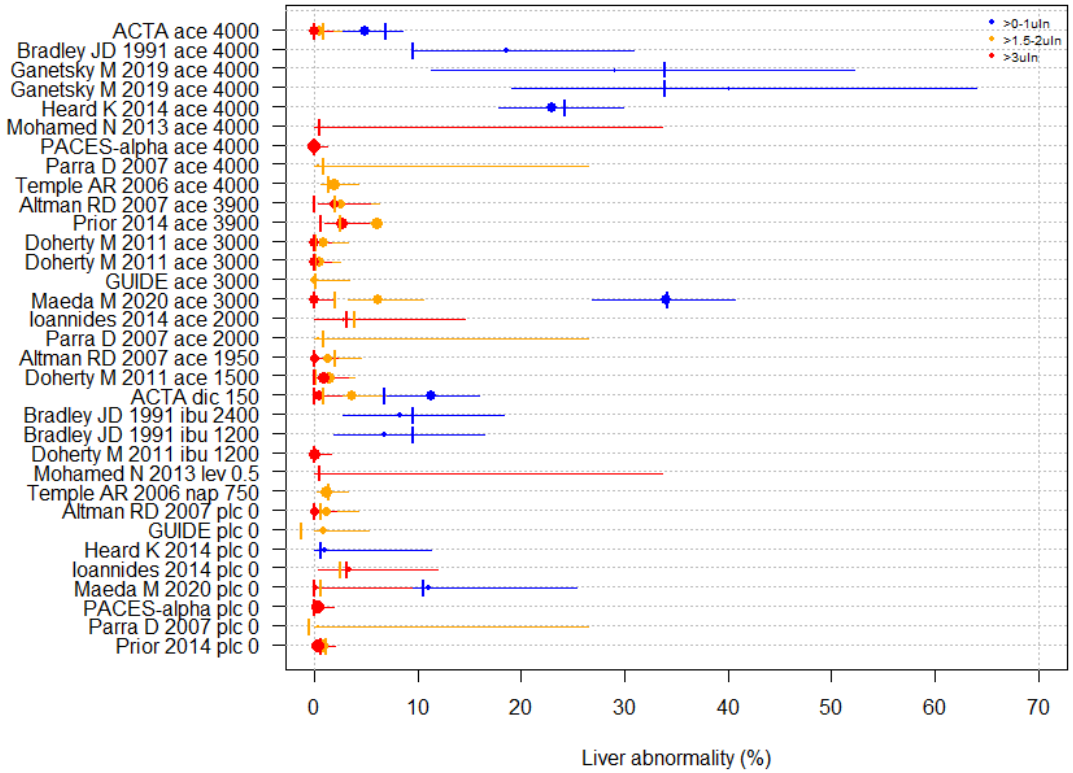


Figure 5.9. Observed (circle) and model-estimated (vertical bar) liver abnormality (+/- 95% CI) by included study/treatment arm at primary time. Colors (blue: >0-1 ULN, orange: >1.5-2 ULN, red: >3 ULN) represent different ULN-based threshold for ALT/AST elevations. Circle size is proportional to sample size of each arm. The horizontal lines present the respective 95% CIs or reported event. ace: acetaminophen; dic: diclofenac; ibu: ibuprofen; lev: levobunolol; nap: naproxen; plc: placebo

Simulations based on the maximum likelihood final model showed an increased risk of 23% for 0-1 ULN elevation in ALT/AST with APAP treatment, which corresponds to mild liver abnormality. Moreover, APAP use was associated with an extremely low risk of moderate and severe liver abnormality (1.3% and 0.01% elevation in >1.5-2 ULN and >3 ULN, respectively) when compared with background/placebo (Table 5.5). The

simulated absolute risk of liver abnormality is presented in Supplementary Table S5.9, where background/placebo were associated with 5.48% (0-1 ULN), 0.6% (>1.5-2 ULN) and 0.25% (>3 ULN) risk of liver abnormality, respectively, for different thresholds.

Table 5.5**.** Simulated placebo-adjusted liver abnormality events due to acetaminophen monotherapy

Drug	Dose (mg/day)	Threshold	% of placebo-adjusted liver abnormality (95% CI)
Acetaminophen	1500-4000	>0-1 ULN	23.58 (17.74, 29.20)
Other drugs*	NA	>0-1 ULN	23.54 (17.79, 29.08)
Acetaminophen	1500-4000	>1.5-2 ULN	1.35 (0.17, 2.51)
Other drugs*	NA	>1.5-2 ULN	1.30 (0.13, 2.46)
Acetaminophen	1500-4000	>3 ULN	0.01 (0.00, 0.32)
Other drugs*	150	>3 ULN	0.00 (0.00, 0.35)

*Other drugs include diclofenac, ibuprofen, levobunolol and naproxen. Values are mean parameter estimates based on maximum likelihood model predictions, with 95% CI of resampling parameter estimates from the final model variance-covariance matrix 1000 times. ULN: upper limit of normal

Discussion

The second objective of the current research was to assess the risk of liver abnormalities associated with the use of therapeutic doses of APAP using summary-level data extracted from RCTs conducted in healthy adult subjects and patients with OA and a range of conditions associated with analgesic and anti-inflammatory drug use. Our aim was to study whether the use of combination therapy comprising APAP and topical DIC is associated with undesirable risk of liver abnormalities, which would lead to an unfavorable benefit-risk ratio for patients with mild to moderate OA.

The MBMA conducted on 15 RCTs and including over 4,800 subjects demonstrates that use of standardized acetaminophen (≤ 4g/day) is associated with a 23%, 1.35% and 0.01% increased risk of mild, moderate, and severe hepatotoxicity (defined by deviations in liver transaminases), respectively, when compared with background/placebo. Our results have considerable clinical implications as levels of liver transaminases in the serum are the most reliable and sensitive indicators of hepatocellular injury (Al-Busafi and Hilzenrat, 2013; Ozer et al., 2008). Whilst a 23% increased risk appears

numerically large, mild elevation in liver transaminases is frequently observed in clinical practice due to non-drug factors such as obesity, and are not considered clinically meaningful because of the self-healing capacity of the liver (Navarro and Senior, 2006). In general, our findings are in agreement with two recent systematic reviews which demonstrated a greater risk of abnormal results on liver function tests in patients consuming APAP while noting that the clinical importance of the findings remains uncertain with respect to patient outcomes (Leopoldino et al., 2019; Machado et al., 2015). Additionally, the estimated risk of liver injury with APAP use is very low when compared with the risk of GI and CV toxicities and renal insufficiency associated with oral NSAIDs or the risk of delirium, falls and fractures, physical dependence and addiction inherent with opioids use (O'Neil et al., 2012). Therefore, APAP is still maintained in OA clinical practice guidelines and suggested for use in combination with topical NSAIDs to achieve better pain relief with a more favorable risk-benefit balance in pharmacological management of OA pain (Bruyere et al., 2019; Freo et al., 2021; Kolasinski et al., 2020; NICE, 2014). Additionally, APAP continues to remain conditionally recommended in individuals with intolerance of or contraindications to the use of other type of OA treatments (Kolasinski et al., 2020).

Topical NSAIDs, especially topical DIC, are generally considered to possess a favorable safety profile in the management of OA (Honvo et al., 2019a; Zeng et al., 2018) and are therefore recommended as first-line treatment by most OA guidelines before use of oral NSAIDs (Bruyere et al., 2019; NICE, 2014). APAP is still one of the most widely used analgesics across different OA populations (Conaghan et al., 2019), in spite of the recent publications doubting its efficacy in OA pain (Leopoldino et al., 2019; Machado et al., 2015). The combination of APAP and topical DIC could help patients achieve better pain relief and potentially reduce the incidences of repeated supratherapeutic ingestions of APAP, which largely occur when individuals experience insufficient pain relief and can result in worse clinical outcomes than an isolated APAP overdose (Conaghan et al., 2019; Craig et al., 2012). Additionally, considering that the safety profile of APAP is not influenced by topical DIC usage (Stanos and Galluzzi, 2013) along with the excellent safety profile of diclofenac (Wadsworth et al., 2016), the combination of the two drugs

may be helpful in monitoring the progression of patients to oral NSAIDs. Moreover, better tolerability of the combination is also likely to translate into greater adherence and result in better clinical outcomes (Barbosa et al., 2012).

The current MBMA could not identify any exposure-response relationship between APAP use and the risk of liver abnormality within the analysed dose range of 1500-4000 mg/day over 2-26 weeks of treatment. Interestingly, a meta-analysis of long-term observational studies identified such a relationship between APAP use and major adverse events (such as mortality, cardiovascular, gastrointestinal (GI) or renal AEs) and suggested considerable degrees of acetaminophen toxicity especially at the upper end of standard analgesic doses (0.5–1 g every 4–6 h to a maximum of 4 g/day)(Roberts et al., 2016). The previous report shows the potential value of using long-term observational studies when assessing the safety of APAP. However, the majority of OA clinical guidelines suggest short-term or episodic APAP use at < 3 g/day and/or ≤ 4 g/day, e.g., in elderly subjects while taking into account its analgesic effect and risk of adverse events (Bruyere et al., 2019; Kolasinski et al., 2020; NICE, 2014). The current analysis also supports the above recommendations by demonstrating short-term APAP use (≤ 4g/day) to be associated with a very low risk of clinically significant liver injury. Whilst the long-term impact of mild liver abnormality might be a cause of concern in clinical practice; however, reducing the dose or adjusting the duration of treatment can rapidly resolve the APAP triggered elevation of liver transaminases (Health, 2012).

To increase the precision of the parameter estimates characterising the drug effects, we also included 7 RCTs conducted in healthy subjects and in patients with other disease conditions (e.g., asthma, glaucoma). Although studies involving healthy subjects generally involved a younger population (mean=31.7 years) in comparison to studies conducted in diseased subjects (mean=60 years); however, no significant trend suggesting increased risk of liver abnormality with increasing age or underlying disease condition (e.g., healthy vs. OA) was observed. Although this finding contradicts existing research which shows increased risk of APAP mediated hepatotoxicity with ageing (Mitchell et al., 2011), reduced liver size in the elderly can also result in significantly less increase in transaminases when compared with a younger

population (Le Couteur and McLean, 1998). Interestingly, RCTs involving healthy subjects reported a temporary elevation in transaminases in some subjects with 4 g/day of APAP, after a mean duration of 2 weeks, which did not increase any further and was mostly resolved on APAP discontinuation (Heard et al., 2014; Maeda et al., 2020). Therefore, the impact of such short-term elevation in studies of <4 weeks duration cannot be fully ruled out and might have precluded accounting for the effect of age or disease state on APAP associated risk of liver toxicity in the MBMA. Furthermore, the relatively short duration of the included RCTs also prevented the assessment of long-term impact of APAP use on liver safety.

In addition, the results of a second MBMA study investigating the risk of liver toxicity associated with APAP use should be interpreted in the light of several limitations. First, our model does not permit any estimation of the risk of liver abnormality with APAP doses >4000 mg/day. Second, the model does not account for the effect of age as a covariate due to limited number of studies. However, our model attempts to account for the age effect as the population analysed in this model ranged from 29 to 70 years. Third, the model is developed using studies with duration ranging from 2 to 26 weeks. Therefore, the effect of APAP usage beyond 26 weeks on the underlying liver abnormality risk is uncertain. However, the probability that this pattern continues beyond 26 weeks is very high, except in case of ageing wherein the vulnerability to liver abnormality increases. Fourth, our model does not distinguish single and repeated liver abnormality events caused by APAP use, as lack of data precluded us from conducting such analysis. Finally, we note that while definitions of liver toxicity, such as liver transaminases in combination with total bilirubin or ratio of alanine transaminase to alkaline phosphatase, could have been more appropriate. However, ALT/AST elevation was considered in the study as it was the most reported outcome for hepatotoxicity across the identified studies. In addition, there was large variation in the definition of liver abnormality across the identified RCTs and choosing other definition could have resulted in increased uncertainty during analysis and difficulty in interpretation of the results.

Summary & conclusion

This chapter presented the study conducted to investigate the liver safety of the combination therapy of APAP and topical DIC in the management of mild to moderate OA pain. It included a summary of the relevant literature, results, discussion, and implication of findings. This MBMA study suggests short-term (~8 to 16-week) APAP use at standard analgesic doses (≤4000 mg/day) to be associated with a very low risk of clinically meaningful liver injury. Given these findings, the use of APAP can be considered as safe when co-administered with topical diclofenac, at least over in short term, as first-line treatment for mild to moderate OA. Although additional long-term studies are required to further assess the long-term liver safety of APAP, it is reasonable to assume that APAP use at therapeutic doses and recommended dosing regimen will show similar liver safety profile in OA patients.

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5B.3 Links and implications

The present study used a MBMA to investigate the association between the use of oral APAP and the risk of hepatotoxicity, particularly in OA management. The MBMA demonstrated APAP at standardized doses (1500-

4000 mg/day) to exhibit 23%, 1.35% and 0.01% increased risk for mild, moderate, and severe liver injury, respectively, when compared with the background/placebo rate. Moreover, at therapeutic doses, no correlation was identified between APAP intake and liver abnormality risk. Therefore, the findings of the study suggest short-term (between 8-16 weeks) APAP use at standard analgesic doses (≤4000 mg/day) to be associated with a very low risk of clinically meaningful liver injury. Given good tolerability profile of topical diclofenac, the findings support the safety of the combination of APAP and topical DIC, at least over short-term, as first-line treatment for mild to moderate OA pain.

Supplementary tables and figures

Supplementary Table S5.1. Search strategy for studies on the combination of oral acetaminophen and oral or topical diclofenac in acute pain

Area/objective		No.	Key words	Results
				MEDLINE via PubMed
I. Intervention	Ia. Diclofenac	1	**("Diclofenac"[Mesh]) OR (diclofenac [tiab] OR Diclophenac [tiab] OR Dicrofenac [tiab] OR Dichlofenal [tiab] OR "Diclofenac Sodium" [tiab] OR "Sodium Diclofenac" [tiab] OR Diclofenac, Sodium [tiab] OR "Diclonate P" [tiab] OR Feloran [tiab] OR Voltarol [tiab] OR Novapirina [tiab] OR Orthofen [tiab] OR Ortofen [tiab] OR Orthophen [tiab] OR SR-38 [tiab] OR "SR 38" [tiab] OR SR38 [tiab] OR Voltaren [tiab] OR "GP-45,840" [tiab])**	**13,438**
	Topical administration	**2**	"Administration, Topical"[Mesh] OR topical* [tiab] OR cutaneous [tiab] OR dermal [tiab] OR transcutaneous [tiab] OR transdermal [tiab] OR percutaneous [tiab] OR skin [tiab] OR massage [tiab] OR embrocation [tiab] OR gel [tiab] OR ointment [tiab] OR aerosol [tiab] OR cream [tiab] OR creme [tiab] OR lotion [tiab] OR mousse [tiab] OR foam [tiab] OR liniment [tiab] OR spray [tiab] OR rub [tiab] OR balm [tiab] OR salve [tiab] OR emulsion [tiab] OR oil [tiab] OR patch [tiab] OR plaster [tiab]	1,525,339
	Oral administration (systemic use)	**3**	"systemic use" [tiab] OR "systemic treatment" [tiab] OR "systemic therapy" [tiab] OR "systemic administration" OR "systemic" [tiab] OR "Administration, Oral"[Mesh] OR "oral administration"[tiab] OR "Oral Drug Administration"[tiab] OR "oral use"[tiab] OR "oral therapy"[tiab] OR "oral treatment"[tiab] OR oral* [tiab] OR "Tablets"[Mesh] OR tablet*[tiab] OR "Capsules"[Mesh] OR "capsule*"[tiab] OR caplet* [tiab]	1,283,569
	Ib. Acetaminophen	**4**	N-Acetyl-p-aminophenol [tiab] OR Acetamidophenol [tiab] OR N-(4-Hydroxyphenyl)acetanilide [tiab] OR "Acetaminophen"[Mesh] OR Hydroxyacetanilide [tiab] OR APAP [tiab] OR Acetaminophen [tiab] OR p-Acetamidophenol [tiab] OR p-Hydroxyacetanilide [tiab] OR Acephen [tiab] OR Acetaco [tiab] OR Tylenol [tiab] OR Anacin-3 [tiab] OR "Anacin 3" [tiab] OR Anacin3 [tiab] OR Datril [tiab] OR Acamol [tiab] OR Algotropyl [tiab] OR paracetamol [tiab] OR Panadol [tiab]	29,414
		5	#2 OR #3	2,666,226
		6	#1 AND #5	4,372
		7	**#6 AND #4**	**317**

II. Disease (pain)	**8**	(("Pain"[Mesh] OR pain [tiab] OR Pains [tiab] OR "Physical Suffering" [tiab] OR "Physical Sufferings" [tiab] OR ache [tiab] OR aches [tiab] OR "joint pain" [tiab] OR "painful knee" [tiab] OR "painful joint" [tiab]) OR (Toothaches [tiab] or Odontalgia [tiab] or Odontalgia* [tiab] OR "Toothache"[Mesh] OR "dental pain" [tiab] OR "painful bunion" [tiab])) OR ((bunionec* [tiab] OR dental [tiab]) AND ("Pain"[Mesh] OR pain [tiab]))	807,686
III. Final results	**9**	**#7 AND #8**	**199**
	10	**#9 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))**	**188**
	11	**#10 AND Filters: English**	**182**

Supplementary Table S5.2**.** Inclusion criteria for studies on the combination of oral acetaminophen and oral or topical diclofenac in acute pain

PICOS framework	Inclusion criteria
Population	Patients (no age restrictions) suffering with pain
Intervention	Combination of oral paracetamol and topical/systemic diclofenac
Comparator	NA
Outcomes	Pharmacokinetic (PK) parameters (AUC, Cl, volume of distributions), Endpoints focused on the measurement of pain reduction expressed both as a rating scale or number of patients with none, mild, moderate, severe pain
Study types	Any
Other	English

Note: No specific exclusion criteria was defined for this combination search

Supplementary Table S5.3. Reported pain score in acute pain studies

Study	Arm	Drug1	Drug2	Endpoint	Endpoint.definition	Baseline	Value	Change
Elzaki WM 2016	1	Ace		Pain score	NRS	8	2.25	-5.75
Elzaki WM 2016	2	Ace	Dic	Pain score	NRS	8	0.5	-7.5
Elzaki WM 2016	3	Placebo		Pain score	NRS	8	2.82	-5.18
Munishankar B 2008	1	Ace		Pain score	VAS at rest	NA	2	-6
Munishankar B 2008	2	Dic		Pain score	VAS at rest	NA	2	-6
Munishankar B 2008	3	Ace	Dic	Pain score	VAS at rest	NA	1.5	-6.5
Riad W 2007	1	Dic		Pain score	Pain rating scale (0-5) change	2.6	0.8	-1.8
Riad W 2007	2	Ace		Pain score	Pain rating scale (0-5) change	3.1	0.5	-2.6
Riad W 2007	3	Ace	Dic	Pain score	Pain rating scale (0-5) change	2.9	0.8	-2.1
Woo WW 2005	1	Dic		Pain score	VAS at rest	2.4	0.8	-1.6
Woo WW 2005	2	Ace		Pain score	VAS at rest	2	0.8	-1.2
Woo WW 2005	3	Ace	Dic	Pain score	VAS at rest	2.5	0.8	-1.7
Beck DH 2000	1	Ace		Pain score	VAS	NA	0.9	-1.6
Beck DH 2000	2	Ace		Pain score	VAS	NA	0.4	-2.1
Beck DH 2000	3	Ace	Dic	Pain score	VAS	NA	0.4	-2.1
Breivik EK 1999	1	Dic		Pain score	VAS	58	38	-20
Breivik EK 1999	2	Ace		Pain score	VAS	60	37	-23
Breivik EK 1999	3	Ace	Dic	Pain score	VAS	57	19	-38
Hannam JA 2014	1	Ace		Pain score	VAS	NA	NA	NA
Hannam JA 2014	2	Dic		Pain score	VAS	NA	NA	NA
Hannam JA 2014	3	Ace	Dic	Pain score	VAS	NA	NA	NA
Montgomery JE 1996	1	Ace		Pain score	VAS	NA	3.4	-4.6
Montgomery JE 1996	2	Dic		Pain score	VAS	NA	1.9	-6.1
Montgomery JE 1996	3	Ace	Dic	Pain score	VAS	NA	2.1	-5.9
Siddik SM 2001	1	Ace		Pain score	VAS at rest	NA	3.5	NA

Study	Arm	Drug1	Drug2	Endpoint	Endpoint.definition	Baseline	Value	Change
Siddik SM 2001	2	Dic		Pain score	VAS at rest	NA	2.3	NA
Siddik SM 2001	3	Ace	Dic	Pain score	VAS at rest	NA	1.5	NA
Siddik SM 2001	4	Placebo		Pain score	VAS at rest	NA	3.2	NA
Hiller A 2004	1	Ace		Pain score	VAS (0-3)	2.25	1.4	-0.85
Hiller A 2004	2	Dic		Pain score	VAS (0-3)	1.5	1.65	0.15
Hiller A 2004	3	Ace	Dic	Pain score	VAS (0-3)	2	1.2	-0.8
Matthews RW 1984	1	Ace		Pain score	VAS	NA	NA	NA
Matthews RW 1984	2	Ace		Pain score	VAS	NA	NA	NA
Matthews RW 1984	3	Ace	Dic	Pain score	VAS	NA	NA	NA

NA: no value reported

Supplementary Table S5.4. Inclusion and exclusion of studies for the development of opioid sparing effect MBMA model

Study	Population	Indication	N	Opioid PCA	Reported PCA unit	Included in final MBMA model
Montgomery JE 1996(Montgomery et al., 1996)	Women	Elective gynecological surgery	59	Morphine	Mg	Yes
Breivik EK 1999(Breivik et al., 1999)*	Adults	Oral surgery	72	Codeine/paracetamol	%	No
Beck DH 2000(Beck et al., 2000)	Women	Hysterectomy pain	65	Morphine	Mg	Yes
Siddik SM 2001[48]	Women	Cesarean pain	80	Morphine	%/mg	Yes
Hiller A 2004(Hiller et al., 2004)	Adults	Tonsillectomy	71	Oxycodone	%/mg	Yes
Munishankar B 2008(Munishankar et al., 2008)	Women	Caesarean pain	78	Morphine	Mg	Yes
Riad W 2007(Riad and Moussa, 2007)**	Children	Postoperative pain	108	Morphine	Mg	No

*study was excluded due to only reported % subjects using PCA in each treatment arm
**study was excluded due to children population

Supplementary Table S5.5. Reported opioid PCA consumption in 5 included studies

Study	Drug	Population	Endpoint	Value (mean mg)
Munishankar B 2008	ace	women	opioid PCA	54.5
Munishankar B 2008	dic	women	Opioid PCA	44.1
Munishankar B 2008	ace + dic	women	opioid PCA	33.8
Beck DH 2000	ace	women	opioid PCA	47.9
Beck DH 2000	ace	women	opioid PCA	41.5
Beck DH 2000	ace + dic	women	opioid PCA	47.4
Montgomery JE 1996	ace	women	opioid PCA	44.9
Montgomery JE 1996	dic	women	opioid PCA	34.5
Montgomery JE 1996	ace + dic	women	opioid PCA	27.1
Siddik SM 2001	ace	women	opioid PCA	61.1
Siddik SM 2001	dic	women	opioid PCA	36
Siddik SM 2001	ace + dic	women	opioid PCA	28.3
Siddik SM 2001	placebo	women	opioid PCA	66.7
Hiller A 2004	ace	adults	opioid PCA	32.8
Hiller A 2004	dic	adults	opioid PCA	27
Hiller A 2004	ace + dic	adults	opioid PCA	23.3

Supplementary Table S5.6. Summary of opioid sparing effect model development steps

NRS model development steps	Model number	Reference model	P-value versus reference model	AIC	logLik
base mod*	0			117	-51
mod0 + interaction term	1	0	0.112	117	-49
base mod, weight by se^2**	2			115	-51

NRS model development steps	Model number	Reference model	P-value versus reference model	AIC	logLik
mod2 + interaction term* **	2.1	2	0.028	113	-48

*Weighted by sample size **weighted by reported SE of mean opioid pca mg ***final model

Supplementary Table S5.7. Search strategy for the evaluation of liver safety on exposure to acetaminophen

Area/objective	S. No.	Key words	Results
			MEDLINE via PubMed
I. Intervention (acetaminophen)	1	N-Acetyl-p-aminophenol [tiab] OR Acetamidophenol [tiab] OR N-(4-Hydroxyphenyl)acetanilide [tiab] OR "Acetaminophen"[Mesh] OR Hydroxyacetanilide [tiab] OR APAP [tiab] OR Acetaminophen [tiab] OR p-Acetamidophenol [tiab] OR p-Hydroxyacetanilide [tiab] OR Acephen [tiab] OR Acetaco [tiab] OR Tylenol [tiab] OR Anacin-3 [tiab] OR "Anacin 3" [tiab] OR Anacin3 [tiab] OR Datril [tiab] OR Acamol [tiab] OR Algotropyl [tiab] OR paracetamol [tiab] OR Panadol [tiab]	29,414
II. Outcomes (liver safety)	2	"liver toxicity" OR "hepatic toxicity" OR hepatotoxicity OR "liver safety" OR ASAT OR ALAT OR aminotransferase OR "liver injury " OR "liver injuries" OR bilirubin	186,378
III. Study design (RCT)	3	random* [tiab] OR "Random Allocation"[Mesh] OR "Randomized Controlled Trial" [Publication Type] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR single blind method [tiab] OR double blind method [tiab] OR randomly [tiab]	1,364,326
IV. Final results	4	#1 AND #2	5,384
	5	#4 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh]))	3,174
	6	#5 AND #3	143

Area/objective	S. No.	Key words	Results
			MEDLINE via PubMed
	7	#6 AND Filters: English	139
	8	#5 AND Filters: Meta-Analysis, Systematic Review, English	28
	9	**#7 OR #8**	**153**

Supplementary Table S5.8. Inclusion criteria for the evaluation of liver safety on exposure to acetaminophen

PICOS framework	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 years), with no further restrictions regarding the disease type, healthy volunteers	In vitro/in vivo studies, animals' studies, children; patients who overdose paracetamol; patients consuming alcohol (including heavy/moderate drinkers, chronic drinkers etc.)
Intervention	Oral acetaminophen	Intravenous acetaminophen
Comparator	NA	
Outcomes	Hepatic aminotransferases (ALT and AST)	
Duration of therapy	At least two weeks	Less than two weeks (14 days)
Study types	RCTs	SLRs, non-RCTS, case studies, observational studies

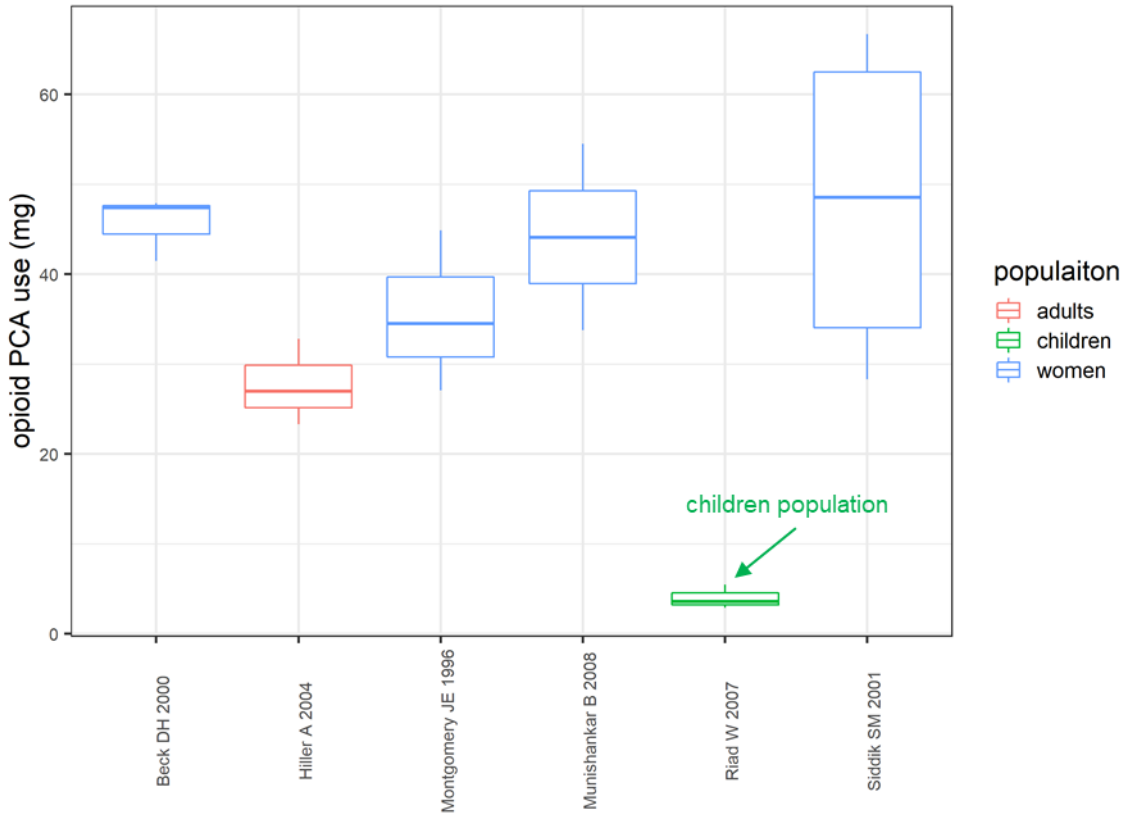
PICOS framework	Inclusion criteria	Exclusion criteria
Language	English	Others

ALT: alanine transaminase, AST: aspartate transaminase, NA: Not applicable, RCT: randomized clinical trials

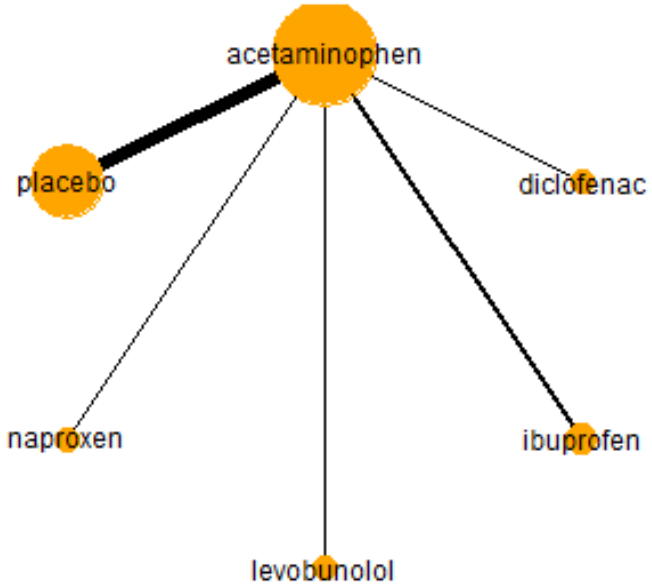
Supplementary Table S5.9. Simulated effect of acetaminophen monotherapy on % absolute liver abnormality events.

Drug	Dose (mg/day)	Threshold	% Liver abnormality (95% CI)
Acetaminophen	1500-4000	>0-1 ULN	29.06 (24.31, 33.58)
Other drugs*	NA	>0-1 ULN	29.02 (24.29, 33.55)
Placebo/background	NA	>0-1 ULN	5.48 (3.73, 7.55)
Acetaminophen	1500-4000	>1.5-2 ULN	1.95 (1.15, 3.05)
Other drugs*	NA	>1.5-2 ULN	1.9 (1.1, 3.07)
Placebo/background	NA	>1.5-2 ULN	0.6 (0.36, 1.17)
Acetaminophen	1500-4000	>3 ULN	0.26 (0.08, 0.64)
Other drugs*	150	>3 ULN	0.22 (0, 0.66)
Placebo/background	NA	>3 ULN	0.25 (0.11, 0.54)

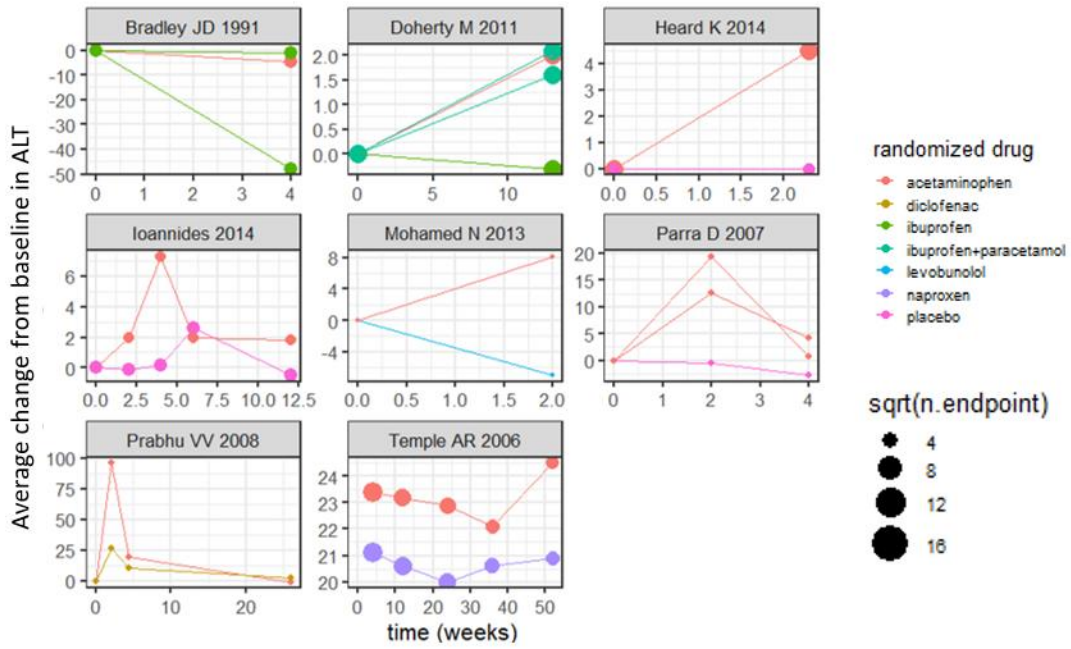
ULN: upper limit of normal; Other drugs include diclofenac, ibuprofen, levobunolol and naproxen. Values are mean parameter estimates based on maximum likelihood model predictions, with 95% CI of resampling parameter estimates from the final model variance-covariance matrix 1000 times



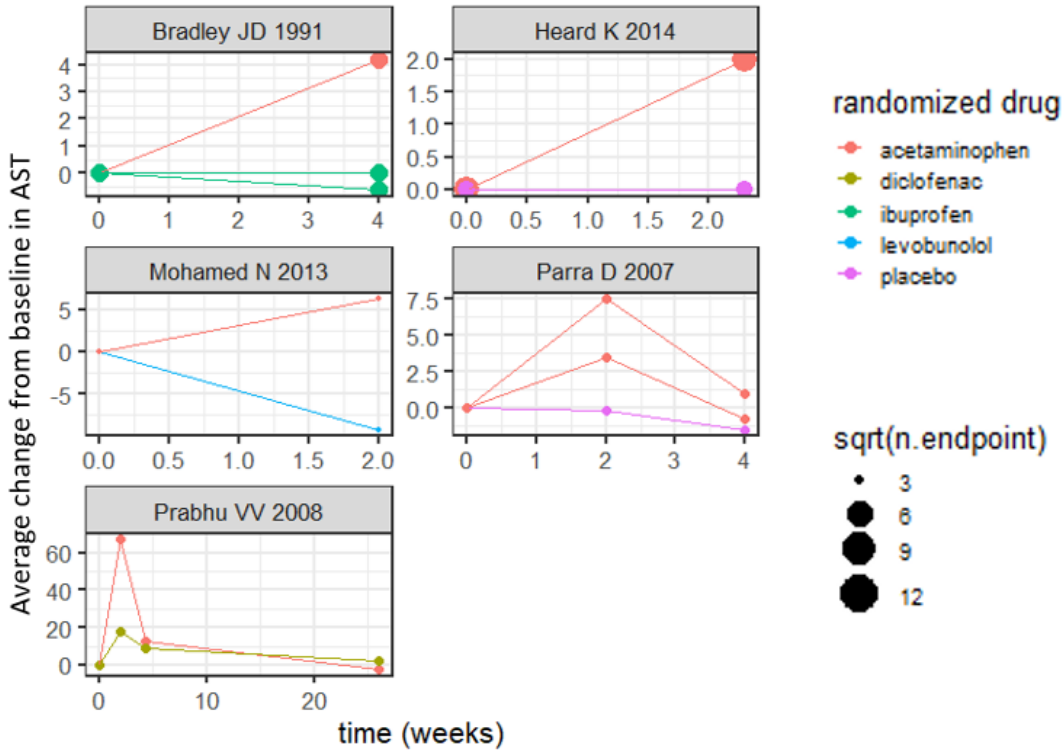
Supplementary Figure S5.1. Reported mean opioid use (mg) across 6 studies. Study “Riad 2007” was based on a population of children, and the remaining 5 studies were based on adults



Supplementary Figure S5.2. Primary/first treatment network plot of included 15 RCTs reporting liver abnormality. Levobunolol was administered topically; remaining treatments were administered orally. The width of solid lines represents the number of clinical trials



Supplementary Figure S5.3. Time course of changes in liver ALT concentrations in plasma for various studies with acetaminophen. Study “Temple AR 2006” reported absolute ALT value at given time points and hence reported no change from baseline due to missing baseline value. ALT: alanine transaminase.



Supplementary Figure S5.4. Time course of changes in liver AST concentrations in plasma for various studies with acetaminophen.
AST: Aspartate transaminase.

Supplementary R codes:

1. For the model assessing opioid sparing effect in acute pain

```
#Final model function for opioid consumption (mg) in acute pain
model= function(drug1, drug2, drug12, eo,
            emax.ace, emax.dic, #drug effect
            inc #interaction coefficient
)
{
 plc<-eo  #placebo effect

  ###---drug1 effect
 emax1=0+emax.ace*I(drug1=="ace")+emax.dic*I(drug1=="dic")

 ###---drug2 effect
 emax2=0+emax.dic*I(drug2=="dic")

 #Interaction coefficient by class combination
 inc<- 0+inc*I(drug12=="ace + dic")

 #--total drug effect
 eff=emax1+emax2+inc*emax1*emax2

#total effect of opioid consumption
 y<-plc+eff

}

#Final model GNLS call for opioid consumption (mg) in acute pain
mod1<-gnls(yo~model(drug1, drug2, drug12, eo,
              emax.ace = emax.ace, emax.dic=emax.dic,
              inc=inc),
       data=dat,
       params=list(eo~-1+study, emax.ace+emax.dic~1, inc~1),
       start= c(eo=c(rep(60, uniql(dat$study))), emax=c(-10, -10), inc=0.01),
       weights=varFixed(~1/n.endpoint),
       control = list(returnObject=T, maxIter=1000))

#final model function for liver safety
model1= function(drug1,drug1.dose,drug2,drug2.dose,time,def,yo, eo,
            emax.ace, emax.dic, emax.ibu, emax.lev, emax.nap,
            aend.m, aend.h
            )
{
 plc<-eo #placebo model

 #drug1 effect
 drugs=c("acetaminophen", "diclofenac","ibuprofen","levobunolol","naproxen")
 drug.tab<-c("",drugs)

 emax.tab<-cbind(0,emax.ace,emax.dic,emax.ibu,emax.lev, emax.nap)
```

```
 idx<-match(drug1,drug.tab,nomatch=1)

# drug effect
 emax<-emax.tab[nrow(emax.tab)*(idx-1)+1:nrow(emax.tab)]

 # additive threhold effect
 eff.drug<-emax+ aend.m*I(def==">1.5-
2uln"&drug1.dose>0)+aend.h*I(def==">3uln"&drug1.dose>0)

#drug effect
 eff=eff.drug

# total effect
 yp<-plc+eff
 yp
}
```

2. For the model assessing liver safety of acetaminophen

```
#final model function for liver safety
model1= function(drug1,drug1.dose,drug2,drug2.dose,time,def,yo, eo,
            emax.ace, emax.dic, emax.ibu, emax.lev, emax.nap,
            aend.m, aend.h
            )
{
 plc<-eo #placebo model

 #drug1 effect
 drugs=c("acetaminophen", "diclofenac","ibuprofen","levobunolol","naproxen")
 drug.tab<-c("",drugs)

 emax.tab<-cbind(0,emax.ace,emax.dic,emax.ibu,emax.lev, emax.nap)

 idx<-match(drug1,drug.tab,nomatch=1)

# drug effect
 emax<-emax.tab[nrow(emax.tab)*(idx-1)+1:nrow(emax.tab)]

 # additive threhold effect
 eff.drug<-emax+ aend.m*I(def==">1.5-
2uln"&drug1.dose>0)+aend.h*I(def==">3uln"&drug1.dose>0)

#drug effect
 eff=eff.drug

# total effect
 yp<-plc+eff
 yp
}
```

```
#Final model GNLS call for liver safety
mod1.02<-gnls((yo) ~ model1(drug1,drug1.dose,drug2,drug2.dose,time,def,yo, eo,
                    emax.ace=emax.ace,
                    emax.dic=emax.ibu,emax.ibu=emax.ibu,emax.lev=emax.ibu,
emax.nap=emax.ibu,
                    aend.m=aend.m, aend.h=aend.h,
                    b.time=0),
          params=list(eo~-1+data.group, emax.ace+emax.ibu~1,
                   aend.m+aend.h~1),
          start= c(eo=c(mod1.011$coefficients[1:uniql(dat$data.group)]),emax=c(0.2,0.1),
end=c(-0.2, -0.2)),
          data=dat,
          weights= varPower(0.5,form=~p(1-p)/n,fixed=0.5),
          control=gnlsControl(returnObject=T,sigma=1))
```

CHAPTER 6: DISCUSSION & CONCLUSION

6.1 Discussion

Chronic pain is the hallmark symptom of osteoarthritis (OA) and results in significant disability, reduced quality of life in older adults and is the major reason for patients to seek medical care. In the absence of a curative treatment, symptomatic drugs (paracetamol (APAP), oral non-steroidal anti-inflammatory drugs (NSAIDs), opioids) comprise the backbone of pain management in OA. However, as the elderly population is the most impacted by this debilitating condition and exhibit multiple comorbidities, oral NSAIDs and opioids pose a significant risk of serious adverse effects on long-term use. Additionally, APAP has recently been shown to exhibit modest efficacy in OA pain. However, this can be attributed to the “tomato effect” which involves rejection or non-recognition of highly efficacious treatments because they do not ‘‘make sense’’ in the light of accepted theories and is highly prevalent in the field of rheumatology (Goodwin and Goodwin, 1984). The recent arguments in favor of lack of efficacy associated with APAP in OA pain can therefore be attributed to other factors such as the lack of meaningful and reliable clinical instruments to measure pain relief rather than the drug as it has been used beneficially in OA pain treatment for several decades.

Therefore, considering the above discrepancy in scientific evidence and clinical practice, we designed an exploratory study to gather the clinical perspectives of healthcare professionals (HCPs) in OA pain in real-world settings using Delphi methodology regarding the use of APAP alone or in combination with topical NSAIDs. Our results showed that a majority of HCPs still considered oral APAP as the gold standard treatment for the management of mild to moderate OA pain in real-world clinical settings despite scientific evidence suggesting otherwise.

Growing evidence suggests OA pain encompasses inflammatory and non-inflammatory pain transmission pathways at both peripheral and central levels of the nervous system. Considering the multi-mechanistic nature of OA pain, combined use of APAP and topical diclofenac, which have

complementary mechanisms targeting pain and inflammation, can be a potential therapy option to achieve effective pain relief in OA pain. However, whilst OA guidelines also recommend concomitant use of topical NSAIDs with acetaminophen in cases of inadequate pain relief with APAP monotherapy, there is an evidence gap on the use of this combination in OA pain. Therefore, we conducted a model-based meta-analysis (MBMA) to evaluate the efficacy of the combination of APAP and topical diclofenac versus the monotherapies by leveraging published clinical evidence on the combination therapy from acute pain indications. Our analysis indicated greater pain reduction and opioid sparing effect for the combination therapy versus APAP monotherapy. Additionally, we conducted a separate MBMA to assess the liver safety of acetaminophen. Our analysis suggested short-term (~8 to 16-week) APAP use at standard analgesic doses (≤4000 mg/day) to be associated with a very low risk of clinically meaningful liver injury. Therefore, given the good tolerability of topical diclofenac, these findings support the safety of the combination of acetaminophen and topical diclofenac, at least over short-term, as a first-line treatment for mild to moderate OA pain.

6.2 Knowledge gap and research propositions

This dissertation aimed to address several gaps in the literature, including (a) the perceptions and clinical practice behaviours of HCPs towards use of oral APAP as monotherapy or in combination with topical NSAIDs for OA pain management after the recent updates in the OA clinical practice guidelines which downgraded oral APAP from first-line treatment to conditionally recommended in mild to moderate OA pain, (b) the efficacy of combination treatment of oral APAP and topical diclofenac versus APAP and DIC monotherapies in mild to moderate OA pain, and (c) the association between use of oral APAP and risk of liver toxicity, mainly in OA management.

It was anticipated that there would be no major change in the clinical practice behaviours and perspectives of HCPs on the benefits and risks of oral APAP either as monotherapy or in combination with topical NSAIDs for OA pain management despite the recent downgrading of APAP by clinical practice guidelines for OA.

The study then proposed that the combination of oral APAP and topical diclofenac would exhibit greater pain score reduction and opioid sparing effects than APAP and NSAIDs (topical diclofenac) monotherapies in the management of OA pain.

Lastly, the study proposed that there would be no significant risk of liver toxicity with use of oral APAP at therapeutic dosages.

6.3 Response to research questions

Research Question 1: What are the current treatment behaviours and perspectives of expert HCPs on the benefits and risks of APAP as monotherapy or in combination with topical NSAIDs for OA pain management considering the recent changes/updates in the clinical practice guidelines recommendations?

The research began by conducting a qualitative study using the consensus-forging Delphi methodology to gather the real-world clinical practice behaviours and perspectives of different categories of expert HCPs (orthopaedic specialists, general practitioners, and senior pharmacists) from three diverse geographies (including Australia, Malaysia, and Sweden) towards use of APAP as monotherapy or in combination with topical NSAIDs in the management of mild to moderate OA pain.

The results of the study showed that all panel members supported APAP use in OA patients while exercising the necessary caution in cases with liver or GI complications despite recent evidence suggesting APAP monotherapy to be associated with inadequate pain relief in OA patients (Bannuru et al., 2010; Machado et al., 2015). Our findings were in line with a recent study which demonstrated that APAP continues to remain universally accepted by HCPs in real-life settings for the management of mild to moderate OA pain despite reports suggesting it to provide modest pain relief in all patients with OA (Freo et al., 2021).

In addition, the HCPs were generally unaware of the recent changes in the OA guideline recommendations especially towards the use of APAP and unanimously agreed that any changes in recommendations to those guidelines in the next 3 to 5 years would have minimal impact on their

prescription practice towards the use of APAP. The lack of awareness of panel members to changes in guideline recommendations could be explained by the presence of different OA guidelines with differing recommendations being followed within the respective countries. For instance, guidelines from two different societies/organisations were referenced in Malaysia - the American Academy of Orthopedic Surgeons (AAOS) and the MOHM OA guidelines. The AAOS guideline recommended APAP monotherapy for pain relief and function in knee OA (American Academy of Orthopaedic Surgeons, 2021), whereas the guideline by MOHM recommended adjuvant use of topical NSAIDs with oral APAP (Malaysia Health Technology Assessment Section (MaHTAS), 2013). The above scenario calls for a need to standardise the recommendations of OA clinical practice guidelines for quick and timely uptake among the HCPs community.

The study also demonstrated the prescribing rate for combination treatment to be highest among the orthopaedists (95%-100%), followed by GPs (30%-80%) and pharmacists (30-50%). This could be attributed to differences in severity levels of OA pain consulting different specialties, e.g., patients with more severe pain were more likely to consult orthopaedists than GPs or pharmacists (Musila et al., 2011). This was an interesting discrepancy where real life practice suggested a strong use of combination therapy despite a lack of supporting scientific evidence.

Although the HCPs were supportive of the use of combination therapies of oral APAP with oral NSAIDs, they exhibited a lack of confidence in the combination therapy of APAP with topical NSAIDs. This was primarily attributed to an absence of strong scientific evidence on their efficacy. In addition, lack of awareness of the benefits and mechanism of action (MOA) of topical NSAIDs was another major reason behind their low popularity among the HCPs. However, the majority of the panel members (87.5%) were open to considering increasing the prescription of topical NSAIDs, despite their preference for oral NSAIDs, in the management of OA pain considering the latest updates in major OA guidelines which recommend topical NSAIDs as a first-line agents (Bannuru et al., 2019; Bruyere et al., 2019).

The absence of scientific evidence on the efficacy of combined therapy of APAP and topical NSAIDs as highlighted above in the Delphi study stimulated the second phase of the research, which involved searching for evidence on combination treatments in OA pain. Therefore, we designed our second phase of the research with an aim to identify existing clinical evidence on the effectiveness and tolerability of the combination treatment in OA pain before conducting a model-based meta-analysis (MBMA) on the extracted summary-level data identified.

Research Question 2: How effective is the combination treatment of oral APAP and topical diclofenac when compared with APAP and DIC monotherapies in mild to moderate OA pain?

While the combination treatment is commonly used in real-world settings with more than a quarter of patients using topical NSAIDs with oral non-opioid analgesics such as APAP (Jackson et al., 2017), there is a scarcity of literature available on the combination of oral APAP and topical NSAIDs (Bell et al., 2019). Our literature search found no clinical studies on the combination of APAP+DIC in OA pain.

Since a growing body of evidence shows overlap in the pain signaling pathways between chronic OA pain and acute pain (Mease et al., 2011) and given that analgesic and anti-inflammatory mechanisms of the two drugs (i.e., APAP and topical DIC) are similar in both acute and chronic pain setting, we decided to extrapolate the effect of combination treatment of APAP+DIC from clinical studies conducted in acute pain setting using pain score reduction and opioid sparing effect as clinical endpoints.

Overall, the combination showed greater pain score reduction compared to APAP alone, mainly for RCTs not allowing opioid PCA use. Moreover, the MBMA of RCTs identified in acute postoperative pain showed a beneficial effect with combination treatment in terms of reduction of opioid use (in RCTs allowing PCA) when compared with acetaminophen monotherapy. The above finding has significant clinical implications considering the widespread opioid use and the serious concerns on the risk of side-effects, addiction, and overdose deaths due to them. In addition, opioid use is associated with significantly greater structural damage, faster progression of degenerative

changes, significantly greater pain, worse symptoms, and a lower quality of life when compared with control (Bodden et al., 2021).

Research Question 3: What is the risk of liver toxicity associated with oral APAP, especially when used in OA pain management?

The second part of the MBMA study aimed to assess the risk of liver toxicity associated with therapeutic doses of APAP monotherapy defined by deviations in the levels of liver transaminases (ALT/AST) in plasma. For this purpose, RCTs reporting the effect of APAP treatment on liver abnormality outcomes were identified through literature searches before implementing an MBMA on the extracted summary-level data. The MBMA, conducted on 15 RCTs and covering over 4800 subjects, demonstrated that APAP use at therapeutic doses (≤ 4g/day) over short-term (~8 to 16-weeks) is associated with a 23%, 1.35% and 0.01% increased risk of mild, moderate, and severe hepatotoxicity, respectively, when compared with the background rate. Our findings have significant clinical implications as levels of liver transaminases in the serum continue to remain the most reliable and sensitive indicators of hepatocellular injury (Al-Busafi and Hilzenrat, 2013; Ozer et al., 2008). Although a 23% increased risk of liver injury appears numerically large, mild elevations in liver transaminase levels are frequently observed clinically and are not considered clinically meaningful because of the large self-healing capacity of the liver (Navarro and Senior, 2006).

In summary, our MBMA shows greater pain reduction and opioid sparing efficacy for the combination of oral APAP and topical DIC versus APAP alone by leveraging clinical evidence from acute pain setting. However, the combination effect was less conclusive when compared with DIC monotherapy. Since OA pain is mediated by both nociceptive and neuropathic mechanisms that share similarity with acute pain which is primarily of nociceptive origin (Committee for Medicinal Products for Human Use, 2016; Mease et al., 2011), the observed beneficial effect of combination treatment in acute pain can be extrapolated to chronic OA pain settings with high probability. The MBMA assessing liver safety of APAP showed that short-term APAP use at therapeutic doses is associated with no clinically

meaningful risk of liver abnormality. Further, since topical DIC is generally considered to exhibit high tolerability, our analysis supports the clinical use of this combination therapy, at least over short-term, as first-line treatment for mild to moderate OA.

6.4 Contributions

The research presented in this investigation showed the panel of experts to reach a high level of consensus on several topics based on of existing data and experiences from real-world practice. Most HCPs agreed that APAP continues to remain the mainstay option for all the HCPs despite the recent downgrade by clinical practice guidelines in OA. This discrepancy in scientific evidence and clinical practice can mostly likely be attributed to the “tomato effect” which involves rejection or non-recognition of highly efficacious treatments because they do not ‘‘make sense’’ in the light of current accepted theories (Goodwin and Goodwin, 1984). This is also suggestive of lack of meaningful, valid and reliable clinical instruments to measure pain relief in OA pain trials which traditionally rely on measuring subjective measures of pain relief that exhibit high likelihood to confounding by placebo effect.

Moreover, the HCPs still have a favorable opinion supporting the combination of oral APAP and topical NSAIDs in mild to moderate OA pain despite the existence of very little clinical evidence on the topic. In addition, the results of the MBMA study have shown the combination of oral APAP and topical DIC to be more effective than APAP monotherapy for pain score reduction and opioid sparing in the management of mild to moderate OA pain. It has been reported that OA patients were 1.2 times more likely to exhibit any comorbidity than non-OA controls and 2.5 times more likely to exhibit ≥3 comorbidities (Swain et al., 2020). Our findings advance the evidence-base on a potential treatment option for the majority of OA patients who, in spite of having higher rates of several comorbidities, are still being treated with analgesics such as oral NSAIDs and opioids that can be associated with a worsening in comorbidity (Fallach et al., 2021). The investigation also provides insights into the mechanism of pharmacokinetic and pharmacodynamic (PK/PD) relationships between the two interacting analgesics and allows for a prediction of the treatment effect. Additionally, the opioid sparing effect observed with the combination therapy vs.

acetaminophen monotherapy has considerable clinical implications when considering the significant risks of adverse effects associated with opioid intake, including development of opioid use disorder (dependency and addiction), overdose fatalities, respiratory depression, falls, and other negative effects on gastrointestinal, endocrine, immune and nervous system (Gewandter et al., 2021). Opioid consumption has also been shown to be associated with significantly greater structural damage and faster progression of degenerative changes when compared with no opioid consumption (Bodden et al., 2021).

Our analysis shows short-term use of APAP at therapeutic doses to be devoid of any clinically relevant risk of liver toxicity. This opens the door for a new valuable treatment option for the ever-increasing aging population suffering from OA, especially those who are restricted from moving to stronger analgesics such as oral NSAIDs and opioids due to CV and GI comorbidities. Additionally, the combination treatment might allow OA patients to achieve adequate pain relief with standard doses of APAP. This will help to potentially limit the incidences of APAP poisoning due to repeated supratherapeutic ingestions which are overdoses with therapeutic intent when taken for symptoms such as pain of APAP and are associated with worse clinical outcomes than isolated acetaminophen overdose (Craig et al., 2012). This information will be helpful to a range of stakeholders including individual patients, clinicians, policy makers and other health care providers. Moreover, it will be helpful in formulating rational treatment algorithms for OA and will stimulate guideline development groups to reconsider their recommendations, especially the first-line drug treatments for mild to moderate knee OA. However, given topical diclofenac is indicated for the treatment of localised OA pain (Herndon, 2012), the combination treatment is expected to be of greater benefit to OA population with pain localized to a few superficial joints, such as the knees and hands.

This research has also confirmed the use of the Delphi method as a qualitative method in forming a consensus on topics where there is complexity or uncertainty. Additionally, the Delphi method is a structured and information-rich process and involves systematically combining the collective knowledge and experience of experts to reach a consensus. Moreover, given

the limited predictive validity of OA pain models for testing the efficacy of novel analgesics under development (Suokas et al., 2014), our research also reiterates the usefulness of MBMA methodology as a valid tool to predict the efficacy of new treatments in one indication by extrapolating the evidence from studies conducted in another indication.

At the time of writing, this dissertation is the first research to evaluate and synthesise clinical evidence on the efficacy of the combination of oral APAP and topical DIC in the management of mild to moderate OA pain. Our exploratory study is the first of any type of consensus study that explores current clinical practice behaviours of HCPs on the APAP alone or in combination with NSAIDs after the spate of recent updates to clinical practice guidelines in OA. Although the results of the MBMA and Delphi study together are not fully conclusive, they do suggest that the combination of oral APAP and topical DIC can be an effective and well-tolerated option for patients with early-stage disease who have not yet moved to stronger systemic analgesics such as oral NSAIDs and opioids.

6.5 Limitations

Specific limitations within individual studies have been highlighted in their relevant chapters. There are, however, some limitations that are applicable to several sets of clinical evidence. These centre mainly on small sample size due to the constraints in the recruitment of expert HCPs or are due to insufficient data which precludes an analysis of the effects of major covariates impacting the results and thus results in the introduction of estimation bias and reduction in the precision of model estimates.

The main limitation of the first study of the thesis, which explored clinical practice behaviours and perspectives of expert HCPs using the Delphi methodology, was the small sample size of each HCP type which limits the generalisability of the findings to a wider HCP population. However, since this was designed to be an exploratory study, the findings could serve as a framework for further research into this line of enquiry with a larger sample size of each HCP type. Additionally, the results of the Delphi method represent a snapshot of expert opinions at a specific point in time (Hasson et al., 2011) and not indisputable facts. Nonetheless, the expert consensus

provided by the Delphi method is stronger and more structured than the consensus obtained from focus group meetings or conferences.

The MBMA study of the dissertation also had some limitations. One cardinal limitation of the analysis was the use of summary-level data, which was not enough to fully address the research questions involving quantification of exposure-response for combination treatment or bridging and extrapolation across pain indications. Second, the combination effect was predicted by adding treatment effect to the non-parametric placebo response. As there was only one placebo-controlled study to inform placebo response on the opioid sparing effect in acute pain (Siddik et al., 2001), this may have resulted in some degree of estimation bias. Third, as the analysis in acute pain was conducted on limited number of studies having small sample size, the impact of study-level variations on model precision cannot be ruled out with the power and reliability of the pooled estimates also impacted as suggested by the wide range of simulated CI. Fourth, the variation in severity levels of acute pain induced due to different types of surgeries could have resulted in high variations in the mean consumption of opioids (e.g., a higher dose of PCA is needed in caesarean surgery vs. tonsillectomy) which could not be accounted for in the current model owing to a lack of studies. Fifth, the applicability of our analysis conducted for the opioid sparing effect in acute pain to the OA patients is limited due to inadequate number of patients in the 5 included trials. Sixth, the efficacy of the drug regimen is governed to a large extent by compliance with the regimen (Dockerty et al., 2016). However, as there was no compliance related information available in the included studies, the model does not account for the effect of compliance as a covariate.

Our second MBMA study, assessing the risk of liver toxicity associated with APAP use, also had limitations which could mainly be attributed to the minimal number of available studies. First, our model does not permit any estimation of the risk of liver abnormality with APAP doses above 4000 mg/day or beyond 26 weeks. Second, the model does not account for the effect of age as a covariate, nor does it distinguish single and repeated liver abnormality events caused by APAP use. Thirdly, there was large variation in the definition of liver abnormality across the identified RCTs which led us to consider liver

transaminases elevation in our study as it was the most reported outcome for hepatotoxicity across the identified studies despite other more appropriate definitions of liver toxicity, such as liver transaminases in combination with total bilirubin or ratio of alanine transaminase to alkaline phosphatase. This could lead to limited applicability of the findings in the general population.

6.6 Recommendations for future research

The work described within this thesis has identified several potential areas for future research:

1. Additional research with a larger HCPs sample size is warranted to support the findings of the Delphi study and to provide suggestions or recommendations necessary to initiate potential changes in clinical practice guidelines.
2. Further research based on the development of quantitative systems pharmacology (QSP) models and informative biomarkers, which provide rapid indication of pharmacologic responses to a therapeutic intervention, is warranted to assess the clinical significance of pharmacodynamic interactions between the drugs and optimise the dose regimen for the combination.
3. Additional studies are required to further assess the long-term liver safety of APAP and to better understand the effective dose of APAP in its combination regimen with topical DIC to achieve effective pain relief in OA without any significant safety complications over long-term use.
4. Given topical diclofenac is indicated for the treatment of localised OA pain, additional research is also needed to confirm the beneficial effect of the combination treatment particularly in population with OA pain localized to a few superficial joints, such as the knees and hands rather than generic OA pain while also accounting for potential confounding factors such as treatment compliance.

6.7 Reflections

The study adopted a work-based learning approach to conducting the research. In essence this approach aims to provide an opportunity for working professionals to acquire a systemic and critical understanding of a substantial and complex body of knowledge at the frontier of their area of

professional practice. Further, it seeks to integrate practice knowledge and understanding with theoretical knowledge as presented in the extant literature. Work-based learning seeks to achieve authentic learning facilitated through professional reflective practice thereby supplementing their enquiry (van der Laan and Neary, 2016). In addition to executing their research program, practitioner researchers interrogate their professional practice within its various contexts and multi-disciplinary knowledge foundations. They identify the emergence of new knowledge while developing and demonstrating professional capabilities associated with being a 'scholarly professional'.

This approach therefore appealed to me as a pathway for personal and professional development in addition to scholarly expertise as it allowed me to undertake learner-driven research of a topic of interest with the capacity to contribute significantly to my existing organisation and the field of osteoarthritis pain management.

Early in my research journey I was asked by my supervisor to complete an extensive self-reflective practice exercise that articulates my key personal and professional learning during the course of my life. This experience was extremely rewarding and encompassed a wide range of personal attributes and professional roles which ensured that I had an extensive list of experiences from which to identify my learnings. As a result of the above reflective analysis, I identified my top five most productive learning areas and professional capabilities as - communication skills; problem-solving; collaboration and/teamwork; emotional intelligence; and analytical skills. On the other hand, my least prolific areas were creativity and innovation; work methods and process logic; critical judgement; technology adoption; and information management and dissemination.

From the reflection, I was asked to develop learning objectives that would underpin this study and consider, not only my academic contributions but also my personal growth and development as a scholarly professional. These objectives are listed below:

1. To develop high level research skills and knowledge by using big data and machine-learning technologies on the use and efficacy and safety

of combination therapy (paracetamol and topical NSAIDs) for OA pain relief in real-world settings and documenting them in research articles to generate meaningful scientific knowledge.

The above learning objective addressed the areas of limited development relating to work methods and process logic, adoption of technology and information management and dissemination as identified from my self-reflection.

2. To enhance critical thinking skills by objectively analysing research studies on the combination of paracetamol and topical NSAIDs and assessing their quality and applicability prior to implementation of big data technologies.

The above learning objective addressed the area of limited development related to critical judgement as identified from my self-reflection.

3. To establish significant intellectual contributions in the body of knowledge in osteoarthritis pain relief by investigating the efficacy and safety of the combination of oral paracetamol and topical NSAIDs and opening the door for a new therapy option for this debilitating disease.

The above learning objective addressed the areas of limited development relating to creativity and innovation.

4. To develop advanced communications skills appropriate to top-tier medical professionals by using effective communication strategies to compose and support my research.

The above learning objective contributed to enhancing my communications skills to a higher level and allowed me to communicate more efficiently with executive management within my organisation.

The above objectives were created with an aim to establish quantifiable and significant evidence-based contributions at three different levels: individual, organisation, and knowledge. Firstly, at an individual level, focusing on areas where I had less exposure to specific learning areas and capabilities to enhance my development both personally and professionally. The program allowed me to learn in authentic work contexts on the practical application of

AIML on real world data and contributed substantially to my self-awareness and intellectual independence. Secondly, achieving the learning objectives also helped to create original knowledge that is relevant and meaningful to my professional capabilities and will also serve to build capacity in my professional practice environment as my current organisation lags in the use of AIML technologies. Lastly, the field of osteoarthritis pain management, an area of research that significantly impacts millions of elderly people across the globe, also benefited from new knowledge on a promising new therapy option.

Challenges are a universal facet of human experience. I also faced several challenges during the doctoral program. Firstly, the area of artificial intelligence and machine learning (AIML) was completely new for me. I had to learn as a novice but in such a way that the work could be executed as an expert. This was the biggest challenge faced and for which I invested a lot of personal time at various phases of work to come up with the best approach within a stipulated timeline. The research work also put my work-life balance to the test several times as I juggled various commitments - a full-time professional, a student, and a mother of two young children. However, the flexibility provided by my open-minded supervisor and employer about the hours and location for the work ensured that I was able to find the best fit for the day-to-day research and writing requirement and allowed me to remain productive and ultimately meet the deadlines. Lastly, carrying out doctoral research involves a lot of independent work that can make one feel lonely. Fortunately, I had a caring and supportive family and a great peer support group created by my supervisor, Dr Luke Van der Laan, to fall back upon in times of need.

Having reached this point and based on my reflections above I now appreciate that I ticked a lot of boxes under the achievements. However, I can also reflect on some areas where I would have done differently. Firstly, there were instances when I felt overwhelmed by the uncertainty of the results which would unfold for the research hypothesis. Secondly, whilst I successfully managed vast amounts of data and converted it into user-friendly information, there were times when I felt challenged by the flood of data and would therefore have wanted to improve my ability to manage

information. Despite these issues, I am content that the learning journey transpired the way it did. It revived my passion for exploring new avenues of learning, provided me with a great depth of knowledge and bestowed a true feeling of discovery.

6.8 Conclusion

This investigation showed that paracetamol remains the primary option for all the HCPs in the real world despite the recent downgrade by clinical practice guidelines in OA. Additionally, a majority of the HCPs have a favorable opinion supporting the combination of oral APAP and topical NSAIDs in mild to moderate OA pain. However, a lack of clinical evidence prevented widespread prescription of the combination therapy by the HCPs. Although several recently updated international guidelines for OA recommend the addition of topical DIC in cases of inadequate pain relief with oral APAP monotherapy, the clinical evidence on the combination use of oral APAP and topical DIC is non-existent in OA. Our first MBMA showed the combination of oral APAP and topical DIC to exhibit greater pain reduction and opioid sparing efficacy than APAP monotherapy in the treatment of acute pain. Given the overlap in pain signaling pathways between acute and chronic OA pain and the complementary mechanisms of the two drugs, comparable performance can be anticipated for the combination on extrapolation to chronic OA pain. Additionally, our second MBMA demonstrated short-term APAP use (~8 to 16-week) at standard analgesic doses (≤4000 mg/day) to be devoid of any clinically relevant risk of liver toxicity. Thus, the findings of the 2 MBMAs support the use of APAP when co-administered with topical diclofenac as an effective and safe, at least over the short-term, first-line treatment option for mild to moderate OA.

The results of the Delphi and MBMA studies have provided a foundation of evidence regarding the effectiveness of oral APAP and topical DIC in the management of mild to moderate OA pain but have also highlighted large gaps in current research. Future research in this area would be justifiable and worthwhile in the form of larger consensus studies, mathematical modelling studies based on quantitative systems pharmacology (QSP) and long-term clinical studies assessing APAP liver safety to guide the development of recommendations for treatment guidelines on the concomitant use of this

combination. At present, though the current research indicates that the combination of oral APAP and topical DIC can be an effective and well-tolerated option, there is insufficient evidence regarding the dosage regimen for both the therapies to be followed. More work is needed before formal guideline recommendations can be formulated for use in clinical practice on the validity of this combination therapy for the management of mild to moderate OA pain.

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