Investigation into Inappropriately Prescribed Analgesia and Patient Care: Focus on Gabapentinoids, Neuropathic Pain and the Role of Community Pharmacy

Jawza Meaadi Alotaibi
(B. pharm, MSc (Clinical Pharmacy), BCNSP)

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Translational and Clinical Research Institution
Faculty of Medical Sciences
Newcastle University

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Thesis Abstract

The prescription of gabapentinoids has significantly increased over the past few years for managing neuropathic pain as a safe alternative to opioids. There have been growing concerns about the abuse potential of gabapentinoids, putting patients with neuropathic pain at risk. Therefore, in April 2019, gabapentinoids were reclassified as a controlled substance in the United Kingdom (UK) to tackle their misuse. The main focus of this thesis was to assess the safety of gabapentinoids in the management of neuropathic pain for adults, including their potential for misuse and abuse, as well as to clarify the role of community pharmacists (CPs) in tackling the misuse risk associated with gabapentinoids.

Firstly, a systematic review and meta-analysis were conducted according to the PRISMA guidelines to investigate the published evidence for the safety of gabapentinoids (*e.g.,* addictive potential and adverse events) (Chapter 2). A search of the MEDLINE (Ovid), EMBASE (Ovid), Web of Science, PsycoINFO, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) was performed. A total of 50 studies met the inclusion criteria. Most adverse events pertained to the nervous system (12 effects) or psychiatric (4 effects) disorders. Pregabalin was associated with more adverse events (36 effects) than gabapentin (22 effects). There was no evidence of addiction to gabapentinoids found. The euphoria was the only adverse event that may correlate with addiction potential, which was reported in six of 29 studies of pregabalin, but not for gabapentin. The literature suggests that gabapentinoids are significantly more frequently misused when taken in conjunction with an opioid analgesic, however the included studies' design did not consider gabapentinoids and opioid drug combinations, and therefore this was not investigated.

To further investigate the abusive potential of gabapentinoids, the *in-vivo* study was carried out to investigate the reinforcing efficacy of pregabalin after exposure to morphine self-administration (Chapter 3). The study was carried out on 12 *naïve* rats (adult male Sprague Dawley). After surgery, rats were trained in operant boxes. Each rat went through three phases: (1) acquisition phase (exposure to morphine), (2) extinction phase (exposure to saline), and (3) reinstatement phase (re-exposure to morphine followed by pregabalin). A significant difference was observed between the number of active lever responses maintained by pregabalin in the reinstatement phase compared to the extinction phase (P=0.0038). The *in-vivo* study concluded that pregabalin might have a reinforcing efficacy when substituted for

self-administering morphine in *naïve* rats.

To tackle gabapentinoid misuse and the evolving role of pharmacists in providing patients care, it is worthwhile to understand how CPs deal with this problem. Another systematic review (Chapter 4) was conducted to synthesise the existing literature on CPs-led interventions and the role of pharmacists in this area. A search of the EMBASE (Ovid), MEDLINE (Ovid), Web of Science and Scopus was undertaken. Six studies conducted in the USA and Ireland were included. The identified CP-led interventions were mapped to the Behaviour Change Wheel (BCW) to investigate the pharmacist and patient behaviours addressed by the interventions. Intervention functions addressing patient and pharmacist behaviours comprised education, training, enablement, and environmental restructuring. One study also identified restrictions as an intervention function targeting patient behaviour.

There was limited evidence about CP-led interventions and a lack of clarity about the role of CPs in identifying analgesia misuse. A qualitative interview study (Chapter 5) was next conducted to explore the perspectives of CPs about addressing inappropriately prescribed analgesia (IPA). Semi-structured interviews informed by the BCW and the Theoretical Domains Framework (TDF) were conducted with 12 CPs. Nine TDF domains were identified as relevant to addressing IPA. Seventeen behaviour change techniques (BCTs) were identified that could be considered in the design of future interventions to facilitate the involvement of CPs in identifying IPA.

In summary, the findings presented in this thesis provide a comprehensive safety profile of using gabapentinoids in patients with neuropathic pain. Despite gabapentinoids' adverse events on the nervous system, they did not appear to cause addiction in RCTs. However, since the self-administration study concluded that pregabalin might have reinforcing properties when substituted for morphine, further investigations are required to confirm this observation, particularly given the literature suggesting that gabapentinoids are significantly more frequently misused when taken in conjunction with an opioid analgesic. Finally, although there is limited evidence of CPs-led interventions to tackle IPA, this thesis provides an in-depth explanation and understanding of the barriers and facilitators to addressing this issue from the perspectives of CPs. Given the growing role of CPs in providing effective patient care, findings may help inform strategies to involve CPs in tackling this significant issue.

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Presentations

1- **Meaadi J**, Nazar H, Obara I. (2019) A systematic review of the evidence on the use and safety of gabapentinoids in the management of neuropathic pain. North East Postgraduate Conference 2019. Newcastle Upon Tyne, UK. (Poster presentation).

2- **Meaadi J**, Nazar H, Obara I. (2019) Current state of safety profile for using gabapentinoids in the management of neuropathic pain: A systematic review and meta-analysis. British Pharmacological Society annual meeting, Pharmacology 2019, Edinburgh, UK. (Oral presentation).

3- **Meaadi J**, Obara I, Nazar H. (2022) A qualitative study to investigate community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia. First International Conference of Deprescribing 2022, Kolding, Denmark. (Poster presentation).

4- Meaadi J, Obara I, Nazar H. (2022) A qualitative study to investigate community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia. Polypharmacy and Ageing – Individualized, Person-Centered Care meeting 2022, Prague. (Poster presentation).

Publications

Chapter 2

1- **Meaadi J**, Obara I, Eldabe S, Nazar H. The safety and efficacy of gabapentinoids in the management of neuropathic pain: a systematic review with meta-analysis of randomised controlled trials. *Int J Clin Pharm*. 2023 Feb 27.

DOI: 10.1007/s11096-022-01528-y

Chapter 4

2- Mills VG, **Meaadi J**, Nazar H, Obara I. A review and narrative synthesis of community pharmacist-led interventions to tackle medicines for pain that are misused. *Int J Pharm Pract*. 2022 Aug 9;30(4):305–14.

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Chapter 5

3- **Meaadi J**, Obara I, Nazar H. A qualitative study to investigate community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia. *Int J Pharm Pract*. 2023 March

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4- Podcast: The Pharmaceutical Journal, PJ, October 2023, Vol 311, No 7978;311(7978)::DOI:10.1211/PJ.2023.1.198751

Awards and Achievements

1. **Award for Excellence** (2019/2020) from the Saudi Arabian Cultural Bureau, London, UK.
2. **Board Certified Nutrition Support pharmacy (BCNSP)** 2020. Credential # 2150317
3. Professional Diploma in leadership and management, 2020.
4. Doctoral College Enhancement Fund for a Conference/Travel Bursary (2021/2022). **One month** at the UKRI Stipend Rate (£15,609 per annum for 21/22 academic year) to be paid monthly.
5. **Opioid Stewardship®** - A Certificate Program for Healthcare Professionals, 2021.
6. **Postgraduate certificate in clinical trials**, University of Edinburgh, 2021.
7. **Award for Excellence** (2021/2022) from the Saudi Arabian Cultural Bureau, London, UK.

List of Scientific Courses, Workshops, and Certificates

1- Introduction to statistics course at Nottingham University, 2019.

2- A systematic review and critical appraisal at York University, 2019.

3- Good Clinical Practice (GCP) certificate, 2019.

4- Academic Integrity & Plagiarism at Newcastle University, 20219.

5- Research Ethics – Application at Newcastle University, 2019.

6- Thesis Writing course at Newcastle University, 2019.

7- Managing Long Documents at Newcastle University, 2019.

8- Statistical Considerations in Experimental Research at Newcastle University, 2019.

9- Introduction to EndNote at Newcastle University, 2019.

10- Introduction to SPSS programme at Newcastle University, 2020.

11- Improving healthcare through clinical research, University of Leeds, and National institute for Health Research, 2020.

12- Evidence-base medicine in clinical pharmacy practice, Taipei Medical University, 2020.

13- Clinical supervision: planning your professional development, University of East Anglia, 2020.

14- Project management: Beyond the basics, The Open University, 2020.

15- Advancing in Academia: Health Sciences course, King's College London, 2020.

16- Introduction to NVivo at Newcastle University, 2021.

17- Introduction to learning and Teaching in Higher Education (ILTHE) course, Newcastle University, 2021.

18- Analysis of qualitative data course, social research association, 2021.

19- Good Clinical Practice (GCP) Refresher eLearning, 2021.

Preface

Thesis Structure

To meet the main aim and subsequent objectives of this research, the thesis was delivered into chapters, as outlined below:

Chapter 1: Introduction.

Chapter 2: Current safety profile for gabapentinoids in the management of neuropathic pain: a systematic review and meta-analysis.

Chapter 3: Pregabalin self-administration in *naïve* rats.

Chapter 4: State-of-the-art review and narrative synthesis of CPs-led interventions to tackle misused analgesia.

Chapter 5: Community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia: A qualitative study.

Chapter 6: Discussion and thesis Conclusions.

Chapter 7: References.

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Author's Declaration

I confirm that the work presented in this thesis is my own, and at the time of submission is not being considered for any other academic qualification. Where information has been derived from other sources, I confirm that this has been indicated in this thesis.

Jawza Alotaibi

April 2023

Abbreviations

Abbreviation	Full name
AERS	Adverse event reporting system
BMI-MTM	Brief Motivational Interviewing and Medication Therapy Management
BCTs	Behaviour change techniques
BCTTv1	Behaviour change techniques taxonomy version 1
BCW	Behavioural change wheel
CASP	Critical Appraisal Skills Programme
CAT	Community addiction team
CCGs	Clinical Commissioning Groups
CD	Controlled drug
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CMS	Chronic medication service
CNS	Central nervous system
COM-B	Capability, Opportunity, and Motivation model of Behaviour
CP	Community pharmacist
CPD	Continuing Professional Development
CPP	Conditioned Place Preference
CPCF	Community Pharmacist Contractual Framework
CPCS	Community Pharmacist Consultation Service

Abbreviation	Full name
CT	Computerised tomography
DMS	Discharge medicines service
DN4	Douleur Neuropathique 4 questions
DPN	Diabetic peripheral neuropathy
EC50	Half maximal effective concentration of a drug
EPL	Laser evoked potential
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GPs	General practitioners
HMM	Harm Minimisation Model
HIV	Human immunodeficiency virus
IASP	International Association for the Study of Pain
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IPA	Inappropriately prescribed analgesia
IUM	Inappropriate use of medications
IV	Intravenous
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LAT	L-amino acid transporter
LAs	Local Authorities
LC	locus coeruleus
MCR	Medicines, Care and Review service
MRI	Magnetic resonance imaging
NA	Noradrenaline
NeuPSIG	Neuropathic Pain Special Interest Group

Abbreviation	Full name
NHS	National health service
NIAVS	National Influenza Adult Vaccination Service
NICE	National Institute for health and Care Excellence
NMDA	N-methyl-D-aspartate
NMS	New medicine service
NNH	Number needed to harm
NNT	Number needed to treat
NPQ	Neuropathic Pain Questionnaire
NRS	Numerical rating scale
ONE-Re	Opioid and Naloxone Education programme
QoL	Quality of life
ORT	Opioid misuse Risk prevention Toolkit
OTC	Over the counter
PDMP	Prescription drug monitoring programme
PD-Q	Pain detects questionnaire
PGIC	Patients' Global Impression of Change scale
PHN	Postherpetic neuralgia
PIM	Potentially inappropriate medication
PMR	Patients medical record
POMI	Prescription opioid misuse index
ProCE	PROvider of Continuing Education for medical professionals
PROMPPT	Proactive clinical Review of patients taking Opioid Medicines long-term for persistent Pain led by clinical Pharmacists in primary care Teams.
PSNC	Pharmaceutical Services Negotiating Committee
PVC	Polyvinyl chloride
QST	Quantitative sensory testing

Abbreviation	Full name
RCTs	Randomised controlled trials
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance framework
ROB	Risk of bias
RPS	Royal Pharmaceutical Society
RR	Risk ratio
SAC	Stoma Appliance Customisation
SMC	Standard medication counselling
SNRIs	Serotonin and Norepinephrine Reuptake Inhibitors
STOPNEP	Study of the Prevalence of Neuropathic Pain
STTT	Sort Throat Test and Treat
TDF	Theoretical Domains Framework
T_{max}	Time to peak drug concentration
$t_{1/2}$	Half-life of a drug
UK	United Kingdom
USA	United States
VAS	Visual analogue scale
VDCC	Voltage-dependent calcium channels
WHO	World health organisation

Chapter 1 Introduction

1.1 Pain

Pain is a highly distressing sensation resulting from injury or intense stimuli that manifests itself as unpleasant feelings. There is a high likelihood that every individual will experience some level of pain at some point in their lifetime. There is no doubt that pain is a personal experience that is affected by biological, psychological, and social factors to varying degrees. Pain is one of the most common reasons for seeking medical treatment. (1) The causes and impact of pain are numerous, and it is itself a highly sophisticated biological phenomenon. Defining pain is difficult, which is reflected in the clinical wisdom that "*pain is what the patient describes it as*". (2)

However, the International Association for the Study of Pain (IASP) defined pain as "*an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described regarding such damage*". (3) There have been several advances in our understanding of pain in its broadest sense over the past few decades that warrant re-evaluating and revising this definition. It has been interpreted that the earlier definition depends on verbal communication (reporting from patients) and excludes non-verbal behaviours as an indication of pain among disempowered and neglected populations (*e.g.,* neonates and the elderly). Moreover, the old definition did not consider the cognitive and social factors that contribute to the experience of pain.

In 2020, the IASP introduced a new definition of pain after a two-year process of review and revision. (4) The revised definition is "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*". The revised pain definition has been modified further to include several aspects, such as those who suffer from pain but are unable to explain or describe it (such as the elderly and infants), a person with cognitive or mental disabilities, and an animal experiencing pain. As part of the revision process, the Task Force consulted with a number of stakeholders, including clinicians, researchers, philosophers, and the general public, which included people with pain and their caregivers. Figure 1.1 shows the updated notes accompanying the new definition of pain. The updated notes accompanying the revised definition of pain provide a better understanding of the factors influencing a patient's experience of pain. This may lead to better communication between the patient and healthcare providers, contributing to better assessment and management of pain.

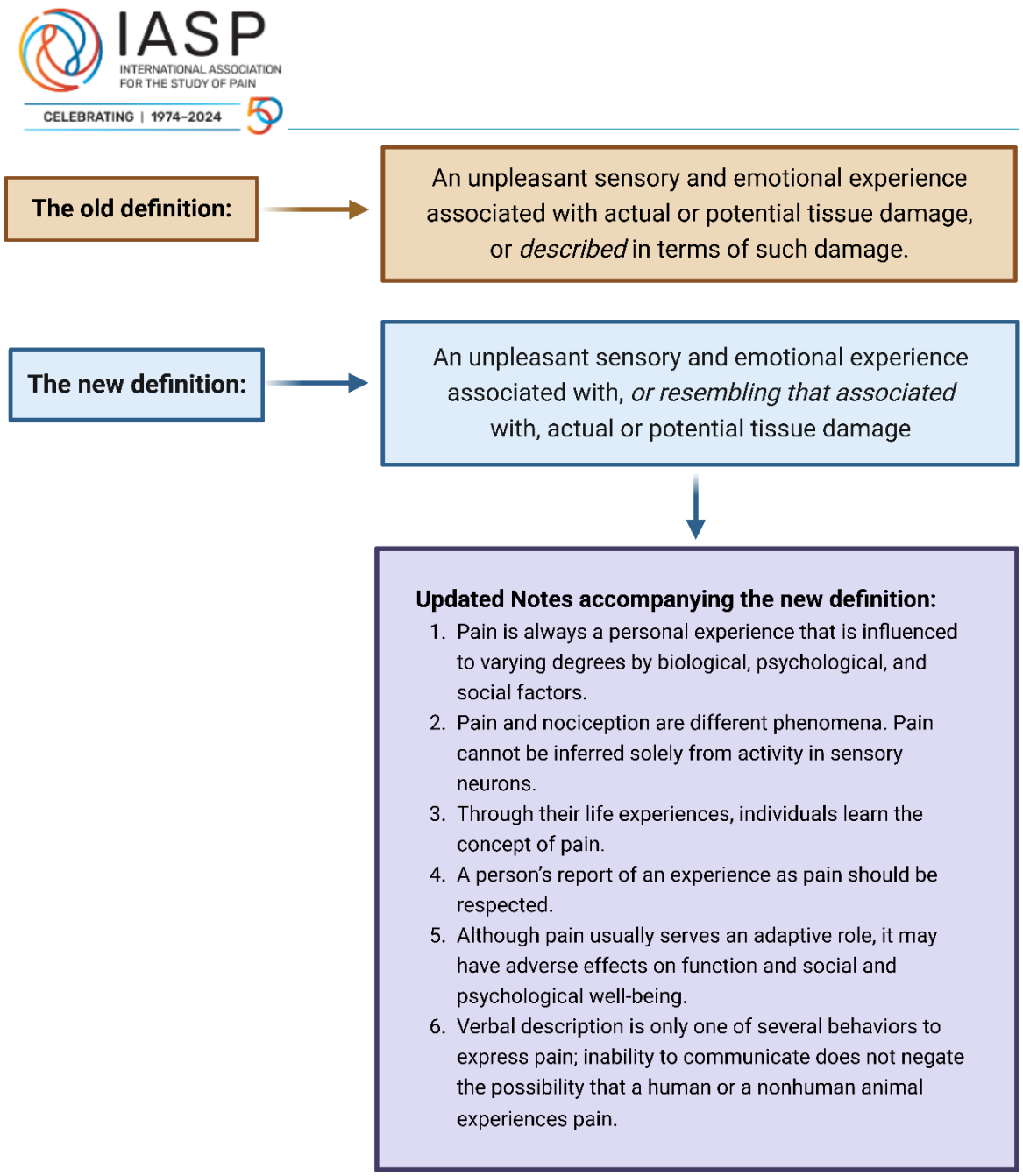


Figure 1-1. *The old and revised definitions of pain according to IASP. Adapted from references. (3,4) Created with BioRender.com.*

1.1.1 Classification of pain

Classifying pain is necessary to assess and diagnose patients with pain and can also assist healthcare professionals in selecting the most appropriate treatment plan for their patients. (5) It is possible to classify pain in different ways due to its heterogeneity in duration, aetiology, intensity or pathophysiology. Moreover, there may be an overlap between different classifications. (5)

The two well-known classifications based on the duration of time that a patient experiences pain are acute and chronic. Acute pain is short-term and lasts from a few minutes to less than three months of onset whenever the underlying cause is treated or healed. (3,6,7) It is the body's response as a protective mechanism to some injury or trauma to protect the body from serious internal damage. (5) On the other hand, chronic pain is defined as pain that lasts for more than three months and persists beyond the normal healing process. (3,6,7) The prevalence of chronic pain is estimated to be 20 % worldwide. (8) It is considered one of the most sophisticated and distressing public health issues, producing a substantial socioeconomic burden. (9) Chronic pain negatively affects the patient's perceptions and emotions, as well as the patient's family, caregivers, and social life. (5,9)

In general, chronic pain is classified based on the pathophysiology of the disease into three main categories: nociceptive, nociplastic, and neuropathic. (10,11) Nociceptive pain develops as a consequence of tissue injury resulting from trauma, non-healing injury or inflammatory processes that evoke pain receptors called nociceptors. (12) While nociplastic pain is pain that occurs when the pain signals are processed abnormally without any evident tissue damage or discrete pathology affecting the somatosensory system. (12,13) Furthermore, neuropathic pain refers to pain that occurs after nerves or sensory pathways within the brain or spinal cord have been injured. (12,13) Neuropathic pain seems to have a higher intensity, lasts longer, and is more likely to remain unrecoverable compared to other types of chronic pain. (11) Neuropathic pain refers to pain that is induced by a lesion or damage to the neurons responsible for signalling pain in the nervous system. (1,14) This damage can be caused by disease (*e.g.,* diabetes), infection (*e.g.,* human immunodeficiency virus (HIV) infection), or injury. (15) In addition, neuropathic pain may also happen in conditions of unknown aetiology, such as idiopathic neuropathies. (16)

1.2 Neuropathic pain

1.2.1 Definition and clinical manifestation

In 1994 the IASP defined neuropathic pain as "*pain initiated or caused by a primary lesion or dysfunction in the nervous system*". (17) Nevertheless, the definition of neuropathic pain has not been widely accepted. (17,18) The term "dysfunction" has been considered vague and does not specify what the term encompasses. In light of this, some non-neurological chronic pain, such as irritable bowel syndrome arising from central dysfunctions of the nociceptive systems, can be considered neuropathic according to this definition. (17,18) Therefore, in 2008, the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP proposed a new definition of neuropathic pain as "*pain arising as a direct consequence of a lesion or disease affecting the somatosensory system*". (19) In the updated definition, neuropathic pain is restricted to the somatosensory system to differentiate it from other kinds of pain, such as musculoskeletal pain that may arise from disorders of the motor system. (17,18) The term "primary" was also excluded from the revised definition because it is difficult to differentiate between primary and secondary causes of neuropathic pain. (17,18)

Neuropathic pain is a condition caused by various aetiologies and can be classified into peripheral and central neuropathic pain based on its pathophysiology. (20,21) Peripheral neuropathic pain is pain caused by a lesion or injury to the peripheral somatosensory nervous system, such as diabetic peripheral neuropathy (DPN). (21) Whilst central neuropathic pain occurs because of injury or disease to the central somatosensory nervous system (brain and spinal cord). (13,21) For instance, pain associated with multiple sclerosis, stroke, and pain associated with spinal cord injury. (13) Despite the different aetiologies that can lead to neuropathic pain, many of these conditions exhibit similar clinical features, leading to the belief that similar mechanisms can explain different types of neuropathic pain. (22)

Neuropathic pain is a complex disease that adversely affects the quality of life (QoL) of patients and daily activities, such as physical, psychological, and social wellbeing. (23) The main clinical features are (ongoing or intermittent) spontaneous pain and evoked pain, as shown in figure 1.2. Patients with neuropathic pain often describe the pain as a burning sensation, shooting, stabbing, or tingling. (24) Spontaneous pain episodes are sometimes characterised by intermittent electric shock sensations with or without ongoing pain, while

evoked pain may seldom occur without spontaneous pain. (24) In light of this, it is evident that spontaneous and evoked pain arise from different mechanisms or may be caused by overlap mechanisms, but preservation or loss of specific afferent nerve fibres defines the presence or absence of evoked pain. (25)

Spontaneous neuropathic pain might occur as a result of ectopic action potential in somatosensory pathways or by a summation of evoked pain induced by daily activities while peripheral and central sensitisation are present. (21,24–26) Evoked pain is generated by normally non-painful (allodynia) or by strong stimuli that increase sensitivity around the site of injury (hyperalgesia). (24,25)

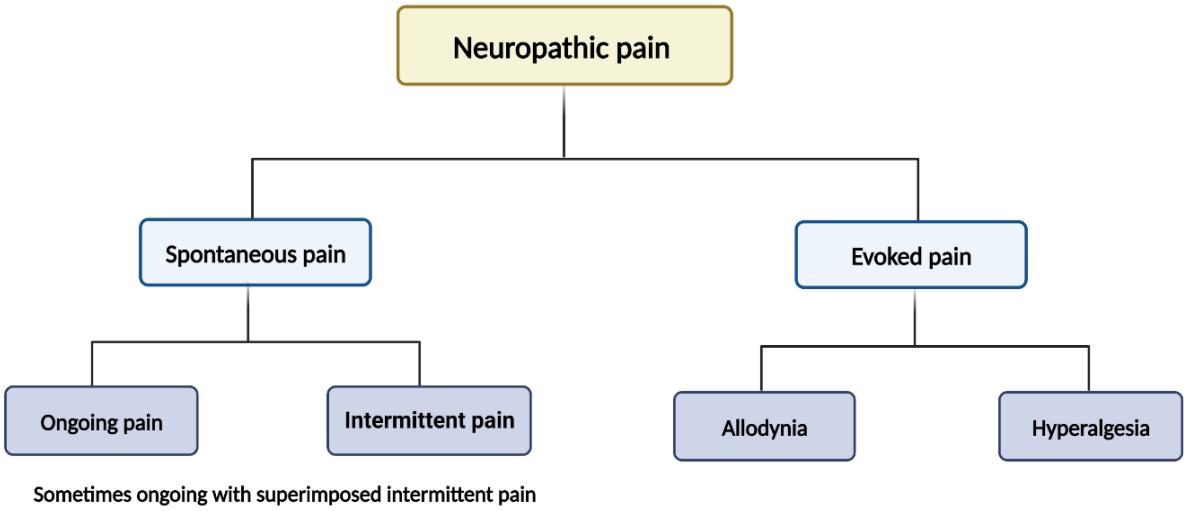


Figure 1-2. *Neuropathic pain elements. Figure reproduced with permission from the publisher. (11) Created with BioRender.com.*

Certainly, neuropathic pain may present with a combination of positive and negative signs and symptoms. (16,27) Positive signs and symptoms indicate a gain in the somatosensory system function, such as paraesthesia (a burning or tingling sensation usually felt in the extremities), spontaneous pain, and increased pain sensation (hyperalgesia). (27) Negative signs and symptoms demonstrate loss of somatosensory function (*e.g.,* hypoalgesia and hypoaesthesia). (16,28) Figure 1.3 shows some characteristics of positive and negative signs and symptoms of the neuropathic pain condition. However, patients with nociceptive pain may also show negative signs, meaning those characteristics are still not specific to neuropathic pain. (29,30)

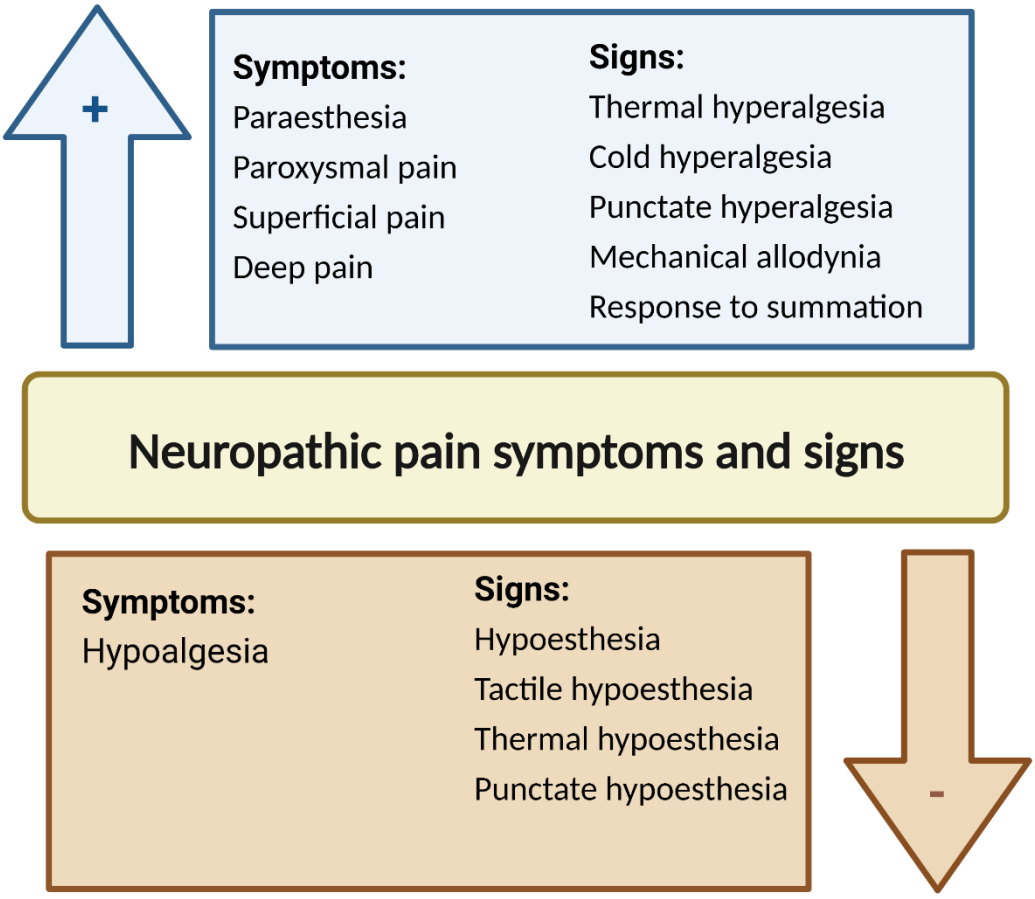


Figure 1-3. *Summary of the main clinical features of the neuropathic pain condition. (-) Negative symptoms and signs indicate a loss of function in the somatosensory system, and (+) positive symptoms and signs indicate a gain of function in the somatosensory system. Figure used with permission from the publisher. (30) Created with BioRender.com.*

1.2.2 Diagnosis and assessment of neuropathic pain

Pain intensity can range from mild to severe depending on the stage of the neuropathic condition and the degree of nerve damage and injury. Due to the complexity of neuropathic pain, its diagnosis is determined by a detailed medical history and a physical examination since there is a lack of definitive diagnostic tests available to diagnose neuropathic pain. (31) Therefore, a clinician, to diagnose it as accurately as possible, should conduct an appropriate clinical examination in addition to taking a comprehensive medical history. (32) It may be necessary to carry out further diagnostic investigations to confirm the diagnosis and aetiology or to reduce the potential list of possible causes. (32) For example, numerous causes of painful neuropathy can be treated, which can be detected and diagnosed by blood tests such as those secondary to cobalamin (vitamin B12), folate deficiency, or alcohol-induced neuropathy. (32)

As mentioned previously, the detection of somatosensory positive and negative signs and symptoms in the region affected by the damaged nervous system often ensures the diagnosis and can avoid the need for unnecessary additional tests. It is important to note that the methods used for diagnosing neuropathic pain are divided into two stages: (1) using screening tools at primary care, and (2) using different instruments at secondary care.

Various screening tools have been designed and developed in the form of questionnaires to summarise the characteristic (positive and negative) symptoms of neuropathic pain. There are two clinician-administered questionnaires (the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), (33) and the Douleur Neuropathique 4 questions (DN4), (34) and three patient-completed questionnaires (Neuropathic Pain Questionnaire (NPQ), (35) ID Pain,(36) and painDETECT (PD-Q) (Table 1.1). (37) However, these screening tools are unable to identify approximately 10–20 % of patients clinically diagnosed with neuropathic pain. (38) These findings suggest that they may provide useful guidance for further diagnostic evaluation and pain assessment, but they cannot replace the use of clinical judgment. (38)

Type of administration	**Clinician administered**		**Self-completed**		
Screening tools	**LANSS**	**DN4**	**NPQ**	**ID Pain**	**PD-Q**
Number of questions	7	10	12	6	7
-Questions about symptoms	✓	✓	✓	✓	✓
- Questions about signs	✓	✓	×	×	×
Validity	✓	✓	×	×	×
Sensitivity	83%	66.6%	83%	Not assessed	85%
Specificity	87%	74.4%	90%	Not assessed	80%

Table 1-1. *Description of neuropathic pain screening tools. Adapted with permission from the publisher. (39) LANSS: Leeds Assessment of Neuropathic Symptoms and Signs, DN4: Douleur Neuropathique 4 questions, NPQ: Neuropathic Pain Questionnaire, and PD-Q: painDETECT.*

In terms of using the instrument in a secondary setting, there are many approaches that need training and specialist skills. Some examples of these methods are quantitative sensory testing (QST), electrophysiological testing (*e.g.*, laser evoked potential (EPL), nerve conduction), structural neuroimaging, and neurobiopsy. (32)

QST and EPL have become crucial as early assessment tools for fibre monitoring in symptomatic or asymptomatic patients. (32,40) QST is a psychophysical test that measures

the severity of sensory deficits and quantifies both the function of large and small nerve fibres. (41) The primary role of QST in neuropathic pain is to determine whether a lesion in the somatosensory system exists. (32) LEP is a neurophysiological method considered the easiest and most reliable tool to assess nociceptive pathways. (42)

Using structural neuroimaging, such as computerised tomography (CT) and magnetic resonance imaging (MRI), can aid in diagnosis by identifying causes of central and peripheral nervous tissue disorders, such as ischemia, demyelination, and compression. (32) However, the changes seen during an MRI cannot differentiate between painful and non-painful nerve lesions, but they can aid in supplementing a differential diagnosis for nerve disease. (32)

An example of electrophysiological tests is nerve conduction studies, which are electromyography and somatosensory evoked potentials that can confirm a neuropathic pain but only measure function in large myelinated fibres. (41)

A nerve biopsy is an invasive procedure that samples only one site, usually the sural nerve (Figure 1.4). (32) Due to the complexity of this procedure, it cannot be performed sequentially, making it impossible to monitor the progress or improvement of neuropathic pain. (41)

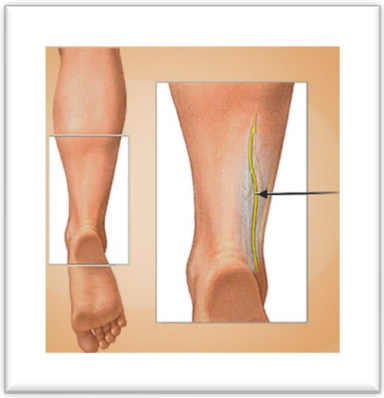
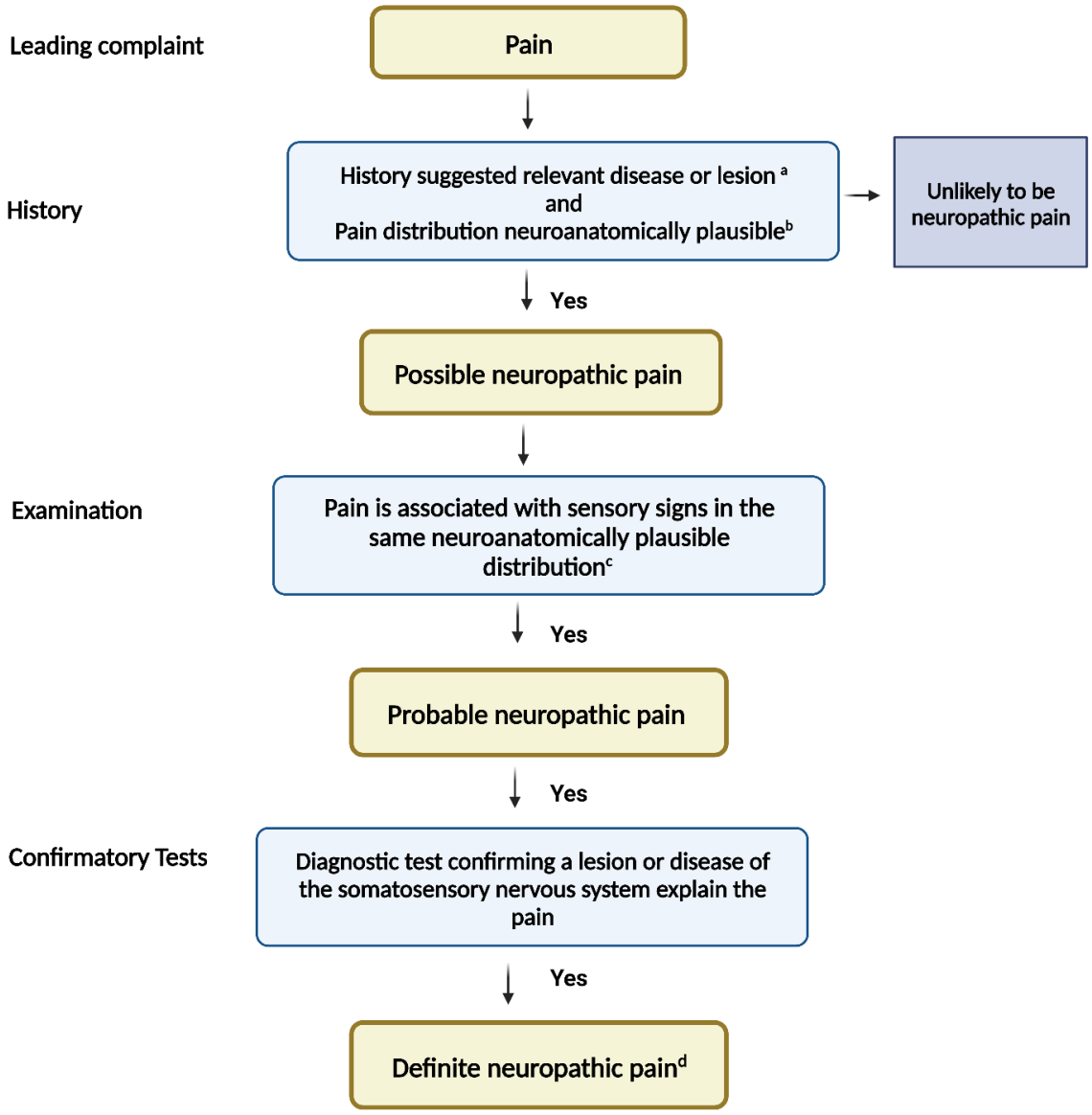


Figure 1-4. *Nerve biopsy at the sural nerve. Through a small incision, a sample of the nerve is removed and examined under a microscope. Created with BioRender.com.*

The revised definition of neuropathic pain by IASP in 2008 has been widely accepted. (19) To recognise the challenges of determining the presence of neuropathic pain by this revised definition, the NeuPSIG developed a grading system. (17,19) Grading systems include three levels of certainty (possible, probable, and definite neuropathic pain). (17) These were proposed to guide decisions regarding the level of certainty when determining whether a patient is suffering from neuropathic pain. (17)

In 2016, NeuPSIG published a systematic review which aimed to evaluate the utility of this grading system. (17) As a result of this systematic review, the following issues have been raised: (1) the role of screening tools, (2) questions about the relative significance of confirmatory tests, and (3) uncertainties about what is considered a neuroanatomically plausible pain distribution. NeuPSIG, therefore, updated the grading system to make it more applicable (Figure 1.5). (17)



a. History, including pain descriptors, the presence of non-painful sensory symptoms, and aggravating and alleviating factors, suggestive of pain being related to a neurological lesion and no other causes, such as inflammation or non-neural tissue damage. The suspected lesion or disease is reported to be associated with neuropathic pain, including a temporal and spatial relationship representative of the condition; includes paroxysmal pain in trigeminal neuralgia.
b. The pain distribution reported by the patient is consistent with the suspected lesion or disease.
c. The area of sensory changes may extend beyond, be within, or overlap with the area of pain. Sensory loss is generally required but touch-evoked or thermal allodynia may be the only finding at bedside examination.
d. The term 'definite' in this context means 'probable neuropathic pain with confirmatory tests' because the location and nature of the lesion or disease have been confirmed to be able to explain the pain. 'Definite' neuropathic pain is a pain that is fully compatible with neuropathic pain, but it does not necessarily establish causality.

Figure 1-5. *Flow chart of the updated grading system for neuropathic pain. Adapted with permission from the publisher. (17) Created with BioRender.com.*

1.2.3 Epidemiology of neuropathic pain

In understanding neuropathic pain, epidemiological studies are essential, as they provide an estimation of neuropathic pain prevalence within populations or individual groups. (43) There are, however, several obstacles limiting epidemiological research on neuropathic pain. (43) These include multiple aetiologies and manifestations of neuropathic pain and a lack of validated diagnostic criteria for all types of neuropathic pain. (44) In addition, symptoms may vary widely from person to person. (16)

The exact estimated prevalence of neuropathic pain in the general population is unknown. However, there is an estimated 15–25% of chronic pain is neuropathic, with the most common neuropathic conditions being DPN, postherpetic neuralgia (PHN), and radiculopathy. (13,45) In addition, there are two large population-based cross-sectional postal surveys have been conducted to estimate the prevalence rate of neuropathic characteristics in the general population. (46,47) The first study employed the self-report LANSS to estimate the prevalence of chronic pain associated with neuropathic pain from 6 general practices in three different cities in the United Kingdom (UK). (47) There were approximately 6000 participants in the study. (47) The estimation of the prevalence of neuropathic pain was 8.2%, according to self-LANSS responses (S-LANSS score ≥ 12). (47) The second study, Study of the Prevalence of Neuropathic Pain (STOPNEP), was conducted in France and included around 30,000 participants. The STOPNEP study used the short version of DN4, and the estimated prevalence of neuropathic pain was 6.9%. (DN4 score ≥3). (46) These two independent studies, which used two different screening tools, have similar results. However, these findings suggest that the prevalence of neuropathic pain may have been underestimated. Therefore, they should be interpreted cautiously because these tools are not formally validated for use in the general population. (32)

A recent study in the UK was considered the largest epidemiological study of neuropathic pain to date. (48) This study included approximately 148,828 participants. (48) DN4 screening tool was used to determine whether a patient had neuropathic pain or non-neuropathic pain. The prevalence of neuropathic pain was estimated to be 9.2%.

Most studies reported that the best estimate of the prevalence of neuropathic pain in the general population ranges between 3.2% and 17.9%. (46,49–54) However, the wide range of prevalence reported is due to differences in the methods used for data collection, the

characteristics of individuals, and the used definitions of neuropathic pain. Therefore, estimates of neuropathic pain have primarily been based on studies conducted by specialised centres that focus on particular conditions, (55) such as PHN (estimated prevalence: 8–10%), (56,57) DPN (estimated prevalence: 14–26%), (58–60) post-surgery neuropathic pain (estimated prevalence: 10–50% based on the surgery), (23) spinal cord injury (estimated prevalence: 30–40%), (61) and cancer (estimated prevalence: 17–19%). (62) The prevalence of neuropathic pain is anticipated to increase in the future due to the increased prevalence of chronic disease and patients living longer (*e.g.,* cancer, diabetes mellitus). (16,63)

Neuropathic pain can have a significant impact on the QoL of patients. It is widely acknowledged that neuropathic pain patients are more likely to experience comorbid conditions such as depression, anxiety, and sleep disorders than those without neuropathic conditions. It has been reported that these comorbidities, such as depression, can exacerbate chronic pain. (46–48) Without treating depression, neuropathic pain is unlikely to be managed effectively. (46–48) In 2009, O'Connor found substantial impairment in all dimensions relating to QoL among patients with neuropathic pain compared to those reporting pain without a neuropathic condition. (64) In addition, it was shown that patients with neuropathic pain had higher healthcare utilisation and expenditures. (64)

Numerous studies have demonstrated significant healthcare utilisation among patients with neuropathic pain, including frequent outpatient physician visits. (65–68) For example, a cross-sectional survey was conducted in six European countries. (69) This study included 602 patients with neuropathic pain. It was shown that during the previous month, 76% had visited their physician at least once, and 19% had visited their physician three or more times. (69) A study by Berger *et al.* conducted in the United States (USA) determined that one-year expenditures for patients suffering from neuropathic pain were three times higher than expenditures for patients without neuropathic pain ($US17,355 vs $US5,715). (70) For this reason, healthcare organisations consider neuropathic pain one of their biggest challenges and burdens.

1.2.4 Neuropathic pain management and treatment options

In recent years, considerable attention has been paid to the issue of neuropathic pain management. It is a formidable challenge facing healthcare organisations. Since the ultimate goal of the management of neuropathic pain is to minimise or alleviate suffering, and this can be achieved by treating the underlying causes in order to improve the QoL of the patients and facilitate their reintegration into society. (48) An essential aspect of neuropathic pain management is that it is developed according to the patient's physical, mental, and social status and addresses the pain individually according to the patient's characteristics.

As neuropathic pain is a complex condition, it is usually treated using two approaches, pharmacological and non-pharmacological interventions (*e.g.,* physical, and psychological therapies (often offered through rehabilitation services) and surgery (often provided by specialists)). Medical practitioners should always guide non-pharmacological approaches and ensure that they are carried out by professionals who are knowledgeable about neuropathic pain. (71,72) A multidisciplinary approach has demonstrated the most effective results for treating chronic pain. A combination of medication treatment, physical therapy, and cognitive behavioural therapy has proven to be the most successful approach to treating chronic pain. (73) According to a systematic review of the effectiveness of multidisciplinary treatments for chronic pain, the pain was significantly reduced, and mood and function were significantly improved. (73) As a result of this strategy's success, many multidisciplinary clinics have been established, and the successful outcomes of these clinics have resulted in behavioural changes in patients regarding their pain. Additionally, painkillers consumption and medical services demand has decreased. (73)

Over the past decade, there have been numerous pharmacological recommendations that have been proposed to manage neuropathic pain. (16,72,74–77) In 2013, the National Institute for Health and Care Excellence (NICE) issued updated guidelines for the pharmacological management of neuropathic pain in non-specialist settings. (78) The recommended first-line pharmacotherapy for neuropathic pain (except trigeminal neuralgia) includes antiepileptic drugs (*e.g.,* gabapentinoids such as gabapentin and pregabalin), tricyclic antidepressants (*e.g.,* amitriptyline), and serotonin-norepinephrine reuptake inhibitors (SNRI) (*e.g.,* duloxetine), and topical 5% lidocaine. (16,79) In the second line of treatment, opioid analgesics, such as tramadol, are recommended (Figure 1.6). (16,78)

If the first-line treatment does not provide adequate pain relief, it is recommended that the patient switch to second-line treatment or combine these agents. (78) Studies have demonstrated beneficial results in reducing pain intensity when pregabalin or gabapentin are combined with either a tricyclic antidepressant or opioid at lower doses as compared to monotherapy. (78,80,81) For example, high-dose monotherapy has proven to be as effective and safe as moderate-dose combination therapy in treating diabetic neuropathy pain. Accordingly, these studies provide a rationale for using combinations of drugs, at moderate dosages, in patients who are not able to tolerate monotherapy at high doses. Figure 1.6 illustrates an algorithm for the pharmacologic treatment of neuropathic pain. However, the majority of these medications have moderate efficacy according to the number needed to treat (NNT) in order to achieve a 50% reduction in pain intensity (Table 1.2). Furthermore, despite advances in the understanding of the causes and mechanisms of neuropathic pain, only about 50% of patients with neuropathic pain achieve adequate pain relief. (82)

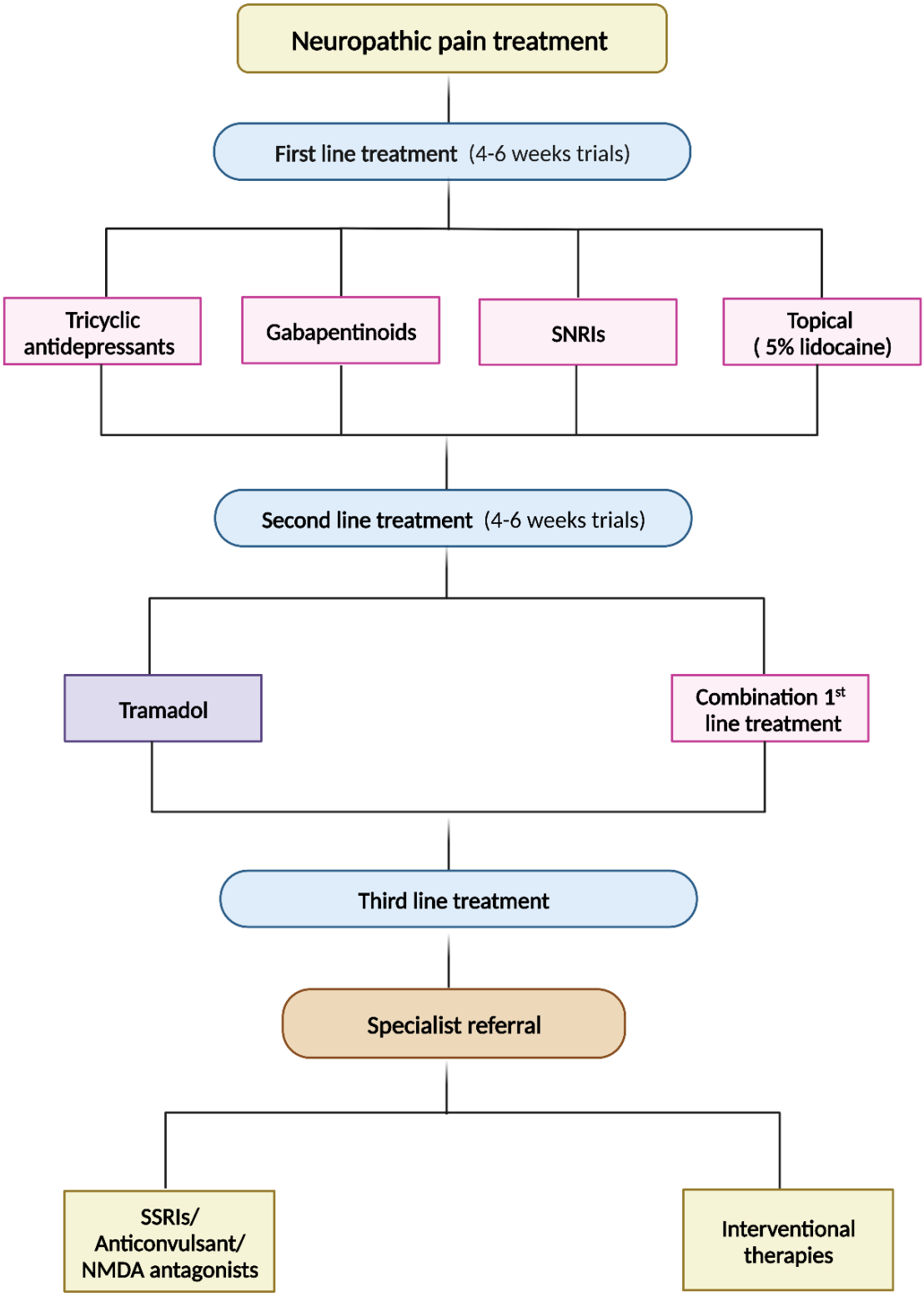


Figure 1-6. *Pharmacological options for the management of neuropathic pain. Adapted with permission from the Oxford University Press. (79) Created with BioRender.com.*

Drug classification	Medication	NNT[1] of 50% reduction in pain intensity, (CI)	Most common adverse events
Antidepressants	Amitriptyline	3.6 (3.0–4.4)	Somnolence, anticholinergic effects (*e.g.,* dry mouth, constipation, blurred vision), and weight gain
Antiepileptics	Pregabalin	7.7 (6.5–9.4)	Sedation, dizziness, peripheral oedema, and weight gain
	Gabapentin	6.3 (5.0–8.4)	
SNRI	Duloxetine	6.4 (5.2–8.4)	Nausea, abdominal pain, and constipation
Opioids	Tramadol	4.7 (3.6–6.7)	Nausea, vomiting, dizziness constipation, and somnolence.

[1] The Number Needed to Treat (NNT) for 50% pain relief in placebo-controlled trials represents the number of patients needed to treat for one to have significant pain relief as compared to placebo). The higher the NNT the lower the proportion of responders compared to the placebo. (81)

CI: confidence interval, SNRI: serotonin-norepinephrine reuptake inhibitors.

Table 1-2. *Recommended pharmacological therapy for neuropathic pain. Adapter with permission from the publisher. (83)*

The complexity of neuropathic pain is not the only factor contributing to the difficulty in the management of neuropathic pain. A lack of awareness exists among patients with neuropathic pain regarding the importance of early diagnosis and treatment. Additionally, patients with neuropathic pain often do not comply with their treatment due to unwanted side effects of pain medications or the need to take multiple daily doses. (84)

1.3 Gabapentinoids

Gabapentinoids (also known as α2δ ligands), including pregabalin and gabapentin, are antiepileptic medications that are commonly prescribed as first-line treatment for neuropathic pain. Pregabalin and gabapentin are licensed in the UK for the management of epilepsy and neuropathic pain, and pregabalin is recommended for the treatment of anxiety disorders. (85) The only pain indication approved by the USA Food and Drug Administration (FDA) for gabapentin is PHN, (86,87) while the FDA has approved pregabalin for PHN, neuropathic pain associated with diabetic neuropathy or spinal cord injury, and fibromyalgia. (75,88)

A Cochrane review showed that in PHN pain was reduced by half or more for 3 in 10 patients treated with gabapentin, and 2 in 10 placebo patients. In addition, 5 in 10 people had pain reduced by a third or more with gabapentin and 3 in 10 placebo patients. (89) Pregabalin reduced pain by half or more in 3 of 10 patients, while placebo reduced pain by 2 of 10. (88) Further, pregabalin reduced pain intensity by a third or more in 5 out of 10 patients compared to placebo, which decreased in 3 out of 10 patients. (88) Numerous clinical studies have demonstrated gabapentinoids' effectiveness in DPN. (88–93) Gabapentin showed pain intensity reduced by half or more for 4 in 10 and 2 in 10 placebo patients, and 5 in 10 people had pain reduced by a third or more with gabapentin and 4 in 10 with placebo. (89) While pregabalin seemed to reduce pain intensity by half or more in 3 or 4 in 10 people and 2 or 3 in 10 with placebo. (88) In addition, pain intensity was reduced by a third or more for 5 or 6 in 10 people compared with 4 or 5 in 10 who received a placebo. (88)

Despite the analgesic efficacy of gabapentionids some associated adverse events have been shown in most patients taking these medications, including drowsiness, sedation, dizziness, dry mouth, peripheral oedema, fatigue, nausea and weight gain. (88,89,94) It is estimated that one in four patients is unable to tolerate gabapentinoid-related adverse events, leading to the termination of the treatment. (94)

Interestingly, there are also studies suggesting that gabapentinoids may be beneficial not only for treating uncontrolled pain, but also for treating opioid withdrawal syndrome. (95,96) This syndrome includes mental and emotional withdrawal symptoms, for example, anxiety, depression, insomnia, poor concentration and memory, and physical withdrawal symptoms (*e.g.,* chest tightness, breathing difficulty, palpitations, nausea, vomiting, diarrhoea, stomach aches, muscle tension, tremors, sweating, and tingling). (97) In addition, the use of gabapentinoids is associated with significant euphoric effects that possess the potential for abuse, and when taken with other central nervous system (CNS) depressants, they can cause death. (98) Therefore, these pharmacological properties of gabapentinoids call even more attention to their therapeutic potential in neuropathic pain. It is still unclear how gabapentinoids may produce these side effects; this necessitates extensive research to establish the risks and benefits associated with the use of gabapentinoids in the treatment of neuropathic pain.

There has been an increase in prescribing gabapentinoids in the UK for the management of neuropathic pain recently. (99,100) Specifically, the Advisory Council on the Misuse of Drugs

illustrated that prescriptions for pregabalin have increased by 350% and gabapentin by 150% within five years. (101) It is believed that this increase is due to the practice of avoiding prescribing opioid analgesics that were shown to be ineffective in the management of neuropathic pain. (99,100) An issue has arisen from the use of gabapentinoids, as evidenced by a recent report from the Office for National Statistics that shows 136 deaths related to pregabalin in 2017 versus four deaths in 2009. Meanwhile, gabapentin deaths increased from 8 in 2012 to 59 in 2016. (102) This issue may directly result from the fact that if more than one CNS depressant is used, an additive effect may potentiate the feeling of drowsiness, sedation, respiratory depression, and even lead to death. (98,103) Indeed, respiratory failure and coma have been reported in patients taking pregabalin with other CNS depressants such as opioids, alcohol, benzodiazepines, and SSRIs. (98)

A growing number of deaths associated with gabapentinoids has prompted the Advisory Council on the Misuse of Drugs to recommend that gabapentinoids should be reclassified as controlled drugs (class C) under the Misuse of Drugs Act to address the issue of misuse and dependence, both of which contribute to the increased mortality rate. (104,105) As a result of this recommendation, the UK government announced in April 2019 that these drugs had been reclassified as class C drugs. (105,106) There is, therefore, a need to fully understand the risks associated with the use of gabapentinoids in conditions for which these medications are recommended as first-line treatment (*e.g.,* neuropathic pain) and, in turn, a need to identify the underlying mechanisms that result in side effects associated with long-term gabapentinoids administration in patients with chronic pain.

A recent study in 2023 was conducted in the UK of trends in gabapentinoid prescribing in primary care, which aimed to analyse the trends in gabapentinoid prescribing before and immediately after reclassification (a period of six months). (107) The study found that there was a marked increase in gabapentin prescribing in 2016-2017. After reclassification, there was a steady decrease in the rate of gabapentin prescribing, which began before and continued after reclassification. Accordingly, the gabapentin prescribing rate decreased by 22% by April 2019. In contrast, the rate of pregabalin prescriptions increased for a longer period before plateauing from 2017 to 2018, and after reclassification, no significant change in the decreasing trend of annual pregabalin prescriptions was found. Conversely, tramadol prescribing dropped immediately and dramatically when a similar reclassification was implemented in 2014. The availability of safe alternatives to tramadol, such as gabapentinoids,

may explain this phenomenon. Additionally, effective pharmacological alternatives are lacking for patients who use gabapentinoids for neuropathic pain. (108) Figure 1.7 shows the annual prevalence of gabapentinoid prescribing trend. However, this trend was for gabapentinoids prescribed for general indications but not specifically prescribed for neuropathic pain.

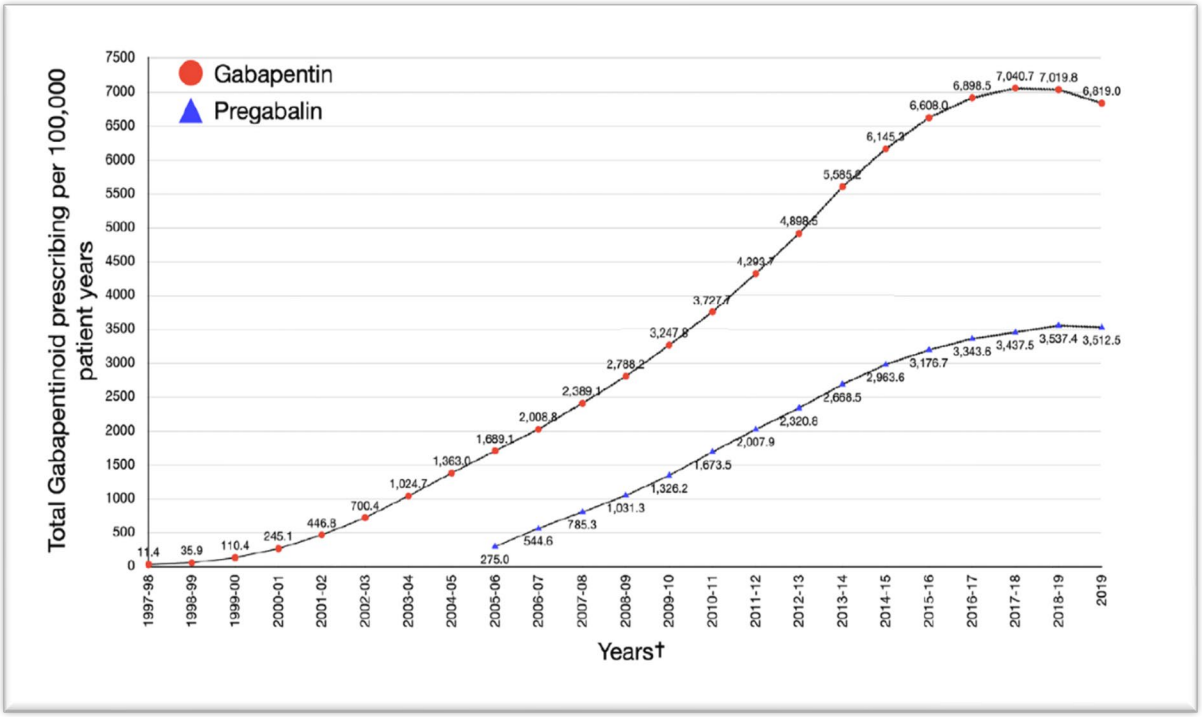


Figure 1-7. *Annual rates of prevalent gabapentinoid prescribing (1997–2019) per 100,000 patient years. Figure used with permission from the publisher. (107)*

1.3.1 Mechanism of action

Both pregabalin and gabapentin are derived from gamma-aminobutyric acid (GABA), but neither affects GABA receptors. (94) Despite their widespread use, their mechanism of action is not yet fully described and understood. (109) Pregabalin and gabapentin have similar mechanisms of action, however, their pharmacokinetic and pharmacodynamic properties differ considerably. (109) The effects of gabapentinoids are believed to result from a reduction in the sensitivity of the dorsal horn through a variety of mechanisms.

It is evident that α2δ-1 subunits contribute to nociception and their levels are raised following nerve injury for several months. Gabapentinoid's mechanism of action is assumed to be due to the direct inhibition of voltage-gated $Ca^{+2}\delta$ channels through the binding to their α2δ-1 subunits in the spinal dorsal horn, resulting in a decrease in presynaptic $Ca^{+2}\delta$ influx and subsequent release of excitatory neurotransmitters (*e.g.,* glutamate, calcitonin gene-related

peptide (CGRP) and substance P) that play a role in the progression of neuropathic pain (Figure 1.8). (110)

The descending noradrenergic inhibitory system from the locus coeruleus (LC) to the dorsal horn has a crucial role as an analgesic mechanism. (110,111) Acute administration of gabapentinoids can contribute to activating LC, by inhibiting the release of GABA and releasing of glutamate, and consequently enhancing noradrenaline (NA) levels in the spinal cord (Figure 1.9). Then, NA interacts with α2-adrenergic receptors in order to blockade noradrenergic signalling and decreases nociceptive transmission. (111,112)

Another mechanism of action by indirect interaction with the N-methyl-D-aspartate (NMDA) receptor in peripheral nerve injury. It is normal for presynaptic NMDA receptors in the spinal cord to be inactive, and they are not actively participating in physiological nociceptive transmission. However, numerous studies have indicated that presynaptic NMDAR activity is elevated in neuropathic pain conditions. A rise in presynaptic NMDAR activity leads to glutamate release from primary afferent terminals to spinal dorsal horn neurons, which is necessary for synaptic plasticity associated with neuropathic pain. It has been found that injury nerve induced increasing α2δ-1 expression at primary afferent terminals and interacts with NMDARs to enhance presynaptic NMDAR activity by facilitating synaptic trafficking of α2δ-1–NMDAR complexes. (113) Gabapentinoids target the α2δ-1-NMDAR complex by inhibiting its forward trafficking, leading to a reduction of neuropathic pain. (Figure 1.9). (114,115)

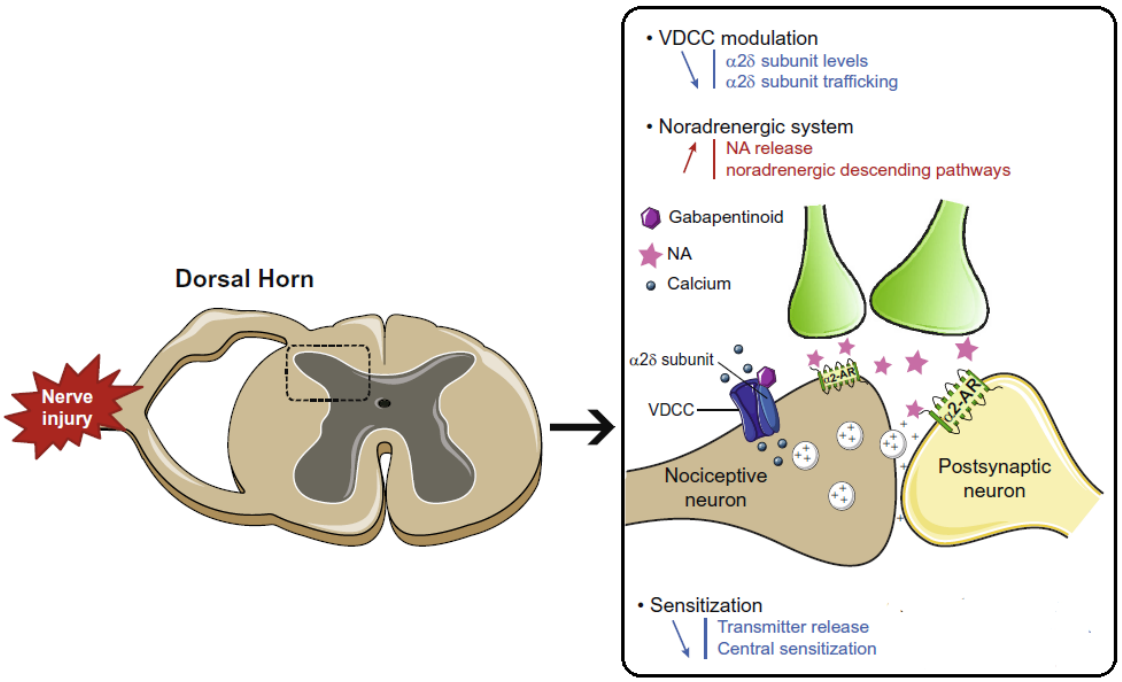


Figure 1-8. *Mechanism of action of gabapentinoids on neuropathic pain. The primary mechanism of action is the VDCC α2δ-1 subunit. Gabapentinoids' binding to these subunits decreases excitatory transmitter release and spinal sensitisation (blue). Secondary mechanisms of action include the activation of the descending noradrenergic pain inhibitory system (red). VDCC: voltage-dependent calcium channels, NA: noradrenaline. Figure reproduced with permission from the publisher. (112)*

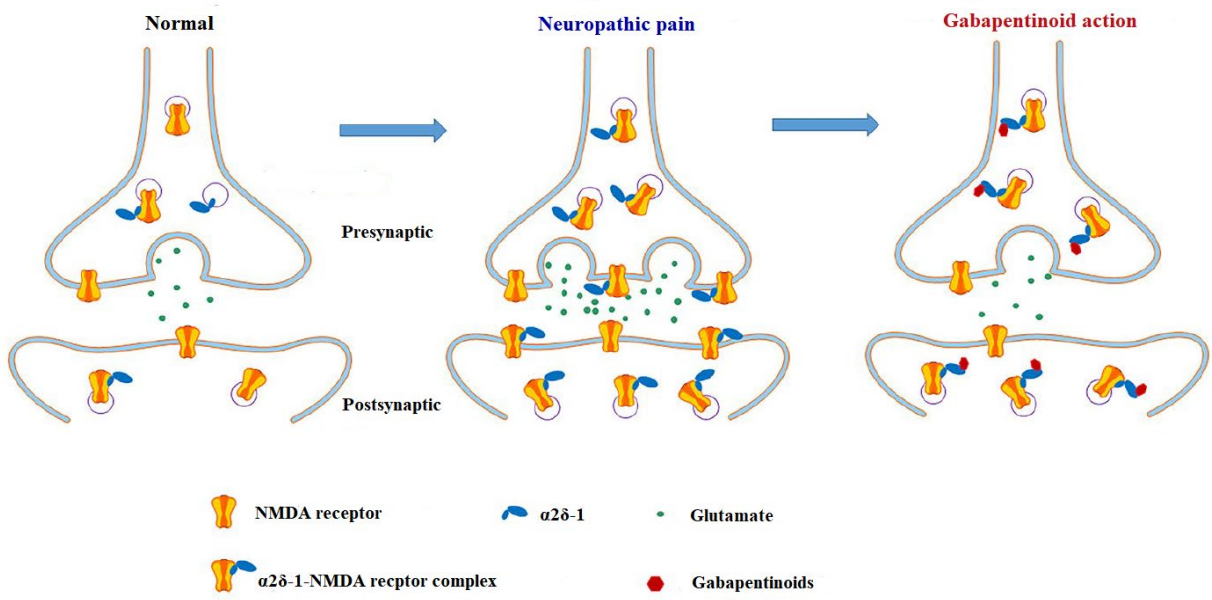


Figure 1-9. *Illustration of the potential role of α2δ-1 in neuropathic pain. Normally, most synaptic NMDARs do not interact with α2δ-1 in the spinal dorsal horn. When neuropathic pain is present, α2δ-1 expression is elevated and binds with NMDARs, at presynaptic and postsynaptic sites. Gabapentinoids bind the α2δ-1-NMDAR complex, reducing neuropathic pain. With permission from the publisher. (116)*

1.3.2 Pharmacodynamics

Pharmacodynamically, gabapentinoids are distinguished primarily by their potency. However, few studies have been conducted to compare their relative potencies (EC50). In 2010, a population pharmacokinetic model was developed, and EC50 values were calculated for gabapentinoids. (117) It has been estimated that in PHN, pregabalin has an EC50 of 4.21 mg/mL and gabapentin has an EC50 of 11.7 mg/mL. Therefore, pregabalin appears to be 2.8 times more potent than gabapentin. Despite the fact that potency is a significant indicator of therapeutic potential, potency might not always be correlated with clinical effectiveness. Moreover, the study found differences in the dose-response curves for analgesia. Analgesic effects of gabapentin plateaued at 3600 mg/day, whereas pregabalin effects continued to increase to 450 mg/day. (117)

1.3.3 Pharmacokinetics

Gabapentinoids act primarily intracellularly and require active uptake. As both drugs have structural similarities to the amino acid leucine, they are transported across cell membranes by the L-amino acid transporter (LAT) system (Figure 1.10). (109) Nevertheless, there are differences in the pharmacokinetic characteristics of gabapentinoids (pregabalin and gabapentin) (Table 1.3).

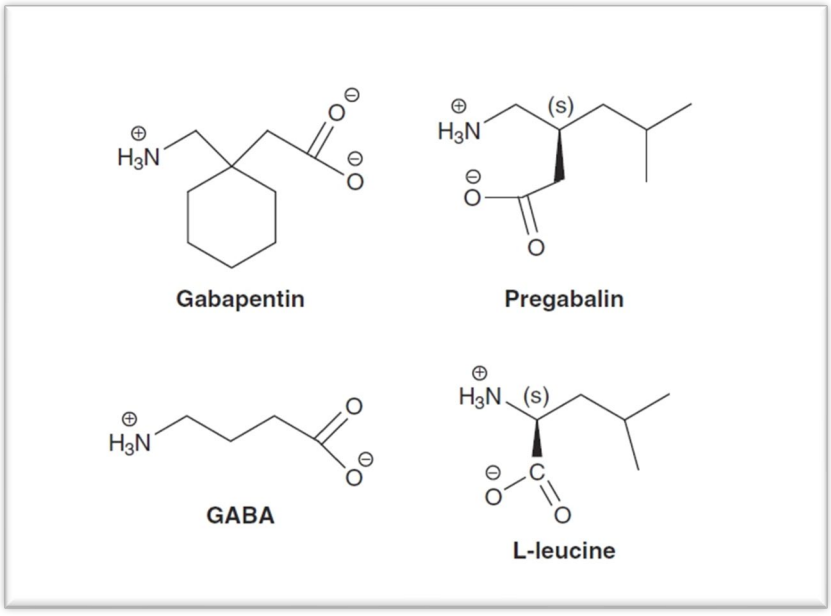


Figure 1-10. *Chemical structures of gabapentin, pregabalin, γ-aminobutyric acid (GABA) and L-leucine. Adapted with permission from the Springer Nature. (117)*

Gabapentinoids	Pregabalin	Gabapentin
T_{max} (hours)	1	2-3
$t_{1/2}$ (hours)	5.5-6.7	5-7
Bioavailability	>90%	33-66%
Plasma protein binding	Linear	Non-linear
Metabolism	Very limited if any metabolism occurs.	Nil
Renal excretion	92–99% unchanged	100% unchanged

Table 1-3. *The difference in pharmacokinetics profile between pregabalin and gabapentin. Adapted with permission. (109,118)*
T_{max}*: Time to peak drug concentration,* ***$t_{1/2}$****: half-life of a drug.*

Compared to gabapentin, pregabalin is rapidly and completely absorbed. (109,117) Pregabalin takes only one hour to reach its peak plasma concentration, compared to three hours for gabapentin. In addition, pregabalin has a higher bioavailability for oral administration of over 90%, whereas gabapentin has a 33–66% bioavailability. (109,117) The mechanism of absorption can explain these differences. Pregabalin and gabapentin are absorbed in the small intestine; besides, pregabalin is absorbed in the proximal colon. Gabapentin absorption depends solely on LAT, which is easily saturated, causing dose-limited absorption. (109,117,119) As the dose of gabapentin increases, the concentration at a steady state does not increase proportionally. In contrast, pregabalin absorption may be mediated by an additional pathway than LAT, resulting in non-saturable absorption and a linear pharmacokinetic. Food only slightly impacts the extent and rate of gabapentin absorption, while pregabalin absorption can be significantly slowed without affecting its bioavailability. (109,117)

Gabapentinoids undergo negligible metabolism (metabolites account for <1% of the dose). They do not bind to plasma proteins; therefore, drug interactions with highly protein-bound agents are unlikely. (117) Their metabolism does not occur in the liver or affect liver enzymes such as the cytochrome P450 system. (120,121) Most of the elimination occurs in the kidney in direct proportion to the amount of creatinine clearance. It is possible for the accumulation of these drugs to result in renal failure and adverse effects.

It is estimated that pregabalin and gabapentin have similar elimination half-life parameters. It has been reported that the elimination half-life of gabapentin ranges between 5 and 7 hours. In contrast, pregabalin is approximately 5.5-6.7 hours, suggesting that both drugs reach a steady state within 24–48 hours of administration. (117,122)

1.4 Potential for misuse and abuse

It is imperative to understand that the main difference between someone who misuses drugs and someone who abuses drugs is their intent. World Health Organisation (WHO) defined psychoactive substance misuse as the "*using of a substance for a purpose not consistent with legal medical guidelines*." (123) In other words, the misuse of a drug refers to taking it to treat a specific disease and using it inappropriately. On the other hand, the abuse of a drug refers to taking it to elicit specific feelings without medical indications.

There has been an increase in evidence of gabapentinoids being misused and diverted. In 2010, 16 reports of abuse of pregabalin were submitted to the Swedish Adverse Event Reporting System (AERS), which was widely accepted as the first evidence of gabapentinoid abuse. (124) Following this, AERS analysis identified 7639 incidences of pregabalin abuse and 4301 incidences of gabapentin abuse between 2004 and 2015, the majority of which occurred between 2012 and 2015. (125) The estimated lifetime prevalence of gabapentinoid abuse within the UK general population was 2.5% in 2013. (126) As evidenced by adverse drug reaction reporting data from the USA and Europe, pregabalin has more potential for abuse than gabapentin. (103,125,127,128)

The mechanism responsible for gabapentinoid abuse remains unexplored. However, gabapentinoids can contribute to a moderate elevation of the extracellular GABA level in the brain, producing weak GABA mimetic properties (*e.g.,* relaxation and euphoria). Generally, these effects are experienced at the start of gabapentinoids treatment and after supratherapeutic doses are administered (*e.g.,* pregabalin > 600 mg and gabapentin > 3600 mg). Indeed, euphoria adverse event of pregabalin has been shown to be dose dependent. Recent systematic reviews of 102 pregabalin clinical trials found that euphoria occurred in 14 of the trials with a prevalence ranging between 1% and 10% (including one study that reported 26%). (129) Furthermore, many case studies related to the abuse of gabapentinoids have suggested that dependence on pregabalin may be stronger and more persistent than dependence on gabapentin. (130) However, gabapentinoids are distinguished from other

substances of abuse by their rapid tolerance to their euphoric effects. (130) There is a possibility that this will lead to a considerable overdose of gabapentinoids. (130,131)

Pregabalin is more likely to be misused and abused than gabapentin due to pharmacokinetics differences, as mentioned previously in table 1.3. (117,130,131) Considering that pregabalin has a linear pharmacokinetic profile, the absorption increases proportionally with the increase in dose. Moreover, pregabalin is rapidly absorbed (T_{max} within 1 hour) when taken orally, and it possesses higher bioavailability than gabapentin, leading to a more rapid onset of euphoria. (117,130,131)

It has been documented that the addictive potential of gabapentinoids is more prevalent among patients with substance use disorders, most notably opioid use disorder. (103,127,132) An estimated 3 to 64% of patients with opioid use disorder abuse pregabalin, while 15–22% abuse gabapentin. (128,133–135) Opioids and gabapentinoids are known to increase the risk of hospitalisation and opioid-related death when used concurrently. This is because these patients, showing long-term opioid tolerance, may desire the euphoric effect resulting from treatment with gabapentinoids. (103,127) Due to the decrease in opioids and benzodiazepine prescribing, patients have substituted them with other licit or illicit drugs depending on their ease of availability. (97) According to a small study of patients who abuse opioids, 11 of 15 purchased pregabalin from drug dealers without a prescription. Additionally, several studies indicated that gabapentinoids were available from drug dealers or online retailers. (103,135)

In the Scotland study, 8% reported that they misused gabapentinoids, and 22% admitted that they abused them. Among these, 38% used gabapentinoids to enhance the euphoric effects of methadone. (134) A large population-based study conducted in France found that the pregabalin misused (12.8%) in new users was higher than the gabapentin misused (6.6%). (136) In the UK, it has been observed that misused gabapentinoids are mostly obtained from healthcare providers (63%). Furthermore, there was a 50% misuse of pregabalin and a 40% misuse of gabapentin among patients with an opioid misuse history. It is important to note that these results conform with those reported by Bonnet and Scherbaumb in 2017. They conducted a systematic review of the addictive properties of pregabalin and gabapentin. They concluded that there is no convincing evidence of gabapentinoids being highly addictive power in patients without a prior abuse history. (130) Consequently, this evidence proved that previous abuse history substantially impacted the misuse and abuse of gabapentinoids.

Overall, there is a lack of studies exploring the misuse and abuse of gabapentinoids among patients with neuropathic pain. Therefore, there is a considerable need to explore the abuse potential of gabapentinoids in the management of neuropathic pain, particularly in patients who have not previously abused opioids.

1.5 The role of community pharmacists (CPs)

In the UK, primary care serves as a doorway into the healthcare system, acting as the first point of contact for patients in the National health service (NHS). (137) It aims to provide an easy access to care, regardless of the patient's condition. (137) Furthermore, primary care provides basic health care, including illness prevention, diagnosis, and treatment of conditions that do not require hospitalisation. The primary care system includes general practices (GPs), community pharmacy, dental care, and optician services. (137) Primary care providers are responsible for treating minor conditions, preventing long-term diseases, and providing advice and screenings to help prevent future illnesses. (137)

For many patients affected by pain related to neuropathic conditions their access to health services begin when these patients visit their GP. Following a physician's assessment of neuropathic pain in non-specialist settings, usually gabapentinoids prescription is written and sent to the patient nominated community pharmacy through either electronic or paper prescription services. (138) As gabapentinoids are controlled drugs (CD), the prescription must contain specific requirements outlined in the Misuse of Drugs Regulations 2001, as follows:

- Patient name and address;
- Drug name;
- Dose ("as directed" on its own is not permitted);
- Formulation;
- Strength (where appropriate);
- Total quantity/dosage units of the preparation in both words and figures (for liquids, total volume in ml);
- Prescriber signature and address;
- Date of issue; and
- For instalment prescriptions, specify the instalment amount and instalment interval.

It is important to note that CD (*e.g.,* gabapentinoids) prescriptions are valid for 28 days after the date of initiation. (138) Patients must obtain their medications from the nominated

community pharmacy during this period. CPs have a limited role to play after receiving prescriptions for gabapentinoids (*e.g.,* pregabalin or gabapentin) (Figure 1.11). They must check the patient's identity and ensure prescription validity. In addition, pharmacists must ensure that the prescription has been written in accordance with the Misuse of Drugs Regulations 2001. Pharmacists in the community setting can only amend typographical errors on paper prescriptions, such as minor spelling errors, minor typographical errors, or when the CD/number of dosage units is indicated in either words or figures but not both. (138)

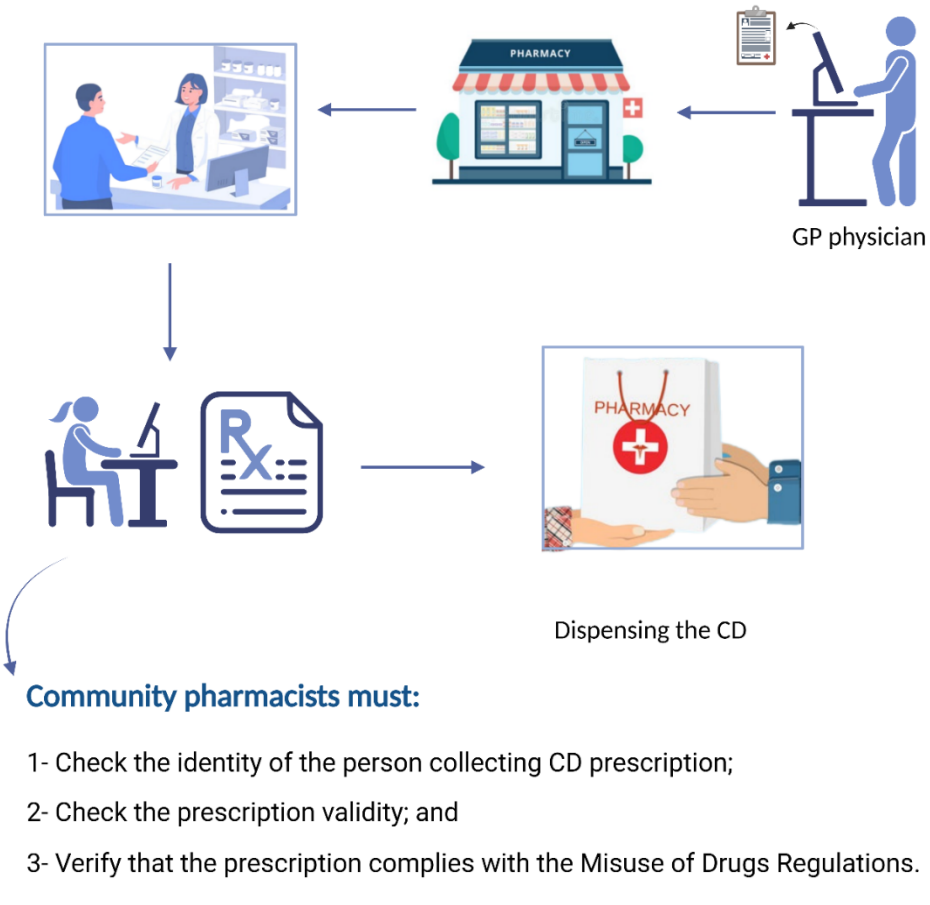


Figure 1-11. *Gabapentinoids prescription process within primary care. Created with BioRender.com. The process begins when the GP sends the prescription to the pharmacy. Pharmacist receives the prescription and verifies patient's identity. The medication is dispensed to the patient after the CD (gabapentinoids) prescription is checked. GP: general practitioner, CD: controlled drug.*

Community pharmacies are amongst the most accessible healthcare providers working closely with patients to ensure pain medication is used safely and appropriately. (139) Many community pharmacies maintain long hours of operation, which allows them to provide patient care when other healthcare services are unavailable. (140) The number of people visiting a community pharmacy in England each day is estimated to be approximately 1.6 million. It is also estimated that English residents visit a community pharmacy on average 14 times each year, with 11 of these visits related to health issues. (141) Additionally, community pharmacies provide healthcare services to small and deprived communities in which access to healthcare is extremely limited. It is estimated that approximately 89.2% of the population in England has access to a community pharmacy within a 20-minute walking distance of their homes. (142)

In the UK, the majority of healthcare services are delivered through the tax-funded NHS model, with responsibility for each nation devolved. Since more than 80% of the population lives in England, NHS England represents the largest health service in the country. (143) Since April 2013, NHS England is responsible for commissioning NHS pharmaceutical services. (144)

There are three different NHS services provided by community pharmacies as outlined in the national Community Pharmacy Contractual Framework (CPCF): essential, advanced, and locally commissioned, as presented in figure 1.12. (145,146) The Department of Health and Social Care (DHSC), Pharmacy representative bodies and NHS negotiate and agree on essential and advanced services nationally. While locally commissioned services might be commissioned by Clinical Commissioning Groups (CCGs), local authorities (LAs) and NHS local teams.

Pharmacists are responsible for providing all these services. It is mandatory that all community pharmacies offer essential services, while advanced and locally commissioned services are optional. As these are optional services, CPs receive payment for offering advanced and locally commissioned services.

There has been an increase in the differences between the three countries within Great Britain (England, Scotland and Wales). Several factors contribute to this, including different health priorities, workforce requirements, and the structure of commissioning bodies.

Community pharmacies in England and Wales provide essential services, including dispensing duties, communication with other healthcare settings (*e.g.,* GPs), disposal of unwanted

medicines and referring patients when needed. In February 2021, Discharge Medicines Service (DMS) became a new essential service within the CPCF. The DMS service aims to support patients transitioning from one care setting to another.

In Scotland, pharmacy contractors are anticipated to deliver all four essential services as part of the contract framework. The four services are as follows:

1. Medicines care and review;
2. Minor ailments service;
3. Public health service (which includes smoking cessation and emergency hormonal contraception); and
4. Acute mediation service.

The advanced services include tasks like new medicine service (NMS), Stoma Appliance Customisation (SAC), National Influenza (flu) Adult Vaccination Services (NIAVS), and supplying emergency medication supplies to patients. (147) As part of the advanced services in Wales, DMR was commissioned in 2011. (148)

NHS England announced on 29 October 2019 that the Community Pharmacist Consultation Service (CPCS) had been added as the latest advanced service within the CPCF. (149) The CPCS is where CPs receive electronic referrals from the NHS 111 helpline, the Integrated Urgent Care Clinical Assessment Service, or GPs for lower acuity conditions. The service mainly aimed (1) to reduce the pressure on GPs and Emergency Departments, (2) to make emergency care more convenient and accessible for patients, and (3) to harness the skills and medicines knowledge of CPs. (149) Furthermore, the CPCS service facilitates the integration of community pharmacies into urgent care systems. (149)

Locally commissioned services are commissioned in accordance with the needs of the local population. LAs are responsible for commissioning a wide range of services, including health care and social services, either directly or by outsourcing contracting administration to other administrations, such as Commissioning Support Units and Local Pharmaceutical Committees. (147) For example, for services commissioned by LAs, smoking cessation, weight management, alcohol screening and brief interventions and sexual health.

Other services are also commissioned by the CCG, including palliative care, medicine optimisation service, and minor ailments service. (147) For example, for minor ailments

service, a sore throat test and treat (STTT) service that extends the current Sore Throat service. (150) The STTT service enables patients with acute sore throat symptoms to access clinical assessment, advice, and appropriate medication. (150)

Based on the Pharmaceutical Services Negotiating Committee (PSNC) database in England, 182 services were commissioned by CCGs in 2016, though the actual number may be higher. (147)

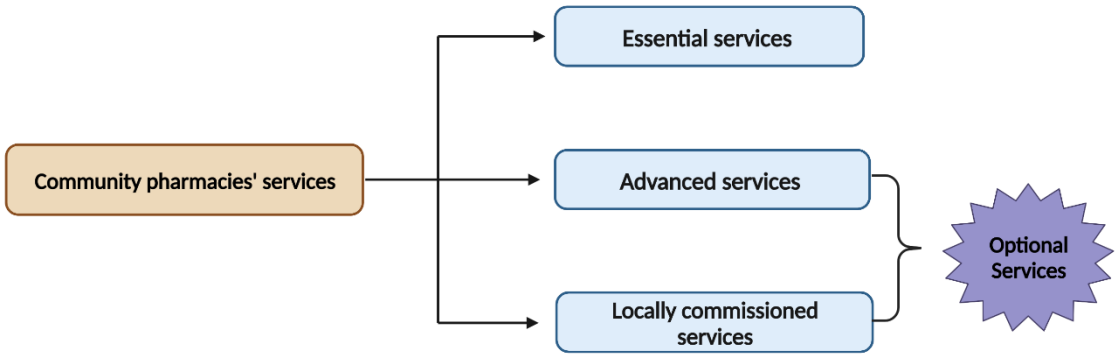


***Figure 1-12**. Community pharmacies services. Created with BioRender.com.*

The accessibility of pharmacists would be leveraged to deliver drug misuse identification and prevention services. (151) However, the roles of community pharmacists dealing with substance misuse have traditionally been limited to providing opioid substitutes and needle exchange services. In the UK, community pharmacy-led informal interventions include refusing sales, referring patients to GP, restricting the number of products sold, and removing products from sight. (152)

In 2021, the Royal Pharmaceutical Society (RPS) in Scotland recommended that community pharmacies should have the tools to prevent and identify possible dependence on prescribed medications by providing brief interventions where necessary. (153) It has also been recommended that promote public health campaigns through community pharmacies to assist individuals who misuse their drugs and prevent addiction from happening. (153) These campaigns aim to increase awareness in society about the growing problem of prescribing and the issue of dependence on specific medications. For campaigns to be successful, all community pharmacists must be trained and engaged, as they are uniquely positioned to deliver the key messages of these campaigns. (153) Furthermore, it has been mentioned that

pharmacy curriculums should focus on preparing future pharmacists to combat misuse issues. Thus, undergraduate courses should cover the basics of addiction, medication management, substance abuse prevention, and extensive pharmacological and non-pharmacological treatment training. In the USA, Skoy *et al.* reported that there is a training programme designed to prepare third-year pharmacy students to identify opioid misuse, prevent overdoses, and prescribe Naloxone. (154) A training program has been added to the curriculum to address the American Association of Colleges of Pharmacy (AACP) call for introducing students to the advancing role of pharmacists in combating the opioid epidemic. As well as becoming familiar with diagnosing and treating opioid misuse and accidental overdoses, students will also learn how to prescribe and administer Naloxone. (154) This training programme showed an increased students' knowledge, self-efficacy, and perceived value in preventing accidental opioid overdoses. (154) By doing so, CPs will be involved in identifying and tackling this issue effectively.

Complexity and severity of drug misuse require intervention by healthcare professionals, and pharmacists are the only health professionals trained specifically in how to use medicines safely and effectively, which deserves more attention. (155,156) It is well known that community pharmacists have successfully provided smoking cessation, alcohol reduction, and weight management through their interventions. (157) Community pharmacists consider the provision of harm reduction services and substance use prevention interventions in community pharmacies to be a significant public health initiative, such as the dispensing of naloxone and the provision of needle exchange programs. Recently, there has been increased attention paid to community pharmacists concerning their involvement in reducing inappropriate medication use, including analgesic medications. (158) However, the specific role of the community pharmacist in tackling analgesic misuse (*e.g.,* gabapentinoids) remains unclear, as much of this research is ongoing. Consequently, more research is needed to better understand how community pharmacies handle gabapentinoid misuse and reduce their harm.

1.6 Aim and objectives

The motivation behind this PhD research was the reclassification of gabapentinoids (pregabalin and gabapentin) as a controlled drug in the UK in April 2019. As identified in the literature review, there has been a dramatic increase in evidence about gabapentinoids misuse and abuse among the general population; and limited evidence describing the role of CPs in curbing this growing problem. In this PhD project, we will investigate the safety profile of gabapentinoids in the management of neuropathic pain in adults, including their potential for addiction and adverse events; and clarify the role of CPs in appropriately managing the risks associated with gabapentinoids. Here are two focused questions related to the main aim:

1- What is the evidence currently available to assess the safety of gabapentinoids in the management of neuropathic pain?
2- What evidence is available regarding the potential role of CPs in addressing the misuse associated with gabapentinoids in neuropathic pain?

In order to achieve this aim, the following research strategies were followed:

Safety profile of gabapentinoids

- Carry out a systematic review and meta-analysis to assess the available evidence concerning the safety (*e.g.,* addictive potential and adverse events) and analgesic efficacy of gabapentinoids to control neuropathic pain in adults. (Chapter 2).
- Conduct an *in-vivo* study to investigate the reinforcing efficacy of pregabalin in the presence of morphine (Chapter 3).

Role of community pharmacists

- Carry out a systematic review to identify and critically assess the evidence of CPs-led interventions to address misuse and abuse of gabapentinoids (Chapter 4).
- Conduct a qualitative study to understand CPs' perceived barriers and facilitators to identify inappropriately prescribed analgesia (IPA), particularly (pregabalin and gabapentin) (Chapter 5).

Following were the milestones for achieving the identified objectives:

- Identify and assess the addictive potential and adverse events of using gabapentinoids in the management of neuropathic pain (Chapter 2).
- Quantify the pooled safety and analgesic efficacy outcomes of gabapentinoids (Chapter 2).
- Assess the abuse potential of pregabalin when used in conjunction with morphine (Chapter 3).
- Identify evidence of CPs-led interventions to demonstrate the effectiveness of these interventions in changing the behaviours of patients and pharmacists (Chapter 4).
- Describe the barriers and facilitators that face the CPs for identifying and addressing the IPA (Chapter 5).

Chapter 2 Current safety profile for gabapentinoids in the management of neuropathic pain: a systematic review and meta-analysis.

2.1 Chapter description

A meta-analysis was done to investigate the safety profile and efficacy associated with the management of neuropathic pain using gabapentinoids (pregabalin and gabapentin) as a first-line treatment.

2.2 Publication

The work of this Chapter has been published as Meaadi J, Obara I, Eldabe S, Nazar H. The safety and efficacy of gabapentinoids in the management of neuropathic pain: a systematic review with meta-analysis of randomised controlled trials. Int J Clin Pharm. 2023 Feb 27 (Appendix A). DOI: 10.1007/s11096-022-01528-y

2.3 Introduction

There have been a number of recommendations proposed to manage neuropathic pain over the last decade. One of the recommended first-line pharmacotherapies is antiepileptic drugs (*e.g.,* gabapentinoids (gabapentin and pregabalin)). (71) The only pain indication approved by the FDA for gabapentin is PHN. (159) While pregabalin is approved for PHN, DPN, and neuropathic pain associated with spinal cord injury, and fibromyalgia. (159) In the UK, gabapentin and pregabalin are currently approved for treating peripheral and central neuropathic pain in adults at a daily dose of 3600 mg gabapentin and 300 mg pregabalin. (160,161)

In the last two decades, gabapentinoids have become blockbuster drugs being used for various conditions, often "off-label" (not for licensed use), such as anxiety, insomnia or withdrawal from recreational drugs. (162) Goodman and Brett (86) challenged this practice, reporting that evidence to support off-label gabapentinoid use for the most painful clinical conditions is limited. (86) Authors reflected that the rapid increase in prescribing of these therapeutics suggests a prevailing assumption that these are effective pain medications and are becoming alternative medications in order to reduce opioid prescribing. (86)

Associated with the rise in gabapentinoid use is a growing conjecture of abuse liability. However, this is generally confounded because many patients using gabapentinoids are currently or previously dependent on other substances, *e.g.,* opiates and sedatives. (162) A recent report from the Office for National Statistics indicates that pregabalin-related deaths increased from 4 in 2009 to 136 in 2017, while gabapentin-related deaths increased from 8 in 2012 to 59 in 2016. (102) Therefore, a growing number of deaths linked to gabapentinoids prompted the Advisory Council on the Misuse of Drugs advising their reclassification as controlled drugs (class C) to tackle the perceived misuse and dependence. (104,105) The UK government acknowledged this recommendation and reclassified gabapentinoids as class C drugs in April 2019. (102) According to a recent systematic review, there is insufficient evidence to support claims of addictive power in patients without a history of substance abuse. (162) In addition to other studies, it is recommended to avoid the use of gabapentinoids or to be used in caution in patients with current or previous substance use disorders. (98,162,163)

The current landscape of gabapentinoid prescribing is not supported by clinical evidence. The addictive potential of gabapentinoid remains controversial; thus, the surveillance and assessment of ongoing evidence are needed to fully understand the risk associated with the use of gabapentinoids for conditions where this group of medications is recommended as a first-line treatment (*e.g.,* neuropathic pain). Therefore, to have an overview of the current evidence on gabapentinoid safety, this Chapter aims to summarise the recent evidence for these medications from RCTs conducted in patients with neuropathic pain. This approach has been underpinned by the principles that: (1) evidence-based medicine often relies on RCTs as the "gold standard", (2) adverse events must be reported during RCTs as a matter of ethical responsibility, and (3) lack of meta-analysis based on RCTs assessing the use of gabapentinoids in neuropathic pain.

Despite RCTs remain underpowered for adverse events, it would be unethical to lose either the quantity or accuracy of the available information. (164) It has been recommended that different types of evidence be used to obtain a more comprehensive and robust picture of drug safety, including RCTs, observational studies and spontaneous reports. (164,165)

Meta-analysis should ideally be restricted to one type of study design. (166) Including different study designs (*e.g.,* observational studies which are subject to both bias and confounding) in one meta-analysis will reduce its quality. (167) Because when different designs are combined in a meta-analysis, multiple biases will be included along with the results of interest, leading to misleading conclusions. (168) Accordingly, this Chapter focused on summarising the evidence on gabapentinoid safety based solely on RCTs.

2.4 Aim

To summarise and assess the available evidence concerning the safety and analgesic efficacy of gabapentinoids in treating neuropathic pain in adults.

2.5 objectives

1- Identify and retrieve current RCTs assessing the safety of gabapentinoids for the management of neuropathic pain.

2- Identify and assess the addictive potential and adverse events of using gabapentinoids in the treatment of neuropathic pain.

3- Identify and assess the analgesic efficacy of gabapentinoids.

4- Assess the quality and evaluate the homogeneity of the identified RCTs.

5- Quantify the pooled safety and analgesic efficacy outcomes in gabapentinoids and placebo.

2.6 Materials and Methods

2.6.1 Protocol and Registration

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (169) The complete protocol methodology was documented and registered in advance in an international prospective register of systematic reviews (PROSPERO: CRD42019123869). The protocol can be assessed at:

https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=123869&VersionID=1561285 (Last accessed on 22 July 2022)

2.6.2 Search Strategy

Scoping searches have been carried out to better understand the key issues of gabapentinoid misuse and abuse related to the management of neuropathic pain. This provides a rough estimate of how many studies may be found when conducting the main search. This step was performed prior to the finalisation of the systematic review question and the writing of the protocol, which was then registered with PROSPERO.

The Cochrane Collaboration glossary of terms and the University of York guidelines for the conduct of systematic reviews and search strategies were utilised to frame the search. (152,153) Following several scoping searches, five electronic databases were searched to identify evidence: (MEDLINE (Ovid)), (EMBASE (Ovid)), Web of Science, PsycoINFO, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) database. This step was discussed between the research team and then consulted with an experienced medical librarian who is familiar with database searches. These electronic databases were searched for published studies up to October 2021 (the last search was performed on 28 June 2022).

An additional search was also performed via the Internet using Google and Google Scholar search engines.

Strategies were designed from multiple test searches and discussions of the search findings with an expert librarian and reviewed by two other reviewers (Hamde Nazar (HN) and Ilona Obara (IO)). It is common practice to use search filters as a search strategy to retrieve relevant articles from the large volumes of literature that are included in the chosen databases. Additionally, search filters help focus on specific diseases, study designs, and healthcare settings. (171) Table 2.1 presents the search strategies were utilised in MEDLINE and EMBASE databases. A combination of keywords and Medical Subject Heading (MeSH), as outlined in table 2.2, was used in Web of Science. The search for the other databases included the free text search terms “pregabalin”, “gabapentin”, “gabapentinoids” and “neuropathic pain”. The search strategy was restricted to the English language, and there was no limitation by date.

MEDLINE (via OVID) 1. pain.mp. or Pain/ 2. pain*.mp. 3. analgesia/ 4. analges*.mp. 5. neuralgia/ 6. 1 or 2 or 3 or 4 or 5 7. pregabalin/ 8. gabapentin/ 9. 7 or 8 10. randomized clinical trial.mp. 11. 6 and 9 and 10
EMBASE (via OVID) 1. (pregabalin OR lyrica):ti,ab. 2. (gabapentin OR Neurontin);ti,ab 3. 1 or 2 4. pain/ or neuropathic pain/ 5. analgesi*.mp 6. 4 or 5 7. controlled clinical trial/ or randomised clinical trial.mp. 8. 3 and 6 and 7

Table 2-1. *Search strategies entered into MEDLINE and EMBASE.*

#1 Topic = (“neuropathic pain” OR neuropath* OR neuralgi* OR “nerve pain”)
#2 Topic = (Gabapentin* OR Pregabalin* OR Neurontin OR Lyrica)
#3 Topic = (cancer OR neoplasm*)
#4 #1 AND #2
#5 #4 NOT #3

Table 2-2. *Search terms entered into Web of Science.*

2.6.3 Eligibility criteria

There are different frameworks that can be used to help structure the review question and facilitate the search strategy. Examples of frameworks used in health and medicine are PEO (Patient/Population/ Problem, Exposure, and Outcomes) and PICOS (Population, Intervention Comparison ,Outcome, and Study design). (172)

The inclusion and exclusion criteria of studies were conducted in accordance with the PICOS framework. (173) PICOS is a specialised framework commonly used in evidence-based practice

(EBP) to construct specific questions and facilitate literature searches, encompassing each key component of a focused question. (173) PICOS was used as it facilitates the formulation of a question focused on the most relevant issue for the patient. (173) Moreover, it facilitates finding relevant information most efficiently and enables search terms to be grouped into thematic groups to identify medical literature for systematic review.

2.6.3.1 Inclusion criteria

Inclusion criteria were adopted using the PICOS as presented in table 2.2. (174) Fully published RCTs assessing the safety and efficacy of gabapentinoids (pregabalin and gabapentin) for neuropathic pain treatment were identified. The participant in the included studies had to be adults aged ≥ 18 years who had a diagnosis of chronic neuropathic pain. The interventions included using gabapentinoids (pregabalin or gabapentin) consisting of dose, strength, tapering procedure, concomitant medication use, and length of exposure. The comparison arms included patients using other medications to treat neuropathic pain or placebo.

	Inclusion criteria
Participants (P)	Adult patients with neuropathic pain
Intervention (I)	Gabapentinoids (pregabalin or gabapentin) to detail dose, strength, tapering procedure, concomitant medication use, length of exposure, and prior exposure to opioids
Comparison (C)	Placebo or active controls to treat neuropathic pain
Outcomes (O)	*Primary outcomes:* Studies were included if they assessed the safety of gabapentinoids to treat neuropathic pain *Secondary outcomes:* Analgesic effect of gabapentinoids (≥30 or 50% pain intensity reduction) and patient global impression of change PGIC (much improved and very much or much improved)
Study Design (S)	RCTs

***Table 2-3**. The PICOS elements that framed the inclusion criteria. RCTs: randomised controlled trials.*

Types of outcome measures

Primary outcomes

1. Participants who experienced any adverse events especially that affect the central nervous system.
2. Withdrawals due to adverse events.
3. Serious adverse events.
4. Abuse and misuse disorder of gabapentinoids.

Secondary outcomes

The pain has been measured in previous studies using different tools. Most studies used a visual analogue scale (VAS) or numerical rating scale (NRS), or both for measuring pain. Therefore, this study followed the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies. (175) These were defined as:

1. The proportion of participants who achieved ≥50% pain reduction (substantial)
2. The proportion of participants who achieved ≥ 30% pain reduction (moderate)
3. The proportion of participants who reported global impression of clinical change (PGIC) very much improved (substantial)
4. The proportion of participants who reported global impression of clinical change (PGIC; moderate) much or very much improved.

2.6.3.2 Exclusion criteria

Any study focused on animal or in-vitro trials, or paediatric patients were excluded.

2.6.4 Study selection

References and studies retrieved from the electronic databases were imported and placed into Mendeley (reference manager software) as a bibliographic library. Mendeley de-duplication tool was used to identify duplicates (studies that existed in more than one database) that were then removed and placed in a separate library.

The primary researcher Jawza Alotaibi (JA) independently screened and reviewed all titles for relevance. Moreover, duplicates were manually identified by scanning references sorted by

title. Only the primary researcher was responsible for the bibliographic library maintenance and amendment.

Then, two researchers (JA) and (HN) independently assessed the abstracts of these papers against the predetermined inclusion criteria (see section 2.6.3.1). The two authors (JA and HN) independently performed a detailed assessment of the full text of potentially eligible papers against the predetermined inclusion criteria, as mentioned previously, when a decision could not be reached solely based on the abstract. Any differences were resolved by discussion with reference to a third reviewer (IO) if necessary.

2.6.5 Data extraction

Data extraction can be collected using a variety of forms, including the Cochrane Data Collection Form (for RCTs), systematic review software (*e.g.,* Covidence, Review software (RevMan)) or in Excel format. (176) In this study, the data extraction form was developed and adapted from Cochrane Consumers and Communication Review Group's data extraction template. (177) The data extraction form was piloted on random sample studies (JA and HN) and refined accordingly. Discrepancies were resolved by discussion among the research team. (156) Then, two researchers (JA and HN) extracted data independently from each eligible study. A third researcher (IO) was consulted for additional review where appropriate. Data extraction included:

- Bibliometric data (*e.g.,* authors, year of publication);
- Study characteristics (*e.g.,* study design, random sequence generation, allocation concealment, blinding of participants and blinding of outcomes assessment, incomplete outcome data, selective reporting, other bias, and sample size);
- Participants (*e.g.,* age, gender, duration of pain, and type of pain);
- Interventions and controls (*e.g.,* drug class, dose, and treatment period); and
- Outcomes and results (*e.g.,* primary, secondary, adverse events, and the number of withdrawals).

Identified articles for the systematic review were recorded using Mendeley Reference Manager and the extracted data were entered in a table using Word Microsoft Office 365.

2.6.6 Risk of bias in included studies

There are various tools available in order to assess the quality of RCTs, such as the Critical Appraisal Skills Programme (CASP), (178) the Joanna Briggs Institute critical appraisal (JBI), and the Cochrane Risk of Bias (RoB) tool. (179,180) The RoB tool is the most commonly recommended tool for RCTs included in systematic reviews or meta-analyses since it is considered to be one of the most comprehensive tools to assessing bias potential. (179–181) It gives more transparency than other tools by including details of trial conduct, upon which judgments about risk of bias are made. (180) This allows readers to determine whether they agree with the conclusions reached. Therefore, the methodological risk of bias of included studies was assessed and reported using RoB tool as recommended in the Cochrane Handbook for Systematic Reviews of Intervention. (179,180) The risk-of-bias tool (RoB) was used for RCTs which includes five domains: selection bias (randomisation, allocation concealment), performance bias (blinding of participants and study personnel), detection bias (blinding of outcome assessors), report bias (selective outcome reporting) and other factors which may cause bias. Each domain was assigned either low, high, or unclear risk of bias based on the method used. (180)

2.6.7 Statistical analysis

Meta-analysis was performed to compare the safety and efficacy of gabapentinoids (pregabalin and gabapentin) when these outcomes were reported in ≥2 studies. All the statistical analysis was performed using Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

The primary and secondary outcomes (dichotomous outcomes) were pooled using the Mantel-Haenszel method within a random-effects model and presented as risk ratios (RRs) with the corresponding 95% confidence intervals (95% CIs). The random-effects model was chosen based on the anticipated variation between studies due to the inclusion of different types of neuropathic pain (*e.g.,* PHN, DPN, etc.). (182) Meta-analysis results were displayed as a forest plot. Each study can be displayed by a horizontal line (CI). The box in the middle of each line represents effect estimates (RRs). The size of the box is proportional to the weight of the included studies in the meta-analysis. The diamond represents the overall RRs of the

meta-analysis, and the width of the diamond represents the 95% CI of the overall effect (RRs). (183)

A subgroup analysis was performed based on the drug administered (pregabalin and gabapentin) to explore the average effect of these drugs compared to placebo. (184) Furthermore, subgroup analyses were conducted to determine whether there is unexplained heterogeneity between subgroups. Therefore, a *Q* statistic also known as Cochran's chi-square test was performed. The *Q* statistic tests the null hypothesis (H_0) that all included studies have the same true treatment effects. The criterion alpha for the *Q* statistic test is conventionally set at 0.1 rather than the usual 0.05 as recommended. (185–187) For example, if the *P*-value of subgroup analysis <0.1 means that there is a statistically significant subgroup effect. (184) This is due to the low power of the *Q* statistic test of heterogeneity and to prevent false negative errors (type II errors when the H_0 is accepted wrongly, but the H_0 is actually false). (183,185)

Statistical heterogeneity among included studies was assessed by graphical examination of the forest plot, and then evaluation of the heterogeneity using a chi-square test and tau squared (I^2) test. (183) According to the Cochrane interpretation of I^2 statistic value as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

If the I^2= 40% indicates moderate heterogeneity, that means 40% of the observed variance is due to real heterogeneity (subgroup differences) and 60% of the variance is due to chance (*e.g.,* sampling error).

Number needed to harm (NNHs) and NNTs were calculated with the corresponding 95% CI to assess the clinical impact of the beneficial or harmful effect of the treatment. NNHs and NNTs were calculated only if the findings showed statistically significant. The NNH and NNT were calculated through Quickcals (GraphPad software).

The funnel plots are utilised as a visual tool to assess the potential impact of publication bias in analyses of ≥10 studies. (188) In the absence of bias, the plot will resemble approximately a symmetrical inverted funnel. (179) All analyses were performed by JA and reviewed by IO and HN.

2.7 Results

2.7.1 Literature search

Overall, 9359 titles were identified from the literature search, after removing duplications, 7741 titles remained; 7229 articles were removed after screening the titles and abstracts. The remaining 512 potentially relevant studies were assessed for eligibility, and only 50 RCTs were identified that fit the inclusion criteria for the systematic review (Figure 2.1).

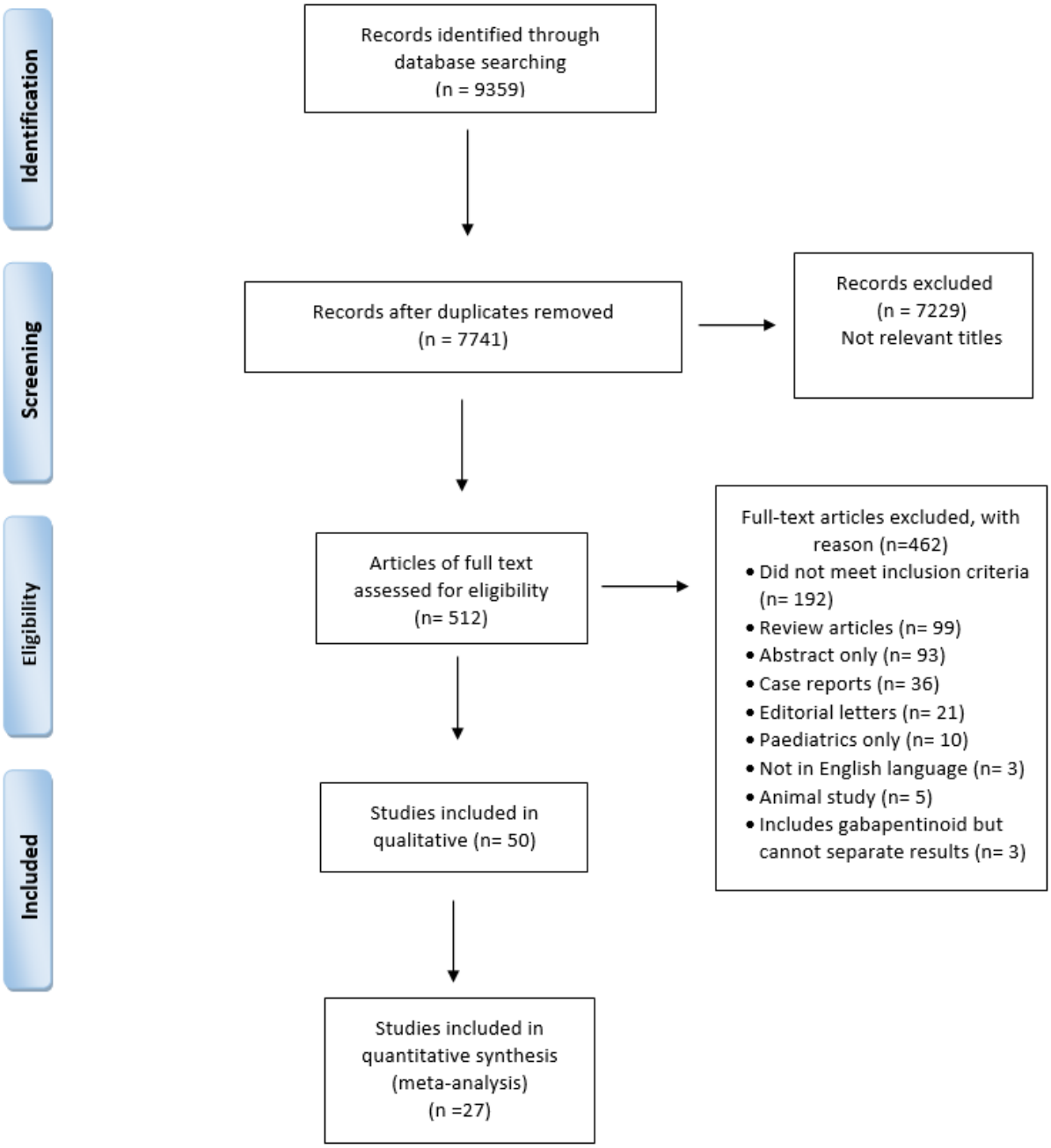


Figure 2-1. *PRISMA flow diagram depicting the search strategy of the included studies in the systematic review and meta-analysis.*

2.7.2 Characteristics of included studies

Out of the 50 RCTs selected for this systematic review, twenty-nine investigated pregabalin (91,92,159,189–214), 16 investigated doses of gabapentin, (215–230), and five studies assessed pregabalin and gabapentin compared to placebo-controlled trials (Table 2.4 and 2.5). (115,231–234)

Half of the included studies were conducted in the USA (n=25). (92,191,194,196,197,200,203–207,215,217–219,221–225,228,230–233) Smaller numbers of studies were undertaken in India (n=3), (192,202,227) China (n=3), (159,209,211) UK (n=2), (190,229) Turkey (n=2), (115,234) and Japan (n=2). (91,189) The review also included one study from Canada, Iran, Germany, Australia and Pakistan. (199,208,212,220,226) Eight studies were reported from an international multicentre. (193,195,198,201,210,213,214,216)

In total, these studies included 12,398 patients randomised to receive gabapentinoids, a placebo or a combination of drugs as comparators. Study sizes ranged from 14 to 804 participants, and the duration of the trials was from 4 to 20 weeks. As summarised in figure 2.2, pregabalin was used at doses of 150, 300, 450 or 600 mg daily and was titrated from 75 mg daily up to the maximum dose of 300 or 600 mg daily, with titration periods between 1 and 4 weeks. As summarised in figure 2.3, gabapentin was used at doses of 1200, 1800, 2400 or 3600 mg daily, with titration periods from 1 to 8 weeks.

Characteristics of studies (*Pregabalin*)											
Author/ year	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	75 mg (n)	150 mg (n)	300 mg (n)	450 mg (n)	600 mg (n)	Flexible dose (n)
Arshad *et al.* 2018. (208)	DPN	NRS ≥4 points 7 days pre-enrolment period ≥ 5 years history of diabetes and symptoms of Pain	6	1 w	BID			160			
MU *et al.* 2017. (209)	DPN	VAS pain ≥50 mm ≥ 1 year history of diabetes and symptoms of Pain	11	1 w	BID	313					
Liu *et al.* 2017. (159)	PHN	VAS pain score ≥ 40 mm	8	1 w	BID		111				
Huffman *et al.* 2017. (210)	PHN	NRS > 4 Pain present for >3 months after herpes zoster infection	17	4 w	OD Controlled release					208	
Pandey *et al.* 2015. (233)	DPN	VAS pain ≥40 mm or pain severity Likert scale ≥4	6	1 w	BID					111	
Liang *et al.* 2015. (211)	PHN	NRS ≥ 4 Pain occurring within 90 days of rash onset	4	1 w	OD					150[a]	
Yilmaz *et al.* 2015. (115)	Neuropathic Pain associated with spinal cord injury	-Leeds Assessment of Neuropathic Symptoms and Signs score > 12	18	8 w	BID		15				
Razazian *et al.* 2014. (212)	DPN	VAS pain score ≥40 mm History of neuropathic pain for at least 3 months	5	1 w	BID		86				
Simpson *et al.*2014. (213)	Neuropathic pain associated with HIV neuropathy	VAS pain score >40mm ≥ 3 months before screening Patient had at least two of the three following neurological signs: reduced or absent achilles tendon reflexes; reduced super- facial sensation in the distal lower extremities bilaterally (using the pinprick test); and reduced vibratory sensation in the lower extremities.	17	4 w	OD					183[a]	

Characteristics of studies (*Pregabalin*)											
Author/ year	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	75 mg (n)	150 mg (n)	300 mg (n)	450 mg (n)	600 mg (n)	Flexible dose (n)
Raskin *et al.* 2014. (214)	DPN	VAS pain score ≥40 mm or NRS≥4 ≥ 3 months diagnosis of painful diabetic distal symmetrical sensorimotor polyneuropathy	20	4 w	OD			147[b]			
Irving *et al.* 2014. (232)	DPN	NRS > 4	12	1 w	BID or TID			138			
Tesfaye *et al.* 2013. (201)	DPN	The diagnosis had to be confirmed by a score of ≥3 on the Michigan Neuropathy Screening Instrument at screening. 24-hour average pain severity of ≥4 on BPI-MSF	8	0	OD					403	
Ohta *et al.* 2012. (189)	Fibromyalgia	NRS > 4 or VAS pain score ≥40 mm Fibromyalgia Diagnostic Criteria*	15	3 w	BID				451		
Boyle *et al.* 2012. (190)	DPN	LANSS score > 12 ≥ 1 years history of neuropathic pain of diabetes	4	1 w	BID					27	
Achar *et al.* 2012. (192)	PHN	VAS pain score ≥40 mm Pain occurring within 30 days of rash onset	8	1 w	OD		25				
Kelle *et al.* 2012. (234)	Neuropathic pain due to peripheral injury	LANSS score ≥ 12	12	0	BID	15					
Rauck *et al.* 2012. (231)	DPN	11-point Numerical Rating Scale ≥4 Diagnosed type 1 or 2 diabetes and distal symmetric sensorimotor polyneuropathy for 6 months to 5 years	20	1 w	OD			56			
Gilron *et al.* 2011. (92)	Peripheral neuropathic Pain	NRS ≥4	9	1 w	OD						300-600 (80)
Simpson *et al.* 2010. (191)	Painful HIV neuropathy	NRS ≥4 Painful HIV-DSP for ≥ 3 months	14	2 w	OD					151	
Satoh *et al.* 2010. (91)	DPN	NRS ≥4 or VAS pain score ≥40 mm	14	1 w	BID					140	

Characteristics of studies (*Pregabalin*)											
Author/ year	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	75 mg (n)	150 mg (n)	300 mg (n)	450 mg (n)	600 mg (n)	Flexible dose (n)
Van Seventer *et al.* 2010. (197)	Post-traumatic peripheral neuropathic pain	VAS pain score ≥40 mm Post-traumatic peripheral neuropathic pain, confirmed by a pain specialist, pain persists≥ 3 months	8	1 w	OD					127	
Baron *et al.* 2010. (198)	Neuropathic pain associated with chronic lumbosacral radiculopathy	NRS ≥4 Pain had to be present ≥ 3 months prior to the study, stable for ≥4 weeks	10	4 w	OD						150-600 (110)
Hewitt *et al.* 2010. (205)	Chronic neuropathic pain	NRS >5, <10 Pain present for >3 months after herpes zoster infection	8	2 w	OD						150-200 (53)
Stacey *et al.* 2008. (193)	PHN	VAS pain score ≥40 mm Pain present for >3 months after herpes zoster infection	4	1 w	OD			91			150-600 (88)
Arezzo *et al.* 2008. (194)	DPN	VAS pain score ≥40 mm Duration of painful DPN ≥ 3 months	13	1 w	BID				82		
Tolle *et al.* 2008. (195)	DPN	VAS pain score ≥40 mm ≥ 1 year history of diabetes and symptoms of Pain	12	1 w	BID		99	99		101	
Mease *et al.* 2008. (207)	Fibromyalgia	NRS ≥4	13	1 w	BID			185	183	190	
Vranken *et al.* 2007. (196)	Central neuropathic pain	LANSS score > 12 -Pain persists≥ 6 months	4	3 d	OD						150-600[d] (20)
Siddall *et al.* 2006. (199)	Central neuropathic pain associated with spinal cord injury	VAS pain score ≥40 mm or NRS > 4 ≥ 1 year history of symptoms of Pain	12	1 w	OD					70	
Richter *et al.* 2005. (200)	DPN	VAS pain score ≥40 mm or NRS ≥ 4 1- 5 years history of diabetes and symptoms of Pain	6	2 w	OD		79			82	

Characteristics of studies (*Pregabalin*)											
Author/ year	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	75 mg (n)	150 mg (n)	300 mg (n)	450 mg (n)	600 mg (n)	Flexible dose (n)
Van Seventer *et al.* 2006. (206)	PHN	VAS pain score ≥40 mm or NRS > 4 Pain present for >3 months after herpes zoster infection	13	1 w	BID		87	98		90	
Rosenstock *et al.* 2004. (202)	DPN	VAS pain score ≥40 mm or NRS ≥ 4 1- 5 years history of diabetes and symptoms of Pain	8	0	TID			76			
lesser *et al.* 2004. (204)	DPN	VAS pain score ≥40 mm or NRS ≥4 Diagnosed type 1 or 2 diabetes and distal symmetric sensorimotor polyneuropathy for 1 to 5 years	10	1 w	OD	77		80		82	
Dworkin *et al.* 2003. (203)	PHN	VAS pain score ≥40 mm or NRS ≥4 Pain present for >3 months after herpes zoster infection	8	1 w	OD					89	

Table 2-4. Characteristics of studies (Pregabalin).

*Presented in chronological order.

[a] *up to 600 mg/day according to the tolerability of adverse events*
[b] *up to 300 mg/day according to the tolerability of adverse events*
[c] *up to 600 mg/day according to creatinine clearance*
[d] *increased the dose according to pain relief*
OD: once daily, BID: twice daily, TID: thrice daily, BPI-MSF: Brief Pain Inventory Modified Short Form, DPN: Diabetic Peripheral Neuropathy, PHN: Postherptic Neuralgia, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs score, NRS; Numerical Rating Scale, VAS: Visual Analogue Scale.
** The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia.*

Characteristics of studies *(Gabapentin)*										
Author	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	1200 mg (n)	1800 mg (n)	2400 mg (n)	3600 mg (n)	Flexible dose (n)
Yilmaz *et al.* 2015. (115)	Neuropathic Pain associated with spinal cord injury	LANSS score > 12	18	8 w	TID		15			
Freeman *et al.* 2015. (223)	PHN	NRS ≥4 Neuropathic pain for > 3 months or ≥6 months after the healing of herpes zoster skin rash	10	2 w	OD		357			
Pandey *et al.* 2015. (233)	DPN	VAS pain scale ≥40 mm or NRS ≥4	6	1 w	BID					900-3600 mg
Irving *et al.* 2014. (232)	DPN	NRS ≥4	12	1 w	OD					900 mg/day
Sang *et al.* 2013. (216)	PHN	NRS ≥4 Persistent pain for 6 months to 5 years	10	2 w	OD		221			
Gupta and Li 2013. (230)	PHN	NRS ≥4 Neuropathic pain for > 3 months or ≥6 months after the healing of herpes zoster skin rash	8	2 w	OD		359			
Sandercock *et al.* 2012. (224)	DPN	NRS ≥ 4 Diagnosed type 1 or 2 diabetes and distal symmetric sensorimotor polyneuropathy for 6 months to 5 years	4	2 w	OD BID				3000 mg 46	1800 am +1200 pm
Kelle *et al.*2012. (234)	Neuropathic pain due to peripheral injury	LANSS score ≥ 12	12	0	OD			15		
Rauck *et al.*2012. (231)	DPN	NRS≥4 Diagnosed type 1 or 2 diabetes and distal symmetric sensorimotor polyneuropathy for 6 months to 5 years	20	1 w	OD	56		56	117	
Backonja *et al.* 2011. (225)	PHN	NRS ≥4 or visual analogue scale pain ≥40 mm Diabetic neuropathy for 1-5 years	4	1 w	TID	47				
Wallace *et al.* 2010. (215)	PHN	NRS ≥ 4 Pain present for >3 months after herpes zoster infection	10	2 w	OD BID		136			600 am +1200 pm

Characteristics of studies *(Gabapentin)*										
Author	Disease	Diagnostic test	Study duration (weeks)	Titration Phase	Drug regimen	1200 mg (n)	1800 mg (n)	2400 mg (n)	3600 mg (n)	Flexible dose (n)
Dworkin *et al.* 2009. (217)	Acute pain in herpes zoster	Herpes zoster within 6 calendar days of rash onset The worst Pain in the past 24 h ≥ 3 on NRS	4	1 w	TID		29			
Arnold *et al.* 2007. (228)	Fibromyalgia	NRS ≥ 4 Fibromyalgia Diagnostic Criteria*	12	1 w	BID		75			
Chandra *et al.* 2006. (227)	PHN	NRS ≥4 or VAS pain score ≥40 mm Pain present for >2 months after herpes zoster infection	9		TID			38		
Gilron *et al.* 2005. (220)	DPN	NRS ≥4 or VAS pain scale ≥40 mm	5	0	OD			57		
Hanh *et al.* 2004. (226)	Painful HIV neuropathy	Symptoms of painful HIV-SN, Diagnosed by a neurologist based on history, as well as clinical and neurophysiological examination	4	4 D	TID			15		
Rintala *et al.* 2007. (221)	Neuropathic Pain associated with spinal cord injury	NRS >5 SCI occurred at least 12 months before entering the study Persistent Pain for 6 months to 5 years	9	0	TID	38				
Tai *et al.* 2002. (219)	Neuropathic Pain associated with spinal cord injury	NRS ≥4 Neuropathic pain confirmed by an SCI physician Traumatic injury for ≥ 30 days	10	1 w	OD		7			
Rice *et al.* 2001. (229)	PHN	NRS ≥4	7	4 D	OD		115	108		
Backonja *et al.* 1998. (218)	DPN	NRS ≥4 or VAS pain score ≥40 mm Persistent pain for 1 to 5 years	8	4 w	OD				84	
Rowbotham *et al.* 1998. (222)	PHN	NRS ≥4 or VAS pain score ≥40 mm ≥ 3 months after healing of Herpes zoster rash skin	8	4 w	TID				113	

Table 2-5. *Characteristics of studies (Gabapentin). *Presented in chronological order.*
OD: once daily, BID: twice daily, TID: thrice daily, BPI-MSF: Brief Pain Inventory Modified Short Form, DPN: Diabetic Peripheral Neuropathy, PHN: Postherptic Neuralgia, LANSS: Leeds Assessment of Neuropathic Symptoms and Signs score, NRS; Numerical Rating Scale, VAS: Visual Analogue Scale.

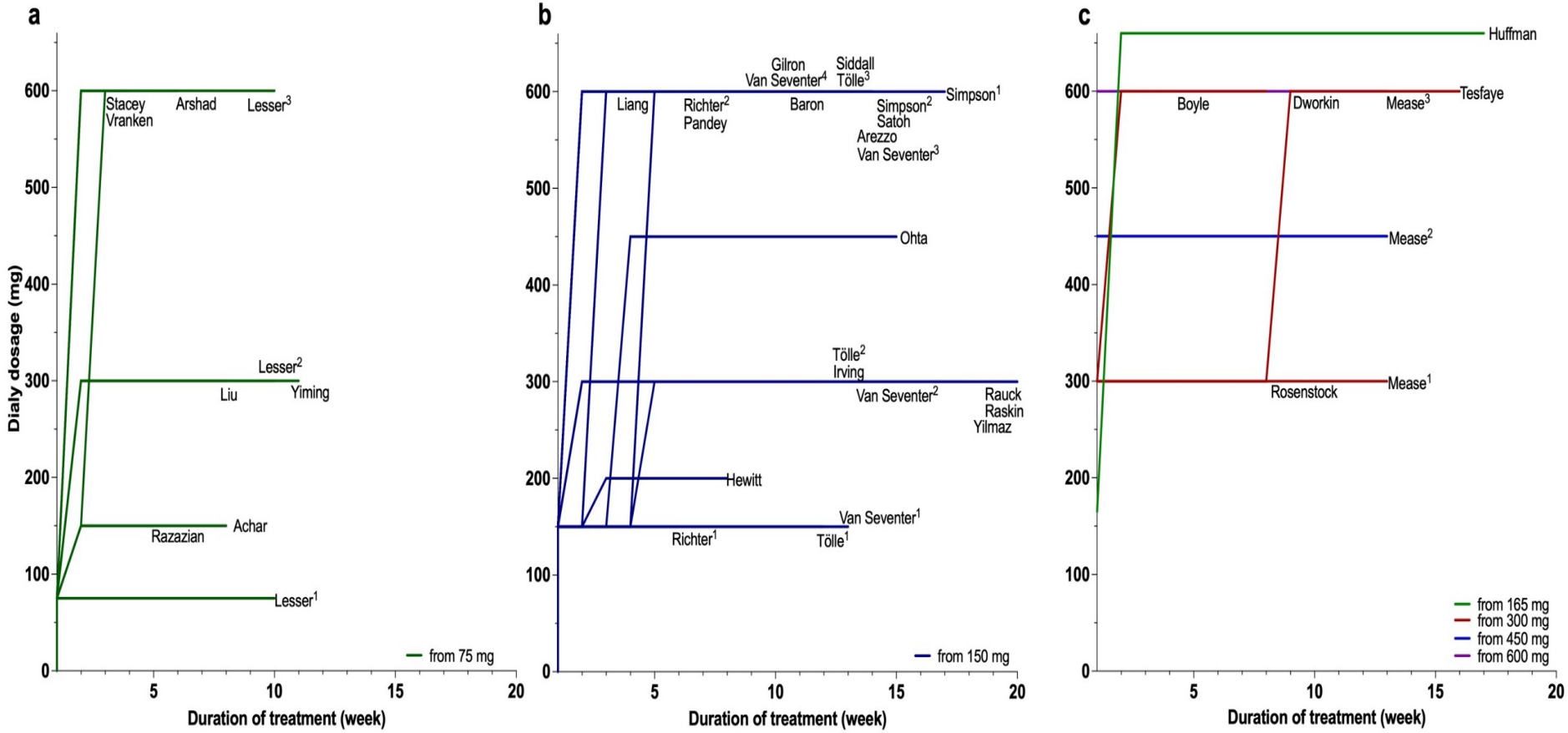


Figure 2-2. *Dose escalation chart and maximum daily dose used in the included studies for pregabalin. Number 1, 2 or 3 next to the name refers to the arms in the included study.*

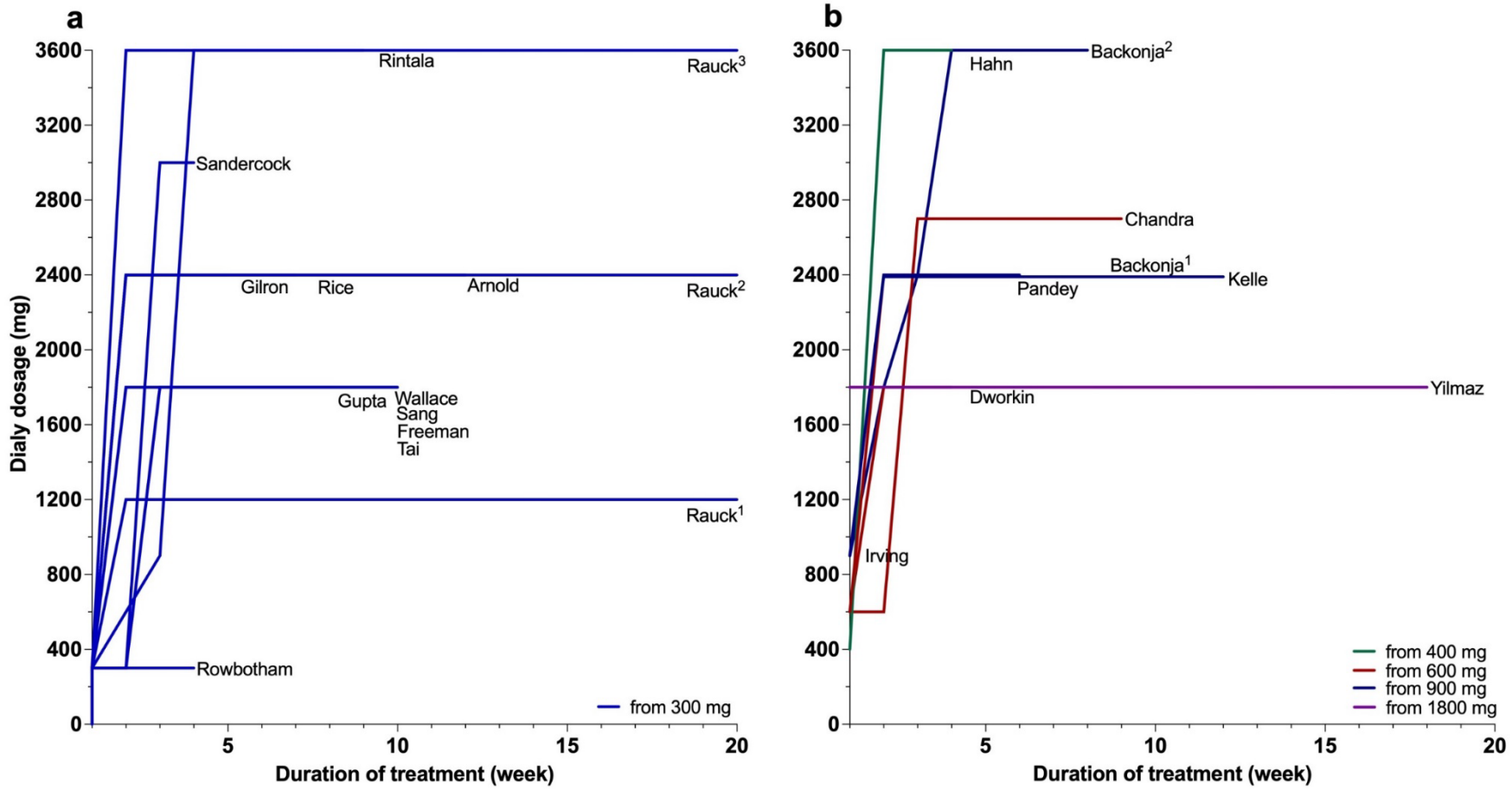


Figure 2-3. *Dose escalation chart and maximum daily dose used the included studies for gabapentin. Number 1, 2 or 3 next to the name refers to the arms in the included study.*

2.7.3 Quality assessment of included studies

The risk of bias across all included studies is summarised in figure 2.4 presented as percentages (%). Of the 50 included trials, 27 (54%) studies appeared to have an unclear risk of bias (91,159,189–191,193–195,197,199–204,206,207,209,210,213–216,222,228,229,231), while the remaining 23 (46%) studies were considered as having a high risk of bias. (92,115,192,196,198,205,208,211,212,217–221,223–227,230,232–234) The studies at high risk were excluded from the meta-analysis (Appendix A).

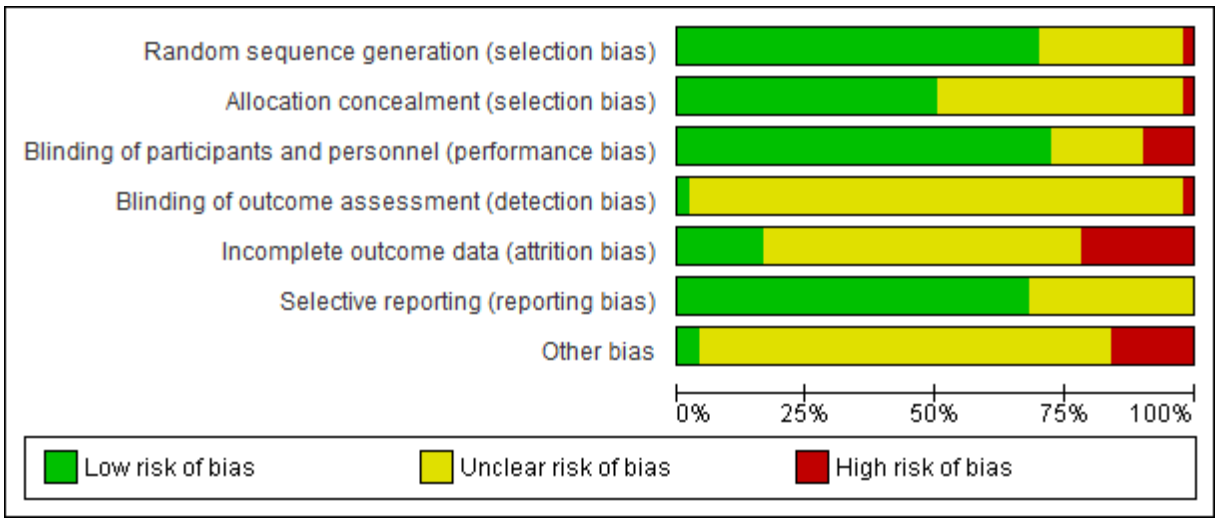


Figure 2-4. *Risk of bias graph: review authors' judgements about each risk of bias item, presented as % across all included studies.*

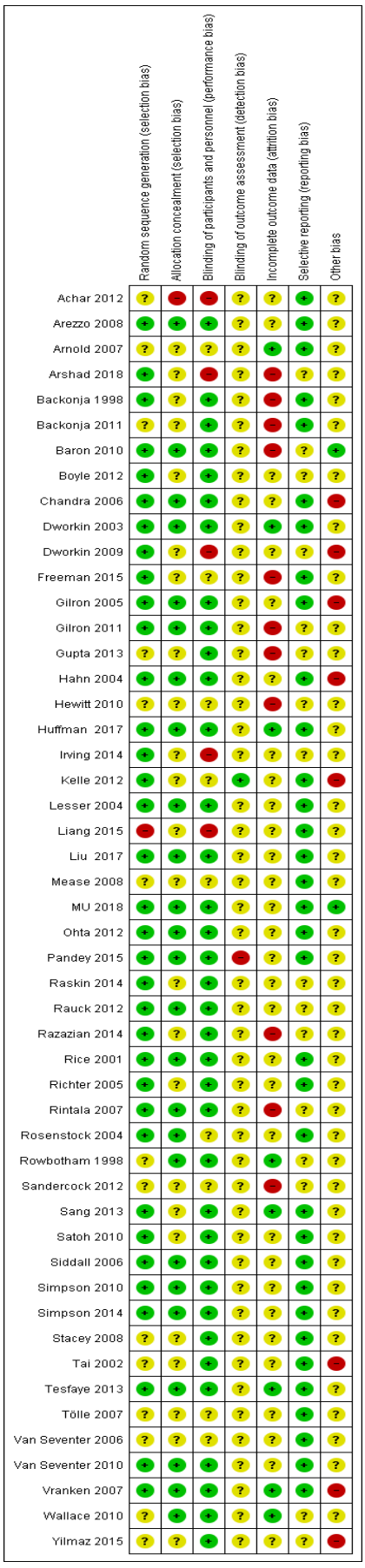


Figure 2-5. *Risk of bias assessments for the included studies: review authors' judgements about each risk of bias item for each included study. Any study judged as a high risk for any element of quality assessment was later excluded from the meta-analysis.*

indicates low risk *indicates unclear risk* *indicates high risk*

2.7.3.1 Selection bias: randomisation and allocation

As shown in figure 2.5, random sequence generation method was clearly described in 35 (70%) of the included studies. (91,92,159,189–191,194,196–204,208–210,212–214,216–218,220,221,223,226,227,229,231–234) The most common method used for random sequence generation method was computer-generation-randomisation using either a computer-generated random number or random schedule. Fourteen (28 %) included studies were judged as unclear risk of bias since the random sequence generation method was not reported (115,192,193,195,205–207,215,219,222,224,225,228,230) and one (2%) study was judged as high risk of bias due to using the sequences of patients who came to the hospital. (211)

Allocation concealment was adequate in 25 (50%) of the included studies and were judged to have a low risk. (92,115,159,189,191,194,196–199,201–204,209,210,213,215,221,222,226,227,229,231,233) While in the other 24 (48%) studies the information provided was inadequate to assess the risk of bias and was considered unclear. (91,115,190,193,195,200,205–208,211,212,214,216–220,223–225,228,230,232) One (2%) study was considered at high risk of bias because of using odd or even numbers for the allocation concealment method. (192)

2.7.3.2 Performance bias: blinding participants and personnel

Thirty-six studies (72%) of the included studies were double-blind studies (blinding both participants and researchers), and blinded treatments (active medication and placebo) were described as externally identical in some trials. (91,92,115,159,189–191,193,194,196–201,203,204,207–210,212–216,219,221,222,225–227,229–231,233,234) Accordingly, these studies were considered at low risk of performance bias. The blinding method was not reported in 9 (18%) of the included studies were considered to have unclear preference bias. (195,202,205,206,218,220,223,224,228) The remaining 5 (10%) studies were considered to have a high risk of bias in two single-blind and two open-label studies as both researchers and participants were aware of the assigned arm. (192,208,211,217,232)

2.7.3.3 Detection bias: blinding outcome assessment

Blinding of outcome assessment was insufficiently reported in 48 (96%) of included studies and was judged as an unclear risk of bias. (91,92,115,159,189–232) One (2%) of included studies was deemed as a low risk of bias (234), and one (2%) study was considered to have a high risk of detection bias. (233)

2.7.3.4 Attrition bias: incomplete outcome data

In total, 30 (60%) out of the 50 included studies were deemed to have an unclear risk of bias due to an insufficient description of outcome data. (91,115,159,189–200,202,204,206,207,209,211,213,214,217,219,220,226,229,232,233) While 12 (24%) were assigned as a high risk of bias due to the use of per-protocol analysis (*e.g.,* excluded participates who loss to follow-up). (92,205,208,212,218,221,223–225,230,231,234) The remaining 8 (16%) studies were assessed as at low risk of bias and the data were analysed based on an intention-to-treat (ITT) which included all participants who had received at least one dose of treatment in the analysis process. (201,203,210,215,216,222,227,228)

2.7.3.5 Reporting bias: selective reporting

Overall, 37 (70%) studies reported all pre-specified outcomes. Therefore, these studies were judged as a low risk of reporting bias. (91,159,189,191–197,199–204,206,207,209–211,213,216,218–221,223,225–229,233,234) Whereas in the other 15 (30%) of the included studies the provided information was inadequate to judge and was considered unclear of bias risk. (92,115,190,198,205,208,212,214,215,217,222,224,230–232)

In term of other potential sources of bias, the majority (78%) of studies were considered as unclear risk of bias (91,159,189–195,197,199–208,210–216,218,222–225,228–232,234), while 9 (18%) studies were deemed to have a high risk of bias due to the study design of these studies (*e.g.,* crossover or enriched enrolment with randomised withdrawal). (92,115,196,217,219–221,226,227) Only two (4%) trials were considered at low risk of bias. (198,209)

2.7.4 Primary outcomes

2.7.4.1 Reported adverse events

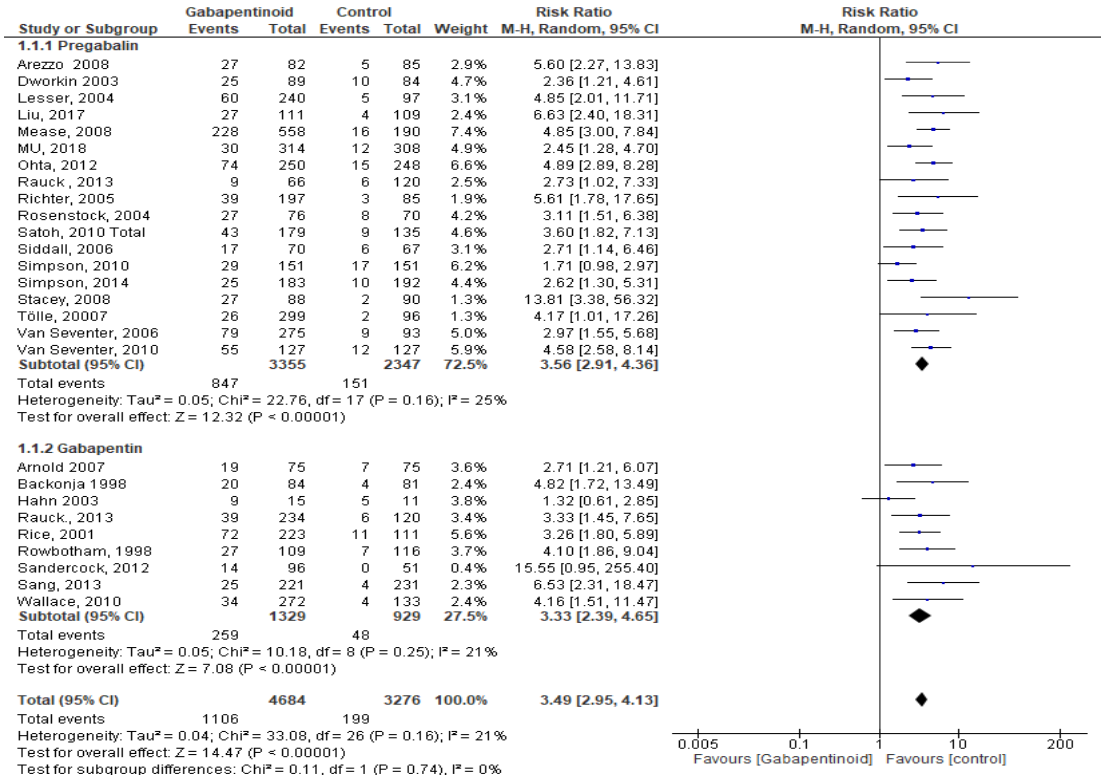
Adverse events are categorised according to the body systems as follows:

Nervous system disorder

1. Dizziness

In 36 trials (7960 participants), as shown in figure 2.6, the risk of dizziness was significantly increased with gabapentinoid use (RR 3.49; 95 % CI 2.95, 4.13; *P*<0.0001). There was no significant heterogeneity across the included studies (I^2=21%).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.74). The included studies reported the risk of dizziness as an adverse event in 27 pregabalin studies and nine gabapentin studies. The risk ratio of dizziness demonstrated a statistically significant difference in the pregabalin group compared to the placebo group (RR 3.56; 95% CI 2.91, 4.36; *P*<0.00001; I^2=25%), likewise, gabapentin *versus* placebo (RR 3.33; 95% CI 2.39, 4.65; *P*<0.00001; I^2=21%). The NNH of pregabalin was 6 (95% CI 4.8, 5.8), while gabapentin was 8 (95% CI 5.9, 8.5). Visual inspection of the funnel plot shows a relatively symmetric funnel indicating that publication bias is unlikely, as presented in figure 2.6.



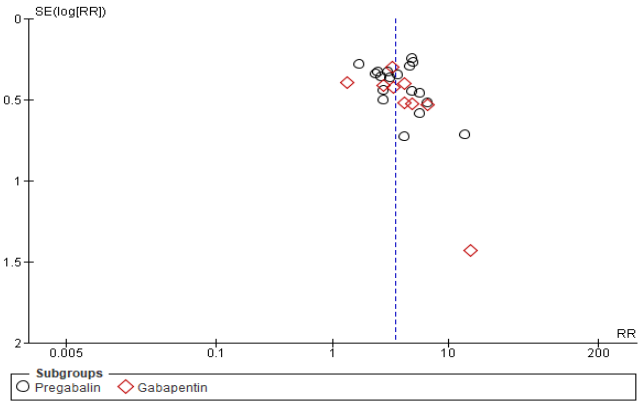


Figure 2-6. *Forest and funnel plots of the risk of dizziness between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin and gabapentin).*
CI: confidence interval, SE: standard error, RR: risk ratio.

2. Somnolence

Overall, 27 RCTs with 7924 participants reported that the risk of somnolence was significantly increased with using gabapentinoids treatment compared to placebo (RR 3.09; 95% CI 2.62, 3.64; *P*<0.00001). There was no significant heterogeneity among the included studies (I^2=5%).

There was no statistically significant effect across the two groups (*P*=0.55). There were 18 pregabalin studies and nine gabapentin RCTs included in the analysis. The risk ratio of somnolence showed a statistically significant difference in the comparison of pregabalin against placebo (RR 3.28; 95% CI 2.62, 4.11; *P*<0.00001; I^2=25%) and gabapentin *versus* placebo (RR 2.91; 95% CI 2.10, 4.03; *P*<0.00001; I^2=0%). There was no significant heterogeneity across the included studies. The NNH of pregabalin was 7 (95% CI 6.4, 8.2) and gabapentin was 3 (95% CI 9.5, 16.6). Visual inspection of the funnel plot shows a symmetry funnel (Figure 2.7).

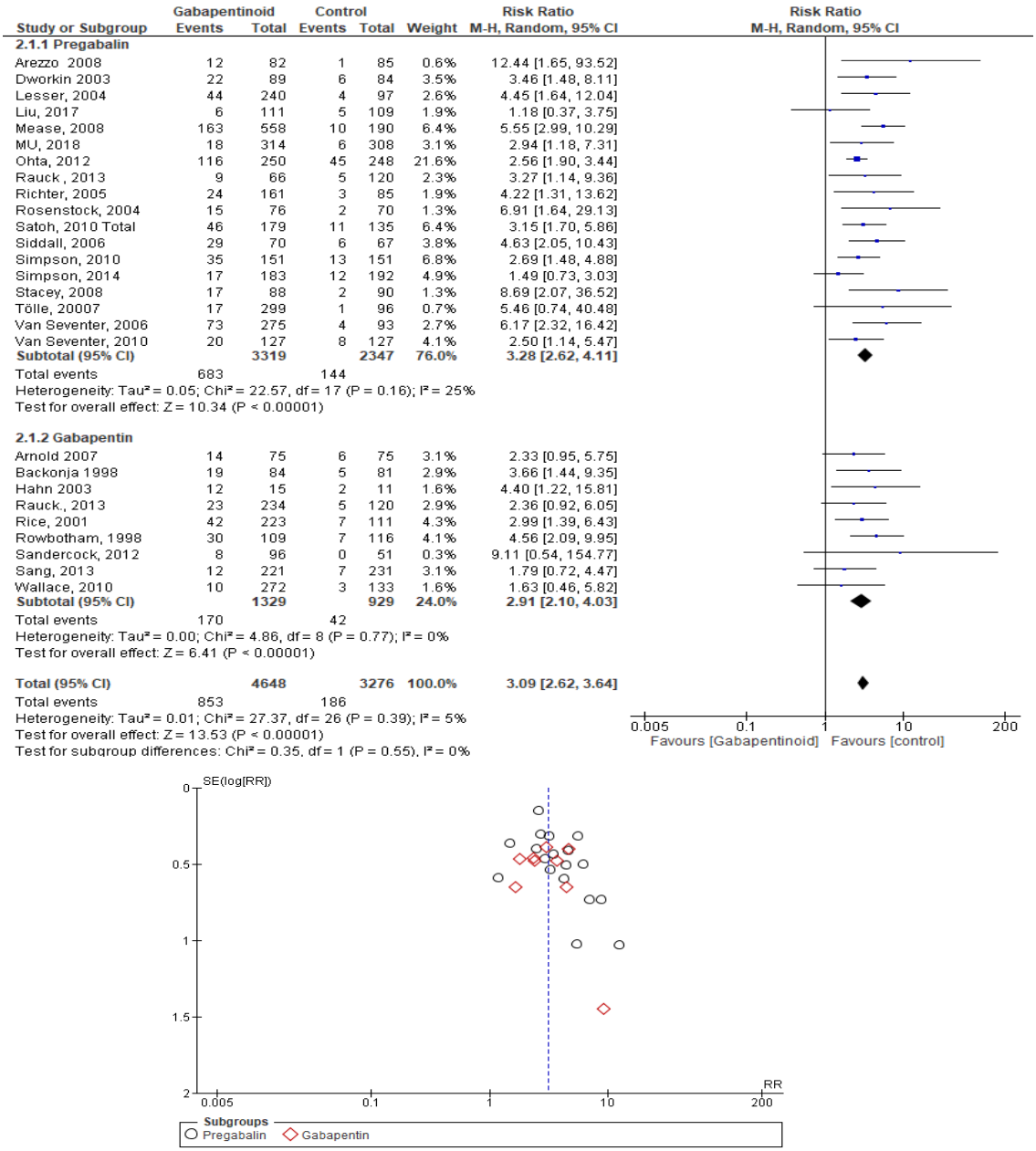


Figure 2-7. *Forest and funnel plots of the risk of somnolence between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin and gabapentin).*
CI: confidence interval, SE: standard error, RR: risk ratio.

3. Ataxia

In 7 RCTs, there was a significant increase in the risk of ataxia with gabapentinoids treatment compared to placebo (RR 4.31; 95% CI 2.06, 9.01). No significant heterogeneity was observed across the included studies (I^2=9%) (Figure 2.8).

Subgroup analysis showed that there was no statistically significant subgroup effect (*P*=0.69). Five pregabalin RCTs (1793 participants) compared pregabalin to placebo. The forest plot illustrated a statistically significant difference between pregabalin and placebo (RR 6.02; 95% CI 2.31,15.68; *P*=0.0002). There was no significant heterogeneity across the included studies (I^2=0%). The pregabalin's NNH was 20 (95% CI 16.6, 27.0).

Only two RCTs of gabapentin (251 participants) reported ataxia as an adverse event. The risk ratio of ataxia showed no statistically significant difference in the comparison of gabapentin against placebo (RR 3.81; 95% CI 0.49, 29.8; *P*=0.20). There was substantial heterogeneity across the 2 RCTs (I^2=69%). The NNH of gabapentin was 9 (95% CI 5.5, 22.4).

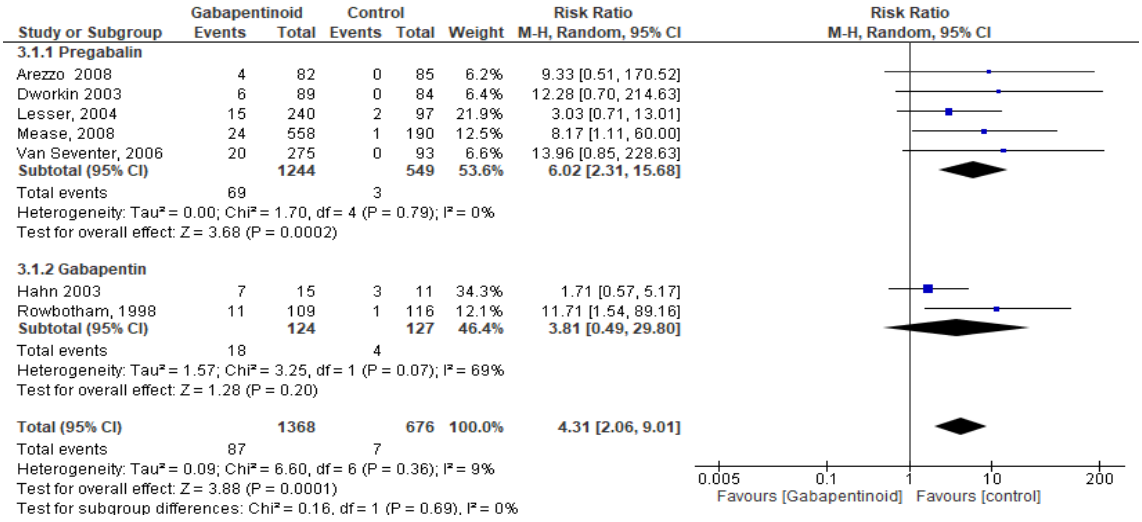


Figure 2-8. *Forest plot of the risk of ataxia between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin). CI: confidence interval.*

4. Amnesia

As shown in figure 2.9, the risk of amnesia was reported in three pregabalin studies (652 participants), and the risk ratio of amnesia showed a statistically significant difference (RR 3.38; 95% CI 1.08, 10.62; *P*=0.04). No heterogeneity was found across trials (I^2 =0%). The NNH of pregabalin was 34 (95% CI 19.3, 201.6).

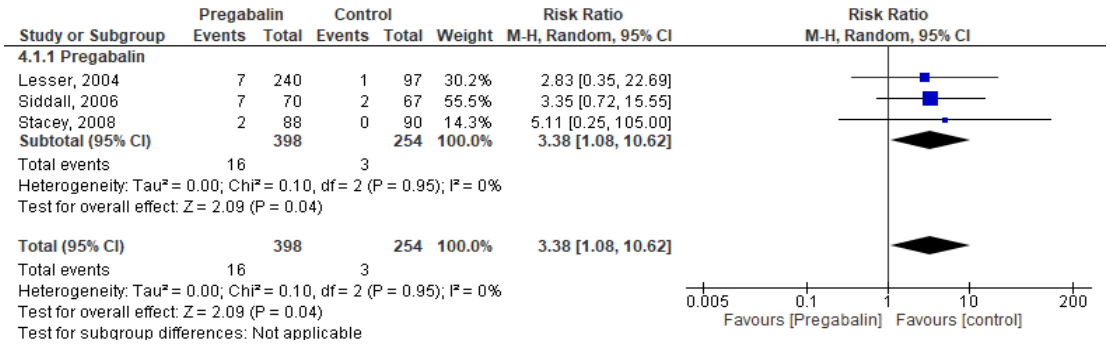


Figure 2-9. *Forest plot of the risk of amnesia between the two groups (gabapentinoids vs placebo). CI: confidence interval.*

5. Abnormal gait

Overall, three RCTs of pregabalin with 719 participants were included in the meta-analysis. The risk ratio of abnormal gait was 6.71 (95% CI 1.57, 28.71; *P*=0.01), with no heterogeneity found across trials (I^2 =0%) (Figure 2.10). The NNH of pregabalin was 29 (95% CI 18.7, 63.6).

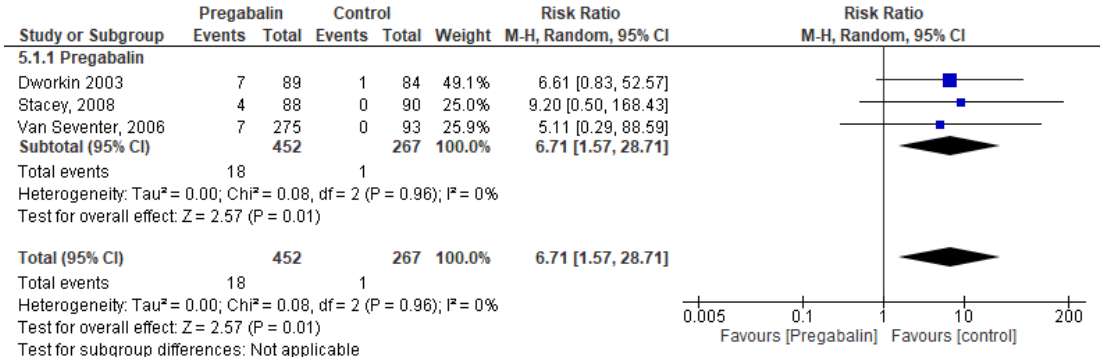


Figure 2-10. *Forest plot of the risk of abnormal gait between the two groups (pregabalin vs placebo). CI: confidence interval.*

6. Incoordination

Only three studies of pregabalin (1294 participants) reported incoordination as an adverse effect. The risk ratio of incoordination demonstrated a statistically significant difference (RR 7.21; 95% CI 1.36, 38.25; *P*=0.02). There was no heterogeneity found across trials (I^2=0%), as shown in figure 2.11. The NNH of pregabalin was 31 (95% CI 22.7, 47.4). The NNH was 31 (95% CI 22.7, 47.4).

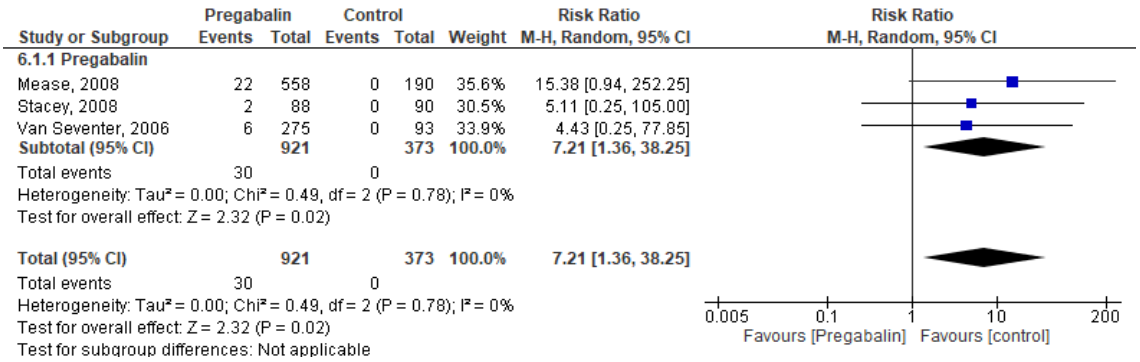


***Figure 2-11**. Forest plot of the risk of incoordination between the two groups (pregabalin vs placebo). CI: confidence interval.*

7. Asthenia

In 10 RCTs (3028 participants), the risk of asthenia was increased significantly with gabapentinoids use (RR 1.83; 95% CI 1.24, 2.71). No heterogeneity was found across trials (I^2=0%) (Figure 2.12).

There was no statistically significant subgroup difference (*P*=0.44). Overall, eight studies of pregabalin (2544 participants) and only two gabapentin RCTs (484 participants) reported asthenia as an adverse event. The risk ratio of asthenia demonstrated a statistically significant difference in the comparison of pregabalin against placebo (RR 2.0; 95% CI 1.28, 3.70; *P*=0.002), while the risk ratio in gabapentin RCTs showed no statically significant difference compared to placebo (RR 1.40; 95% CI 0.64, 3.09; *P*=0.40). The NNH of pregabalin was 33 (95% CI 21.3, 68.5).

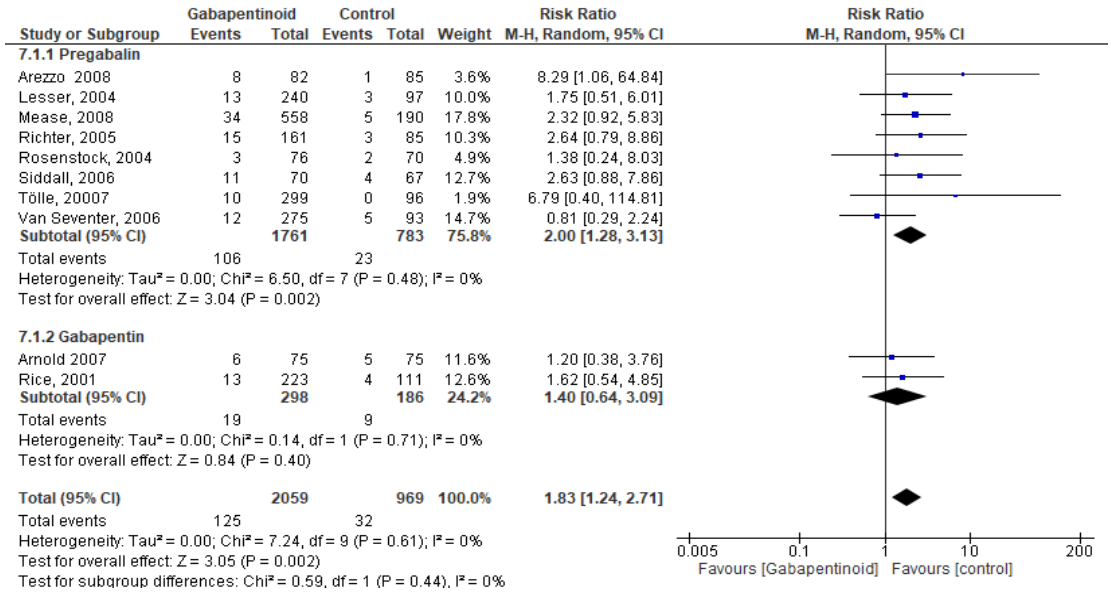


Figure 2-12. *Forest plot of the risk of asthenia between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin and gabapentin). CI: confidence interval.*

There were many adverse events that showed no statistically significant difference compared to placebo as the risks ratio included unity. These adverse events were headache, disturbance in attention, nausea, pain, and back pain.

Psychiatric disorder

1. Confusion

In four RCTs of pregabalin (1056 participants), the risk ratio of confusion showed a statistically significant difference in the comparison of pregabalin against placebo (RR 4.01; 95% CI 1.42, 11.34: *P*=0.002). There was no heterogeneity found across trials (I^2=0%). The NNH was 30 (95% CI 19.5, 62.2). Among the studies comparing gabapentin to placebo, only one reported confusion as an adverse event (Figure 2.13).

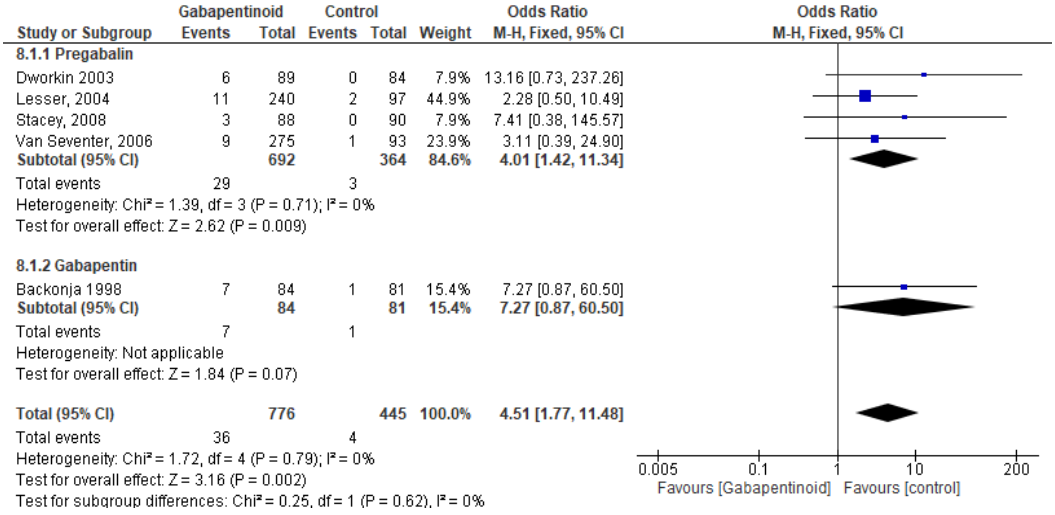


Figure 2-13. *Forest plot of the risk of confusion between the two groups (gabapentinoids vs placebo). CI: confidence interval.*

2. Euphoria

The risk of euphoria was reported in six RCTs of pregabalin (Figure 2.14). The pooled results comparing pregabalin against placebo showed a statistically significant difference (RR 6.01; 95% CI 3.02, 11.97; *P*<0.00001). There was no heterogeneity observed across trials (I^2 =0%). The NNH was 16 (95% CI 12.1, 22.4).

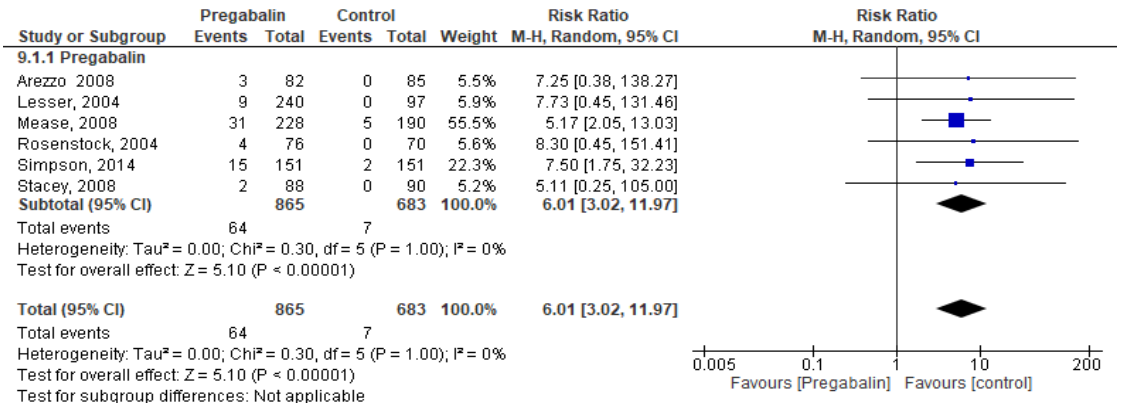


Figure 2-14. *Forest plot of the risk of euphoria between the two groups (pregabalin vs placebo). CI: confidence interval.*

3. Abnormal thinking

Overall, only four pregabalin studies (1420 participants) reported abnormal thinking as an adverse event (Figure 2.15). The risk ratio of abnormal thinking demonstrated a statistically significant difference between pregabalin and placebo (RR 5.46; 95% CI 2.09, 14.32; *P*=0.0005), with no heterogeneity found across trials (I^2=0%). The NNH was 20 (95% CI 14.8, 30.3).

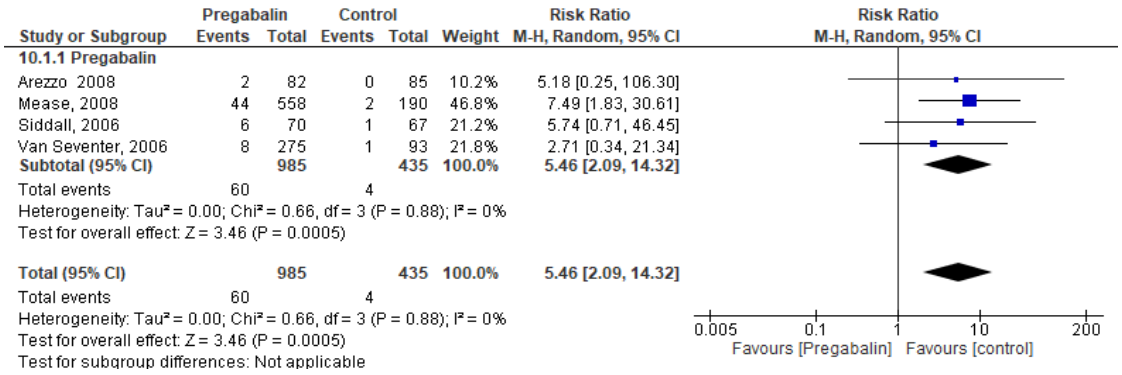


Figure 2-15. *Forest plot of the risk of abnormal thinking between the two groups (pregabalin vs placebo). CI: confidence interval.*

One adverse effect was not significantly different in comparing pregabalin to placebo as the risk ratio included unity. This adverse effect was the abnormal feeling, and the risk ratio pooled results was 3.98 (95% CI 0.78, 20,42).

Eye disorder

1. Amblyopia

As shown in figure 2.16, seven pregabalin studies (2155 participants) reported amblyopia, the risk ratio of the pooled results showed a statistically significant difference compared to placebo (RR 2.90; 95% CI 1.39, 6.03; *P*=0.005), with no heterogeneity found across trials (I^2=0%). The NNH was 25 (95% CI 17.2, 20.2). Only one gabapentin study reported an amblyopia adverse event.

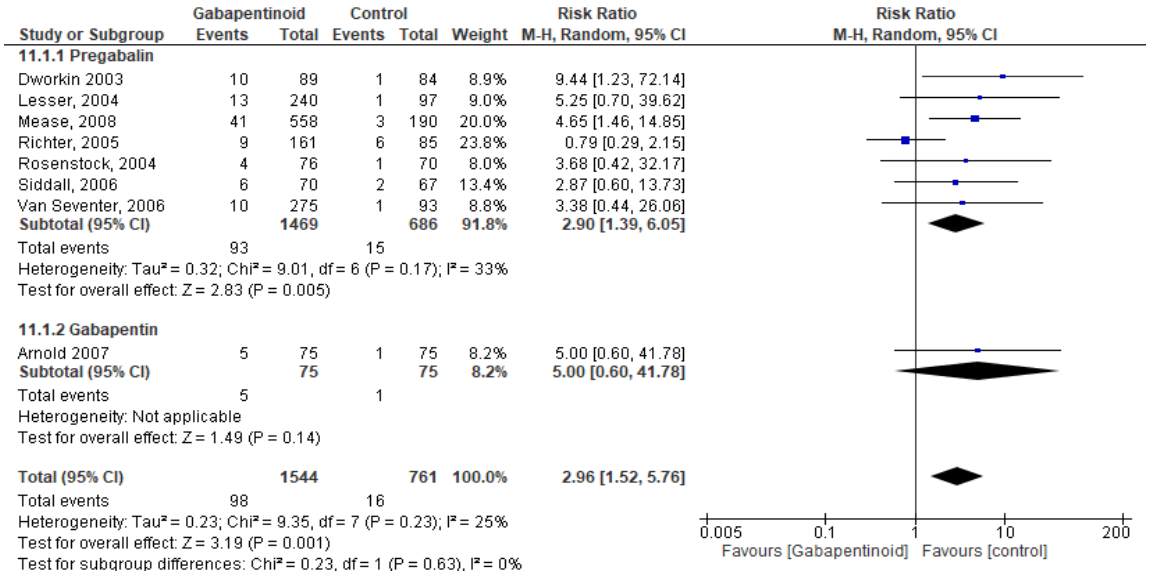


Figure 2-16. *Forest plot of the risk of amblyopia between the two groups (gabapentinoids vs placebo). CI: confidence interval.*

2. Blurred vision

Overall, only four RCTs of pregabalin (1306 participants) reported blurred vision as an adverse effect. The risk ratio of the pooled results demonstrated a statistically significant difference compared to placebo (RR 2.59; 95% CI 1.25, 5.39; *P*=0.01). No heterogeneity was found across included trials (I^2=0%) (Figure 2.17). The NNH was 39 (95% CI 22.5, 138.6). Only one study reported a blurred vision adverse event of gabapentin when compared to placebo.

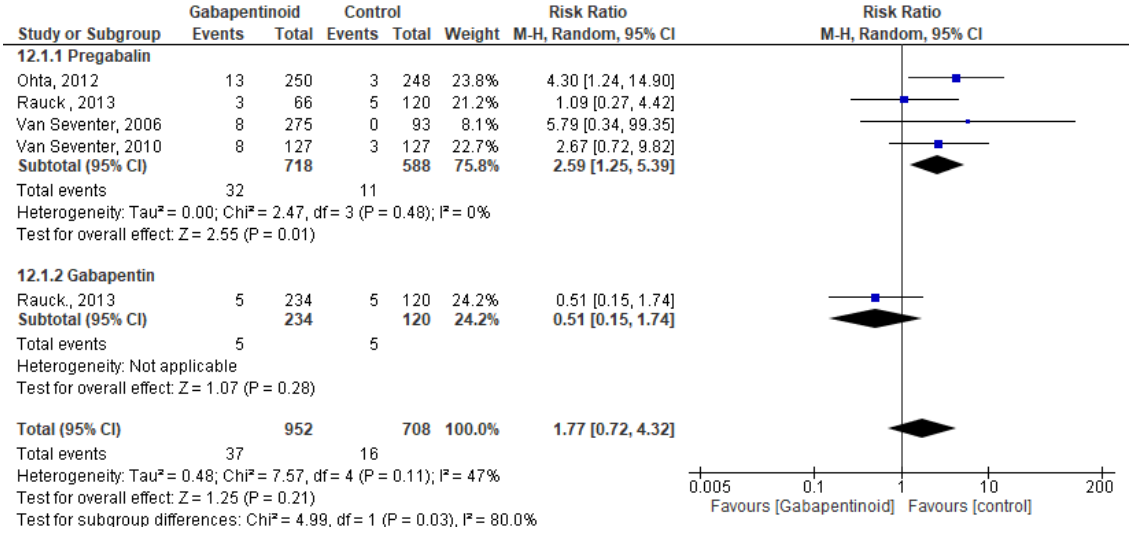


Figure 2-17. *Forest plot of the risk of blurred vision between the two groups (gabapentinoids vs placebo). CI: confidence interval.*

In two RCTs of pregabalin with 637 participants, the risk of diplopia was not significantly different to the placebo since the risk ratio included unity (RR 2.90; 95% CI 0.36, 23.44).

Gastro-intestinal disorder

1. Constipation

Overall, 12 RCTs of pregabalin (3838 participants) reported constipation as an adverse event. The risk ratio of the pooled results of constipation showed a statistically significant difference compared to placebo (RR 2.49; 95% CI 1.75, 3.54; P<0.00001), with no heterogeneity found across trials (I^2=0%) (Figure 2.18). The NNH was 25 (95% CI 18.6, 36.0). Only one gabapentin study reported constipation as an adverse event. An asymmetric funnel plot was observed via visual inspection, suggesting publication bias.

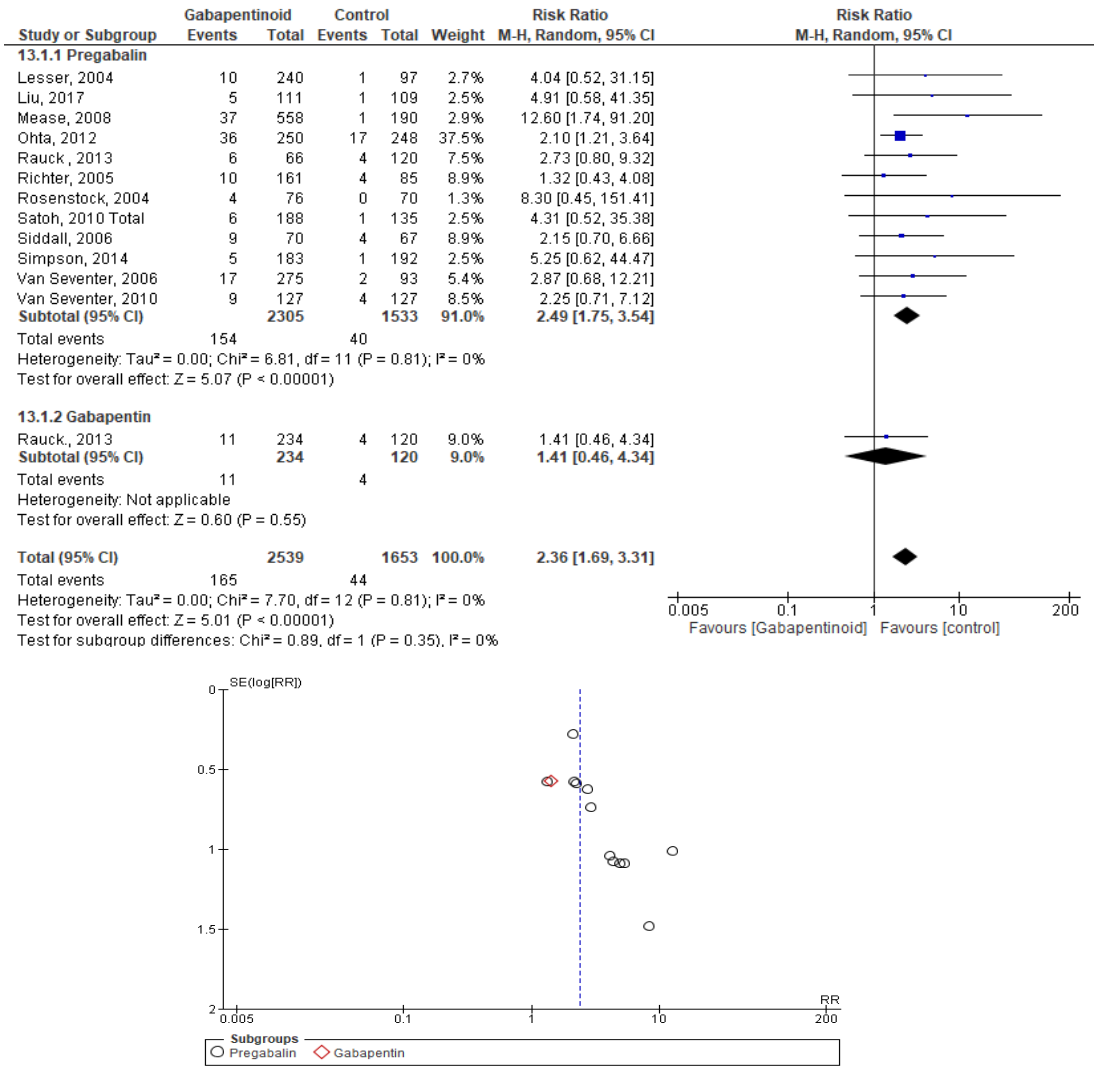


Figure 2-18. *Forest and funnel plots of the risk of constipation between the two groups (gabapentinoids vs placebo).*
CI: confidence interval, SE: standard error, RR: risk ratio.

2. Dry mouth

Overall, there was a notable increase in the risk of dry mouth in 15 RCTs (3690 participants) compared gabapentinoids with placebo (RR 2.72; 95% CI 1.79, 4.15; *P*<0.00001). There was no significant heterogeneity across the included studies (I^2=18%).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.29). In 12 pregabalin trials (3307 participants), the risk ratio of dry mouth showed a statistically significant difference compared to placebo (RR 3.08; 95% CI 2.05, 4.62; *P*<0.0001; I^2=0). The NNH of pregabalin was 18 (95% CI 18.6, 36.0). Only three RCTs of gabapentin (383 participants) reported dry mouth as an adverse event. There was no statistically significant difference in the risk ratio between gabapentin and placebo (RR 1.55; 95% CI 0.47, 5.11; *P*=0.48). There was

moderate heterogeneity found across trials (I^2= 45%). Visual inspection of the funnel plot demonstrates as a symmetry funnel (Figure 2.19).

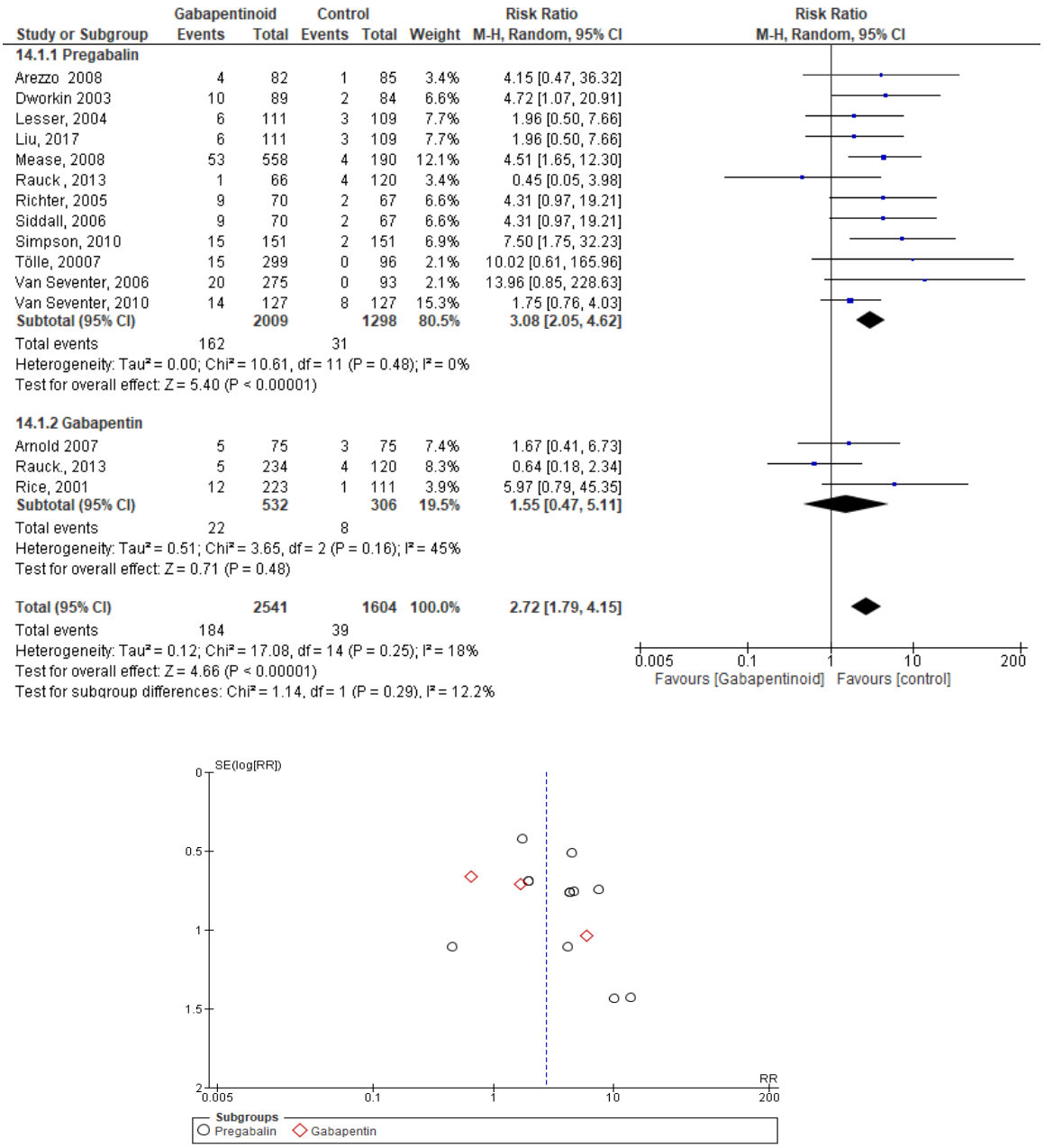


Figure 2-19. *Forest and funnel plots of the risk of dry mouth between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin).*
CI: confidence interval, SE: standard error, RR: risk ratio.

There were a number of adverse events that were not significantly different from placebo because the risks ratio included unity. These adverse events involve diarrhoea, vomiting, and flatulence.

General disorder and administration site condition

1. Oedema

Compared to placebo, five pregabalin studies with 1381 participants were included in the analysis. The risk ratio of pooled results of oedema showed a statistically significant difference (RR 2.82; 95% CI 1.39, 4.74; *P*=0.004), with no heterogeneity found across trials (I^2=0%). The NNH was 24 (95 % CI 16.4, 44.3). Only one gabapentin study reported the oedema adverse event (Figure 2.20).

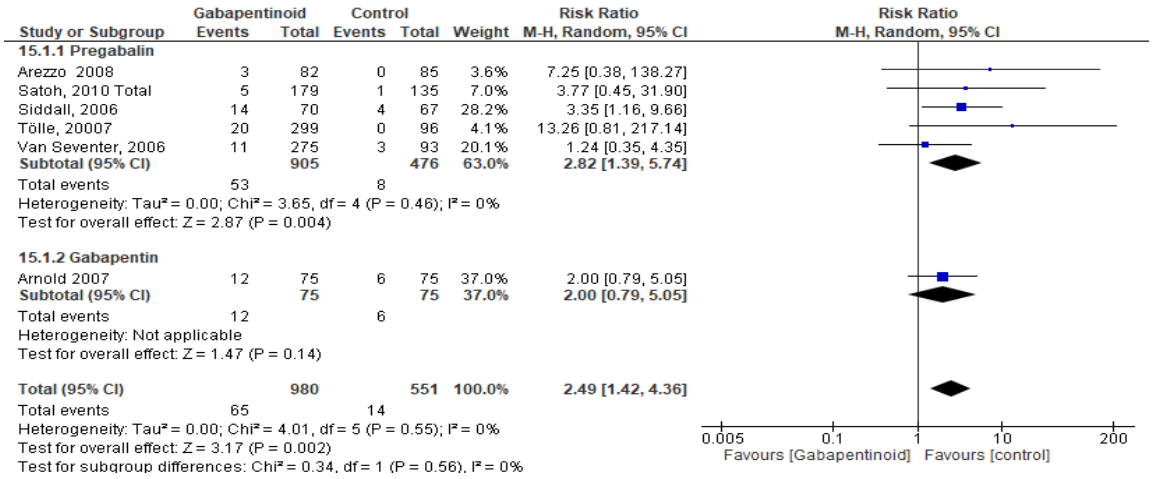


Figure 2-20. *Forest plot of the risk of oedema between the two groups (gabapentinoids vs placebo). CI: confidence interval.*

2. Peripheral oedema

In 22 studies with 3758 participants, the risk of peripheral oedema was markedly increased with gabapentinoids treatment (RR 2.83; 95% CI 2.00, 4.00). There was moderate heterogeneity across the trials (I^2=40%).

Subgroup analysis demonstrated that there was no statistically significant subgroup effect (*P*=0.88). Overall, 17 RCTs of pregabalin with 5529 participants were included in the analysis. The risk ratio of peripheral oedema showed a statistically significant difference compared to placebo (RR 2.82; 95% CI 1.92, 4.17; *P*<0.0001), with moderate heterogeneity found across trials (I^2= 44%). Only five gabapentin RCTs (1770 participants) reported peripheral oedema. The risk ratio of pooled results showed a statistically significant difference in the comparison of gabapentin to placebo (RR 3.06; 95% CI 1.25, 7.48; *P*=0.004). There was moderate heterogeneity found across trials (I^2= 31%). The NNH of pregabalin was 22 (95% CI 17.3, 29.3), while the NNH of gabapentin was 28 (95% CI 19.0, 47.4). Visual inspection of the funnel plot illustrates an asymmetry funnel (Figure 2.21).

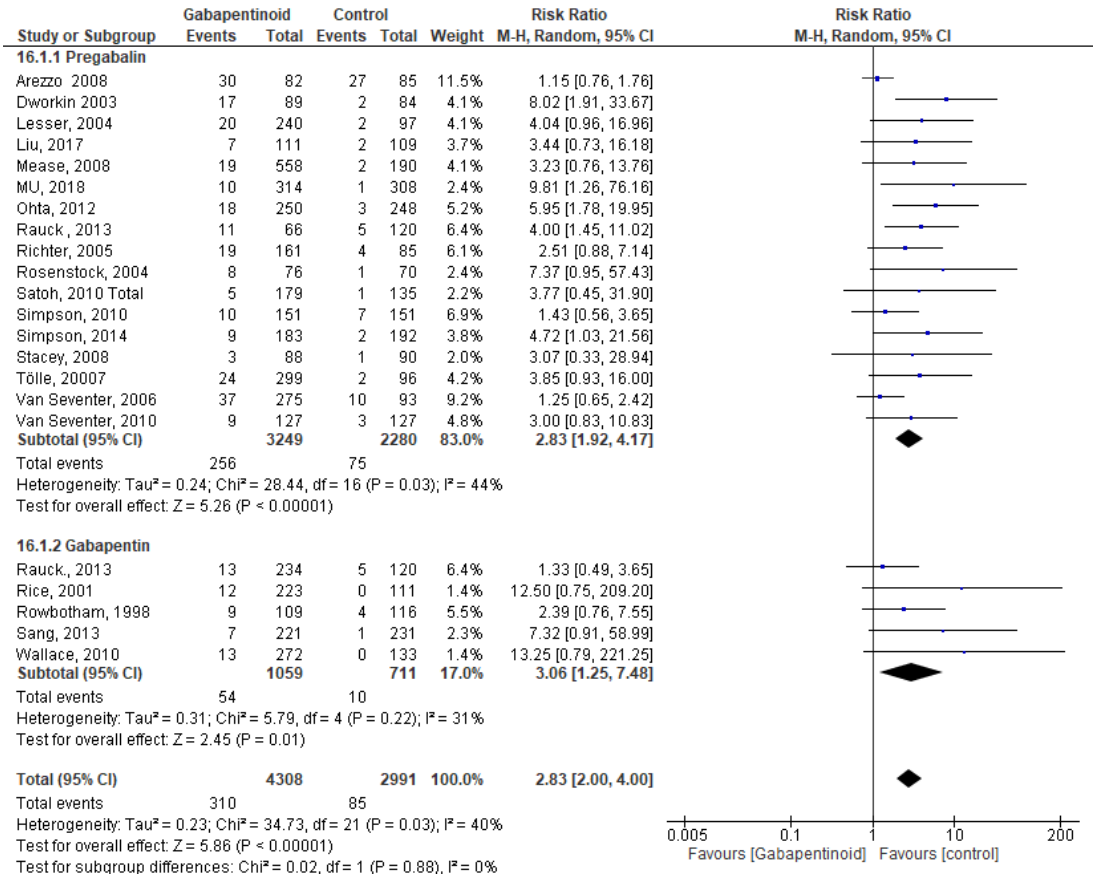


Figure 2-21. *Forest and funnel plots of the risk of peripheral oedema between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin). CI: confidence interval, SE: standard error, RR: risk ratio.*

Only two pregabalin studies with 682 participants reported face oedema as an adverse event. However, the risk ratio was not significantly different compared to placebo as included unity (RR 2.56; 95% CI 0.38, 17.14).

Endocrine disorder

1. *Increased weight*

In 11 trials (3665), the risk of increased weight outcome was increased with gabapentinoids compared to placebo (RR 5.01; 95% CI 3.17, 7.93; *P*<0.00001). There was no heterogeneity across the trials (I^2=0%) (Figure 2.22).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.89). Overall, nine pregabalin with 3161 participants and two gabapentin RCTs with 504 participants were included in the analysis. The risk ratio was a statistically significant difference in the comparison of pregabalin to placebo (RR 4.97; 95%CI 3.08, 8.00; *P*<0.0001). There was no heterogeneity found across trials (I^2= 0%). Similarly, the risk ratio of increased weight with gabapentin *versus* placebo showed a statistically significant difference (RR 5.61; 95%CI 1.04, 30.22; *P*=0.004), with no heterogeneity found across trials (I^2= 0%). The NNH of pregabalin was 16 (95% CI 1.8, 17.7), while the NNH of gabapentin was 28 (95% CI 16.3, 80.5).

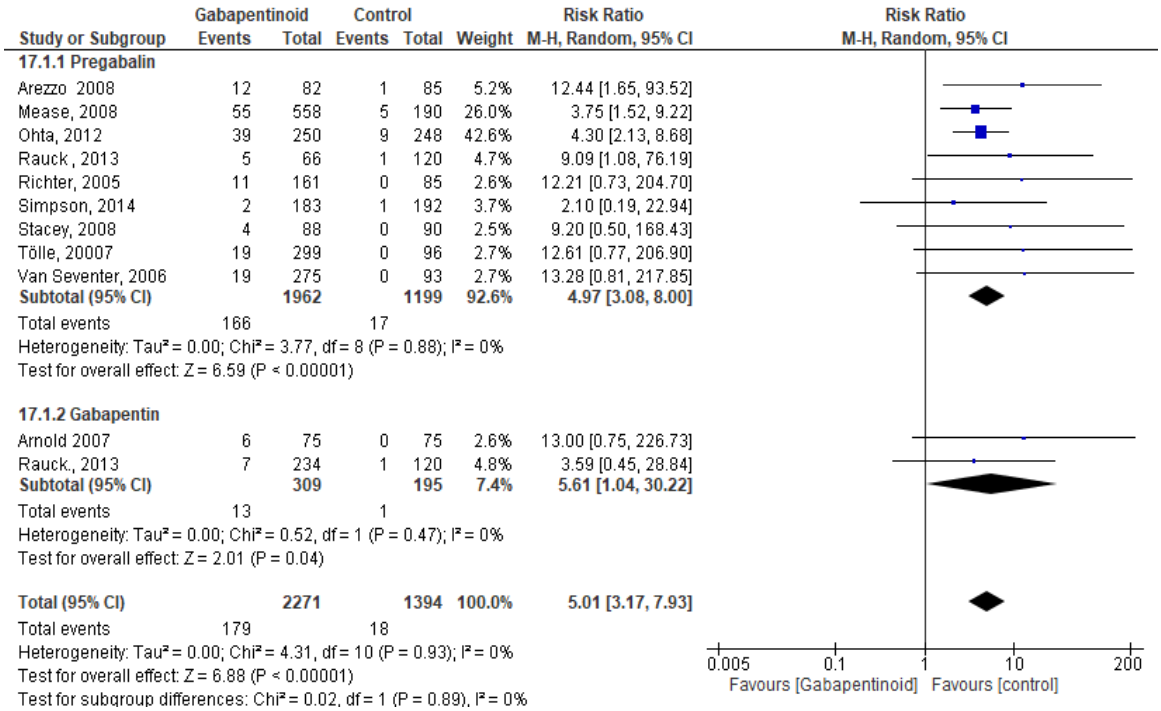


Figure 2-22. *Forest plot of the risk of increased weight between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin). CI: confidence interval.*

Musculoskeletal disorder

1. *Fatigue*

Overall, four pregabalin studies with 838 participants were included in the analysis. The risk ratio was a statistically significant difference in the comparison of pregabalin to placebo (RR 2.00; 95%CI 1.08, 3.70; *P*=0.03), with no heterogeneity found across trials (I^2= 0%) (Figure 2.23). The NNH of pregabalin was 25 (95% CI 14.0, 105.2). Only one gabapentin study reported fatigue as an adverse event.

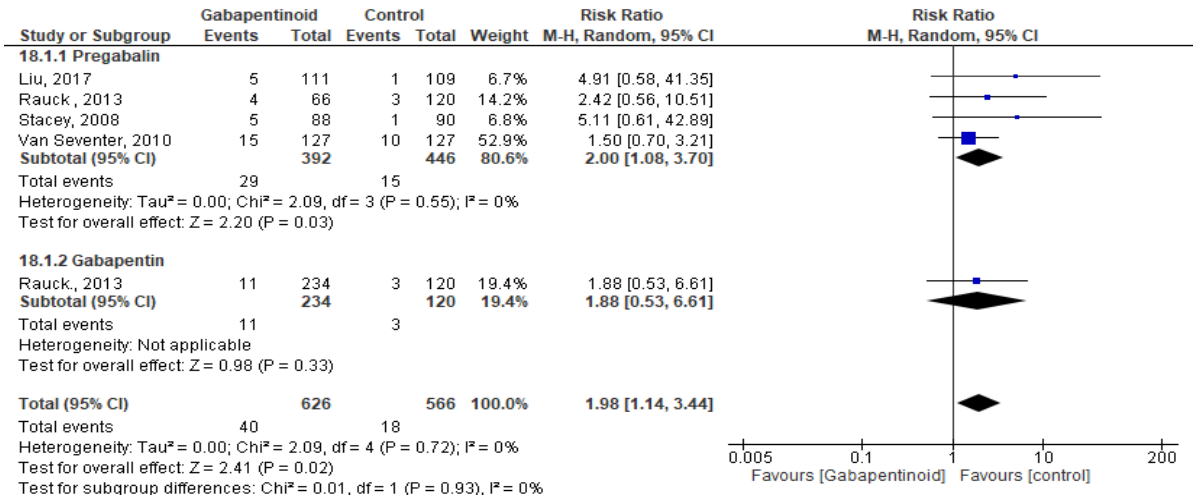


Figure 2-23. *Forest plot of the risk of fatigue between the two groups (gabapentinoids vs placebo).CI: confidence interval.*

Other adverse events with non-significant risks ratio

Several adverse events were reported in the included studies, as shown in table 2.5. These adverse events did not show a statistically significant difference compared to placebo as the risk ratio included unity.

Outcome	Intervention	Comparator	Studies (n)	N	Random-effect RR (95%CI)
Ear and labyrinth disorder					
Vertigo	Pregabalin	Placebo	2	573	6.81 (0.87, 53.39)
General disorder and administration site condition					
Face oedema	Pregabalin	Placebo	2	682	2.56 (0.38, 17.14)
Renal and urinary disorder					
Urinary tract infection	Pregabalin	Placebo	2	808	0.82 (0.3, 1.99)
	Gabapentin	Placebo	1	354	1.33 (0.4, 3.65)
Respiratory disorder					
Nasopharyngitis	Pregabalin	Placebo	4	1279	0.95 (0.69, 1.31)
	Gabapentin	Placebo	2	806	0.79 (0.35, 1.77)
Influenza	Pregabalin	Placebo	2	521	1.57 (0.80, 3.10)
	Gabapentin	Placebo	1	150	0.45 (0.17, 1.24)
Skin and subcutaneous tissue disorder					
Hyperhidrosis	Pregabalin	Placebo	2	546	0.47 (0.03, 8.01)
Accidental injury	Pregabalin	Placebo	3	730	1.15 (0.43, 3.10)
Endocrine disorder					
Increase appetite	Pregabalin	Placebo	3	1112	1.93 (0.80, 4.63)
	Gabapentin	Placebo	1	354	0.51 (0.13, 2.01)
Other					
Infection	Pregabalin	Placebo	4	866	1.18 (0.69, 2.05)

Table 2-6. *Other adverse events with non-significant risks ratio. RR: risk ratio.*

2.7.4.2 Withdrawal due to adverse events

The majority of adverse events were mild to moderate in severity. The proportion of participants who withdrew due to adverse events was not reported in all the included studies. There were some studies that reported the proportion of participants' withdrawal due to adverse events: 18 pregabalin studies and ten gabapentin RCTs. There was a statistically significant difference in the pooled results of gabapentinoids compared to placebo (RR 1.60; 95% CI 1.29, 1.98; *P*<0.0001). There was moderate heterogeneity found across included studies (I^2=34%) (Figure 2.24).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.48). The withdrawals due to adverse events were more common with pregabalin (314 out 3173 participants (10%)) than with placebo (130 out 2352 participants (6%)) (RR 1.71; 95% CI 1.28, 2.29; *P*=0.0003), with substantial heterogeneity found across included studies (I^2= 41%). Similarly, the proportion of participants who withdrew due to adverse events was more with gabapentin (166/1378 participants (12%)) than with placebo (77/981 participants (8%)) (RR 1.47; 95% CI 1.08, 2.00; *P*=0.01; I^2= 21%). By visual inspection of the funnel plot, there is symmetry in the funnel plot on both sides, indicating that publication bias is unlikely.

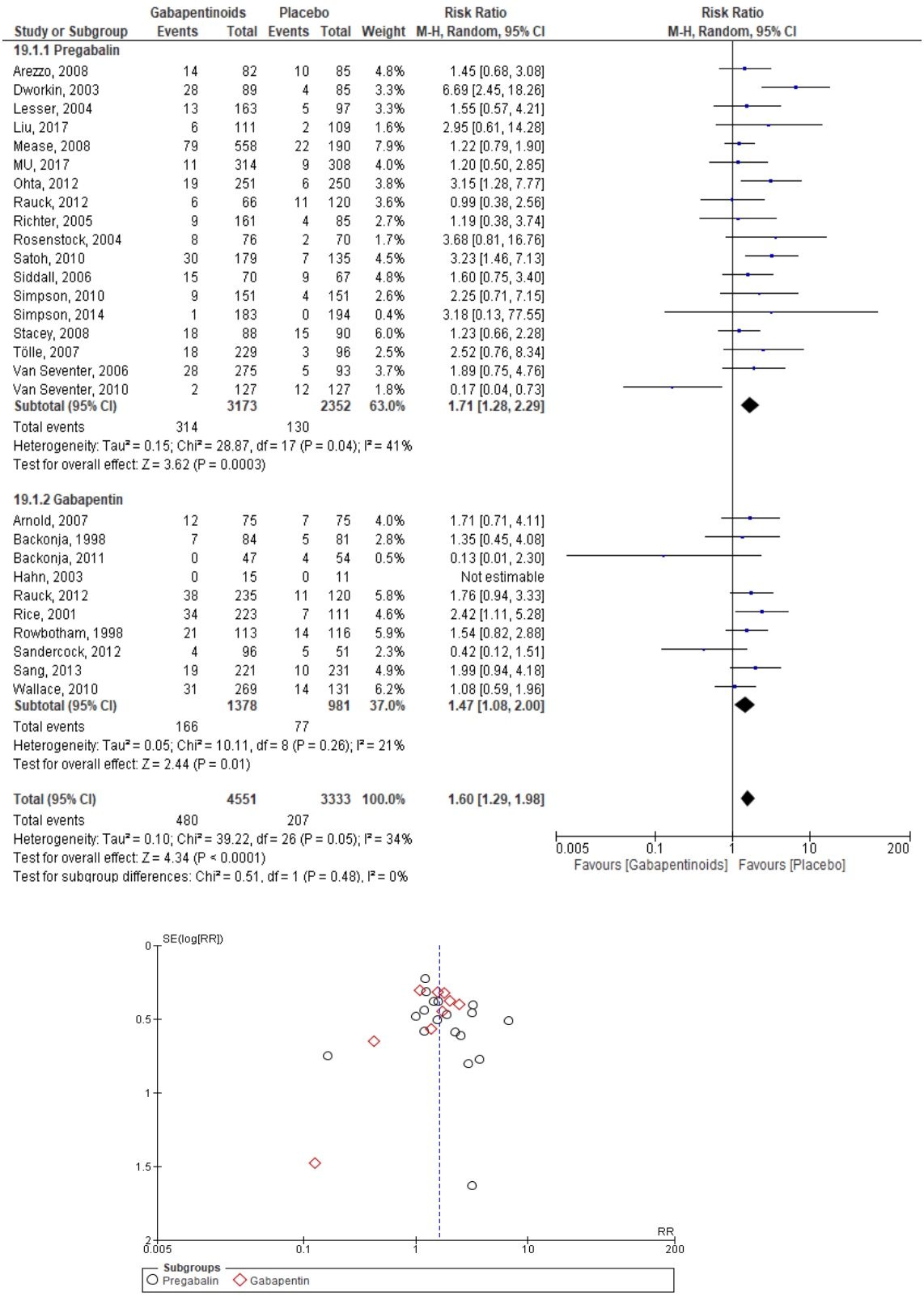


Figure 2-24. *Forest and funnel plots of the risk of withdrawals due to adverse events between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin). CI: confidence interval, SE: standard error, RR: risk ratio.*

2.7.4.3 Serious adverse events

Overall, 11 studies (3939 participants) reported serious adverse events; and the risk ratio of the pooled results showed that there was no statistically significant difference in gabapentinoids group compared to placebo group (RR 1.45; 95% CI 0.92, 2.27; *P*=0.11), with no heterogeneity found across trials (I^2=0%).

For subgroup analysis, there was no statistically significant subgroup effect (P=0.25). Eight pregabalin studies with 2748 participants were involved in the serious adverse events analysis. Serious adverse events were documented in 44 out of 1494 (2.9%) participants with pregabalin and 19 out of 1254 (1.5%) participants compared to placebo. There was no statistically significant difference (RR 1.72; 95% CI 1.00, 2.96; *P*=0.05; I^2 = 0%). Only three gabapentin studies reported serious adverse events. In 15 out 716 (2.1%) participants with gabapentin and 10 out 475 (2.1%) participants with placebo; the pooled results showed that no statistically significant difference (RR 0.98; 95% CI 0.43, 2.21; *P* = 0.95; I^2=0%) (Figure 2.25). By visual inspection of the funnel plot, there is an asymmetry in the funnel plot on both sides.

All reported studies clearly specified that serious adverse events were irrelevant to pregabalin or gabapentin interventions. For example, optic nerve atrophy, (209) cerebral ischemia, (2) myocardial infraction, (193,215,224) breast cancer, (189) ovarian cyst torsion, (193) and hypervolemia. (199)

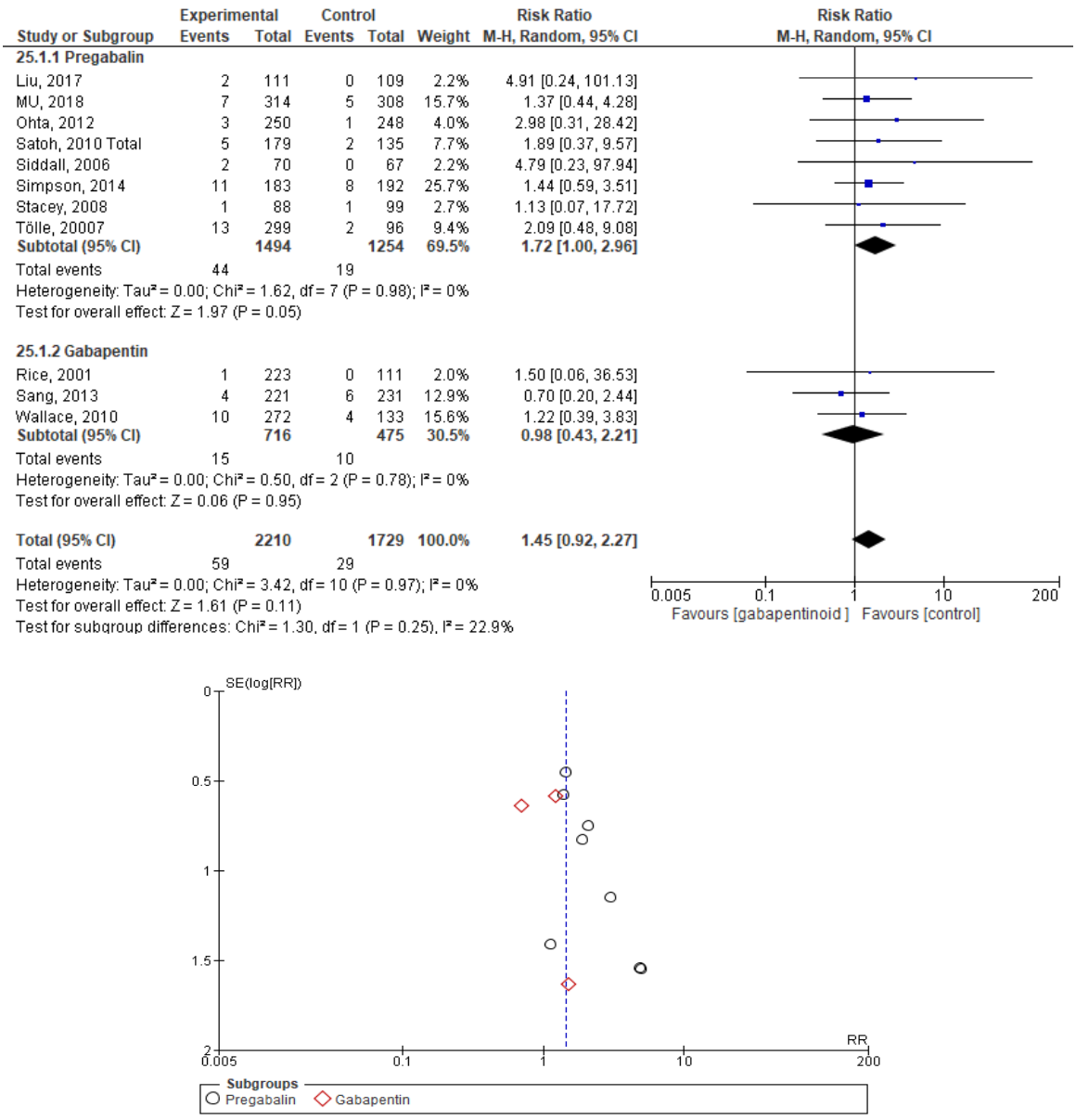


Figure 2-25. *Forest and funnel plots of the serious adverse events between the two groups (gabapentinoids vs placebo), subgrouped by the specific drug administered (pregabalin or gabapentin). CI: confidence interval, SE: standard error, RR: risk ratio.*

2.7.4.4 Abuse and misuse disorder of gabapentinoids

None of the studies assessed abuse of gabapentinoids or gabapentinoid misuse.

2.7.5 Secondary outcomes

2.7.5.1 Proportion of participants who achieved at least 50% pain intensity reduction

In total, 21 studies with 6098 participants were included in this analysis (Table 2.6). There was a statistically significant difference in the pooled results of gabapentinoids compared to

placebo (RR 1.73; 95% CI 1.46, 2.07; *P*<0.00001). There was substantial heterogeneity found across trials (I^2=68%).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.91). The proportion of participants who achieved at least a 50% pain reduction was reported in 15 pregabalin studies. (90,164,170,172,174–176,178,180,181,183–185,187,205) The pooled results showed that the pregabalin group was significantly superior to the placebo group (RR 1.72; 95% CI 1.37, 2.16; *P*<0.00001), with considerable heterogeneity across included trials (I^2=73%). The pregabalin's NNT was 10 (95% CI 6.7, 10.5).

Compared to placebo, gabapentin showed a statistically significant difference in six included studies (RR 1.76; 95% CI 1.34, 2.32; *P*<0.0001). (215,216,218,224,229,231) There was substantial heterogeneity found across studies (I^2=54%;). The NNT of gabapentin was 8 (95% CI 5.8, 10.8). Visual inspection of the funnel plot illustrates that symmetry on both sides of the plot (Appendix A).

2.7.5.2 Proportion of participants who achieved at least 30% pain intensity reduction

Overall, 19 RCTs with 5695 participants were included in this analysis. There was a statistically significant difference in the pooled results in using gabapentinoids compared to placebo (RR 1.55; 95% CI 1.35, 1.78; *P*<0.00001). There was considerable heterogeneity found across trials (I^2=74%).

The pooled results showed no statistically significant effect across the two groups (*P*=0.90). The proportion of participants who achieved at least a 30% pain reduction was reported in 12 pregabalin studies compared to placebo, and the pooled results showed a statistically significant difference (RR 1.56; 95% CI 1.29, 1.88; *P*<0.00001). There was considerable heterogeneity among included studies (I^2=79%). The NNT of pregabalin was 8 (95% CI 6.1, 9.8). (147,164,170,172,174,178,180,184,185,187,180,205) Similarly, gabapentin studies (7 RCTs) showed that the gabapentin group was significantly better than the placebo group (RR 1.53; 95% CI 1.25, 1.88; *P*<0.0001), with substantial heterogeneity across included RCTs (I^2=59%). (215,216,218,224,225,228,231) The NNT of gabapentin was 7 (95% CI 5.2, 9.8). The funnel plot shows a symmetry plot (Appendix A).

2.7.5.3 Much or Very Much Global Pain Improvement scale (PGIC)

Overall, 20 RCTs with 6013 participants compared gabapentinoids with placebo for assessing the improvement in PGIC (much or very much). The pooled results demonstrated a statistically significant difference (RR 1.58; 95% CI 1.36, 1.83; *P*<0.00001), but considerable heterogeneity was found across included studies (I^2=79%).

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.55). The improvement in PGIC was reported in 13 pregabalin RCTs, and the pooled results indicated that the pregabalin group was significantly better than the placebo group (RR 1.53; 95% CI 1.28, 1.83; *P*<0.0001). (147,168,170,172,175,176,178,181,183,185,187,188,205) There was considerable heterogeneity found across (I^2=82%). The pregabalin's NNT was 9 (85% CI 6.5, 10.6). Seven studies of gabapentin showed a statistically significant difference (RR 1.70; 95% CI 1.27, 2.28; *P*=0.0004), with considerable heterogeneity found across studies (I^2=76%). (215,216,218,222,224,225,229) The NNT of gabapentin was 7 (95% CI 5.1, 9.2). Visual inspection of the funnel plot shows symmetry on both sides of the plot (Appendix A).

2.7.5.4 Very Much Global Pain Improvement scale (PGIC)

In total, seven studies with 2523 participants reported very much PGIC assessment. There was a statistically significant difference in the comparison of gabapentinoids to placebo (RR 1.83; 95% CI 1.34, 2.49; *P*=0.0001), with moderate heterogeneity found between studies (I^2= 50%).

For subgroup analysis, there was a statistically significant subgroup effect (*P*= 0.01). The very much improved was reported in four RCTs with pregabalin compared to placebo; and the pooled results demonstrated that the proportion of participants with these results was higher in the pregabalin group than in the placebo group (RR 1.40; 95% CI 1.01, 1.92; *P*=0.04), with no significant heterogeneity across the trials (I^2=22%). (189,191,197,207) The NNT was 25 (95% CI 13.8, 81.9). Only three RCTs of gabapentin reported very much improved on the PGIC scale, and pooled results indicated a statistically significant difference (RR 2.47; 95% CI 1.79, 3.41; *P*<0.0001). (218,222,229) There was no significant heterogeneity across trials (I^2=0%). The NNT of gabapentin was 6 (95% CI 3.9, 7.3). The funnel plot illustrates that symmetry on both sides of the plot (Appendix A).

2.7.5.5 Withdrawal due to lack of efficacy

Overall, 24 RCTs (7134 participants) showed a statistically significant difference compared to placebo (RR 0.44; 95% CI 0.35, 0.55; *P*<0.00001; I^2=17.4%), with no significant heterogeneity between included studies.

For subgroup analysis, there was no statistically significant subgroup effect (*P*=0.27). Withdrawals due to lack of efficacy occurred in significantly fewer patients (3%) taking pregabalin than placebo (7%) (RR 0.41; 95% CI 0.31, 0.54; *P*<0.00001). No significant heterogeneity was observed across trials (I^2=4%). (91,159,189,191,193–195,197,199,200,202,203,206,207,209,213,231) While there was no statistically significant difference between those who used gabapentin (21/1062 participants (1.9%)) and who used placebo (29/796) participants 3.6%)) (RR 0.59; 95% CI 0.33, 1.04; *P*=0.07). There was no significant heterogeneity across included trials (I^2=0%). (216,218,222,224,226,228,229,231)

Secondary outcomes	Gabapentinoids											
	Overall				Pregabalin				Gabapentin			
	No. of trials	No. of participants	Random-effect RR (95%CI)	I^2	No. of trials	No. of participants	Random-effect RR (95%CI)	I^2	No. of trials	No. of participants	Random-effect RR (95%CI)	I^2
≥50% pain intensity reduction	21	6098	1.73 (1.46, 2.07)	68	15	4247	1.72 (1.37, 2.16)	73	6	1851	1.76 (1.34, 2.32)	54
≥30% pain intensity reduction	19	5688	1.55 (1.35, 1.78)	74	12	3926	1.56 (1.29, 1.88)	79	7	1769	1.53 (1.25, 1.88)	59
PGIC much or very much improved	20	6013	1.58 (1.36, 1.83)	79	13	4188	1.53 (1.28, 1.83)	82	7	1825	1.70 (1.27, 2.28)	71
PGIC very much improved	7	2523	1.83 (1.34, 2.49)	50	4	1795	1.40 (1.01, 1.92)	22	3	728	2.47 (1.79, 3.41)	0
Withdrawal due to lack of efficacy	24	7134	0.44 (0.35, 0.55)	0	17	5276	0.41 (0.31, 0.5)	4	8	1858	0.59 (0.33, 1.04)	0

Table 2-7. *Summary Estimates from meta-analysis for the secondary outcomes with subgroup analysis for the type of drug (pregabalin and gabapentin). RR: risk ratio, PGIC: patient's global impression of change scale.*

2.8 Discussion

Gabapentinoids are a cornerstone of pharmacological management for chronic neuropathic pain. This study has included both pregabalin and gabapentin for the treatment of neuropathic pain in adults. As compared to placebo, gabapentinoids were associated with a significant increase in adverse events as well as evidence of pain intensity reduction. This systematic review and meta-analysis demonstrated the most up-to-date comprehensive summary of adverse events reported during the use of gabapentinoids for the management of neuropathic pain. This study is the first systematic review and meta-analysis in which the analysis focused on categorising the adverse events according to the body systems they were affecting to better understand the safety profile associated with the use of pregabalin and gabapentin in the treatment of neuropathic pain patients.

Results from this study showed that pregabalin has more adverse events than gabapentin during the use of these medications in the treatment of neuropathic pain. These results found that pregabalin has more reported adverse events (n=18 significantly associated) than gabapentin (n=4 significantly associated). However, since there have been more studies for pregabalin, and therefore more participants included in studies to investigate pregabalin compared to gabapentin, the identification of a potential difference between these two medications requires further investigation.

In terms of primary outcomes, the meta-analysis results indicated that, compared with the placebo, patients who received gabapentinoids treatment may experience more adverse events. This study identified that the majority of documented adverse events associated with the use of gabapentinoids pertained to nervous system disorders or psychiatric disorders. Specifically, 12 of 18 (65%) adverse events were related to cognition/coordination; of these seven pertained to a nervous system disorder (dizziness, somnolence, ataxia, amnesia, abnormal gait, incoordination, and asthenia), whereas three were related to a psychiatric disorder (confusion, euphoria, and abnormal thinking), and two to an eye disorder (amblyopia and blurred vision). Similar findings have been observed by Perucca *et al.* who found that adverse events associated with the use of gabapentinoids were related to cognition/coordination and were, importantly, also the main issues which impaired the health-related QoL for patients who used these medications. (235)

The adverse events of the nervous system were relatively most common with gabapentinoids treatment; among these adverse events dizziness and somnolence had the lowest (worse) NNHs. As opposed to these adverse events, blurred vision (eye disorder adverse event) and peripheral oedema (general disorder adverse event) were slightly less common (with highest NNHs) with using gabapentinoids in neuropathic pain patients. Moreover, Zaccara *et al.* study examined the adverse event profile of pregabalin of available RCTs and showed that the highest RRs were found for cognition/coordination adverse events. (236) Those findings were similar to this meta-analysis, which had the highest RRs between 3.33 and 7.20 for cognition/coordination adverse events. In addition, the results of the subgroup analyses of gabapentinoids, it was determined that there were no statistically significant differences in the incidence of adverse events between pregabalin and gabapentin.

The occurrence of adverse events is common and sometimes leads to the discontinuation of treatment. (237,238) Therefore, there was evidence that pregabalin and gabapentin increased the withdrawal rate due to adverse events compared to the placebo. (91, 168,170,172,175-178,180-189,192-194,197,200,204,205). This finding is consistent with previous research studies, which have reported a significantly higher withdrawal rate resulting from these medications than the placebo group. (87,88)

In the light of the reported adverse events of gabapentinoids causing nervous system disorder, the question remains as to whether there is any evidence of gabapentinoid use that may lead to addiction. This study did not detect a clear indication of the effects associated with the abusive potential of gabapentinoids. It is possible that the outcome may result from the fact that there is currently a lack of studies that would assess the addictive potential of gabapentinoids in patients who suffer from neuropathic pain. One of the reported adverse events that may suggest some level of abusive potential produced by gabapentinoids could be euphoric effect resulting from the treatment with this group of medications.

This study found that only six of 29 (21%) pregabalin studies reported euphoria as an adverse event in the use of pregabalin in the treatment of neuropathic pain. However, no gabapentin studies reported euphoria as an adverse event. In a recently published systematic review about the abuse potential of pregabalin from 102 RCTs, euphoria was reported in 14 RCTs as an adverse event with rates between 1 and 10%, but 1 study reported a rate as high as 26%. (129) The reason behind the ability of pregabalin to produce euphoria, in contrast to

gabapentin, may lay in the fact that pregabalin shows linear pharmacokinetics as the pregabalin dose increased the plasma concentrations of pregabalin increase. The peak plasma concentration is achieved after 1 hour of oral administration of pregabalin, whereas it takes between 2 to 3 hours for gabapentin to reach the peak plasma concentration. This may suggest that pregabalin has rapid absorption and very high bioavailability compared to gabapentin (>90% for pregabalin *versus* 33-66% for gabapentin), which may explain its greater potential for abuse as compared to gabapentin. (239)

It should also be noted that many studies have suggested that gabapentinoid misuse is significantly higher among individuals with histories of a substance use disorder, particularly in patients taking the drug in combination with opioids (including heroin) when the opioid is misused. (128,227) Nevertheless, none of the included studies permitted using opioids as a concomitant treatment during the study period; therefore, it was impossible to assess this drug combination in this study.

Another challenge in detecting the scale of the abusive potential of gabapentinoids is that neuropathic pain patients who are not addicted to opioids would not be seeking substitution with gabapentionoids, and the change in the medication would only result from an efficacy issue. However, gabapentinoids have GABA-mimetic properties that may lead to drug dependence, especially in patients with a history of opioid abuse. (98) In line with this, in 2017, it was reported that the increase in gabapentionoid diversion might be related to the misuse of prescription of opioids and heroin. (240) This is because these patients, showing long-term opioid tolerance, may desire the euphoric effect associated with gabapentinoids medications. (129) This has been reported particularly with pregabalin. (241) In fact, Evoy *et al.* assessed abuse and misuse of pregabalin and gabapentin and found that the prevalence of abuse of gabapentinoids in patients with opioid use disorders was higher in pregabalin (3-68%) than gabapentin (15-22%) users. (98) Likewise, in the USA, a substance use problem clinic report conveyed that opioid addiction is the most contributing factor to gabapentinoid misuse. (242) According to this study, 22% of patients who were treated for opioid addiction misused gabapentin and 7% misused pregabalin. (242) In contrast, there were no cases of patients with non-opioid addiction misusing gabapentinoids (pregabalin or gabapentin). (242)

It has recently been reported that the prevalence of patients with opioid addiction who illegally use pregabalin (receiving a higher than therapeutic dose or using pregabalin without

a medical indication) has been reported as 7% and 12.1%. (242,243) In another small study on opioid abusers, it was noted that 11 in 15 patients bought pregabalin from drug dealers without a prescription. (98,243) In summary, while the overall outcome of the meta-analysis from this study indicates that there is no evidence for the abuse or misuse potential of gabapentinoids, it seems there is a pressing need for further studies to investigate the abusive potential, particularly pregabalin, in chronic pain as well as mechanisms underlying these unwanted effects.

In relation to secondary outcomes, this study also found that gabapentinoids have proven efficacy in treating adult neuropathic pain. This meta-analysis assessed the efficacy outcomes of moderate or substantial pain relief, as defined by the IMMPACT group. (175) The results of this study confirm the efficacy of gabapentinoids; the findings were significantly superior to the placebo (≥ 30% and ≥ 50 % pain intensity reduction). Nevertheless, there is no clinically significant difference between pregabalin and gabapentin regarding the analgesic effect. The NNT for ≥ 30 % pain relief was 8 for pregabalin and 7 for gabapentin, whereas the NNTs for ≥ 50 % pain intensity reduction for pregabalin and gabapentin were 10 and 8, respectively. These findings are consistent with Finnerup *et al.* who examined the efficacy of gabapentinoids for neuropathic pain in adults and reported that NNT for ≥ 50 % pain intensity reduction for pregabalin was 7.7 and for gabapentin was 7.2. (81)

Moreover, some efficacy outcomes have been reported for the PGIC much or very much improved, revealing that gabapentinoids have a superior analgesic benefit compared to placebo. However, the evidence to support gabapentin's efficacy in the treatment of chronic pain is relatively small as not many studies are currently available. In addition, the withdrawal rate due to lack of efficacy was significantly lower in the participants who received gabapentinoids treatment than placebo.

Statistical heterogeneity was noticed in some of the meta-analyses for the secondary outcomes (I^2≥ 70%); this heterogeneity might be due to the clinical diversity of the included studies examining gabapentinoids with different types of neuropathic pain (*e.g.,* PHN, PDN, and fibromyalgia). In order to overcome this heterogeneity, future meta-analyses should be, for example, conducted based on the same type of neuropathic pain.

2.8.1 Limitations

Among the top of the quality of evidence hierarchy, meta-analysis is the most important method for integrating evidence and summarising outcomes from multiple studies. However, traditional meta-analyses have their limitations. The main limitation of this meta-analysis is that the results are derived solely from the analysis of data retrieved from RCTs. Despite the ethical requirement to report adverse events during RCTs, the outcomes of this study suggest that RCTs may be insufficiently powered to detect adverse effects and therefore provide solid evidence to support the safety of gabapentinoids. Additionally, the included RCTs were relatively short in duration (maximum 20 weeks), potentially limiting the possible occurrence of rare adverse events, such as addiction and misuse disorders.

Another limitation of this study is the scarcity of head-to-head trials to compare the safety of gabapentinoids with active treatment for neuropathic pain. Also, some heterogeneity was found across the included studies and this was not investigated further to assess the source of heterogeneity by performing further subgroup analysis. In addition, subgroup analysis was not undertaken in this study to assess the different doses of gabapentinoids or different types of neuropathic pain because the main aim of this meta-analysis was to focus on the comprehensive safety profile of gabapentinoids in the management of neuropathic pain. Finally, the research was restricted to fully published articles and English language, which may potentiate the risk of publication bias. In addition, the quality of many studies was uncertain (unclear risk based on the Cochrane RoB tool), which decreased the quality of evidence for many outcomes. Therefore, further research, including high-quality studies, is required to assess the safety profile of gabapentinoids in treating neuropathic pain at varying doses, durations, and frequencies.

2.9 Conclusion

This systematic review and meta-analysis presents the evidence to date with regard to the safety and efficacy of gabapentinoids in managing neuropathic pain as reported by RCTs. The reported adverse events of gabapentinoids were mild to moderate in severity, indicating that the drugs can be considered as a safe and well-tolerated treatment. Euphoria was reported as an adverse event with pregabalin, but not gabapentin, at the therapeutic doses. Despite

reports showing the adverse events of gabapentinoids on the nervous system, the meta-analysis was unable to detect any evidence to suggest, and therefore confirm, the potential for gabapentinoid abuse and misuse disorder. Overall, the evidence suggests that gabapentinoids to be efficacious in treating the different conditions of neuropathic pain compared with placebo. In light of the fact that these results were limited to RCTs, this study suggests that RCTs assessing the effectiveness of gabapentinoids do not have sufficient duration and power to detect relatively rare adverse events, including addiction and misuse disorders. Therefore, further research with large-high-quality trials is required to fully understand their analgesic efficacy and addictive properties, particularly in a correlation between gabapentinoids and other misused drugs (*e.g.,* opioids).

Chapter 3 Pregabalin self-administration in *naïve* rats.

3.1 Chapter description

Chapter 2 explored the published evidence of the safety of gabapentinoids in neuropathic pain patients, and it was concluded that there is potentially an association between abuse and misuse of gabapentinoids and history of opioid use disorders. Consequently, as presented in this Chapter, an in-*vivo* study was conducted to investigate the reinforcing efficacy of pregabalin in rats subjected to morphine self-administration. Specifically, rats were exposed to morphine self-administration and upon the development of reinforcement behaviour, morphine was replaced with pregabalin to confirm whether or not this drug could substitute for the morphine-induced reinforcement effect. Thus, this experimental approach could be useful in identifying any association between abuse and misuse of gabapentinoids and history of opioid use disorders that has been observed in patients. (103,244) Pregabalin was selected for the study as it has been reported that individuals who take pregabalin are more likely to abuse or misuse the drug than those who take gabapentin. (132,136) Originally, the experiments were conducted on *naïve* rats with a plan to continue the study with the use of rats subjected to an experimental model of neuropathic pain as behavioural responses to drugs may be altered by the presence of neuropathic pain conditions. (245) However, due to the loss of equipment and inability to continue the study, the experiments were restricted to *naïve* rats only, and the results of this experiment are presented in this Chapter.

3.2 Introduction

It has become more common for gabapentinoids (pregabalin and gabapentin) to be prescribed for patients with neuropathic pain despite mounting evidence of gabapentinoids potential for being abused and misused. (239) Interestingly, it has been reported that individuals who take pregabalin are more likely to abuse or misuse the drug than those who take gabapentin. (132) There are some advantages in the pharmacokinetic profile of pregabalin over gabapentin that may contribute to an improved pharmacodynamic effect that may also explain the higher abuse potential of pregabalin. (103,128) Moreover, as discussed in the previous Chapter, pregabalin has a potential to be misused by individuals with histories of substance abuse disorders compared to the general population, particularly in those using pregabalin concurrent with opioids (*e.g.,* morphine). (246)

There is scientific consensus that drugs abused by humans can function as reinforcers in laboratories using experimental animals. (247) Animal models are commonly used to investigate how medication can elicit substance abuse behaviours. It is known that laboratory animals develop behaviour patterns related to drug-taking and drug-seeking behaviour that are associated with addictive behaviour. (248) Drug self-administration studies in rodent models represent human behaviour of drug seeking and addiction. In general, the drug self-administration model is one of the most powerful experimental models to investigate drug addiction, drug-taking behaviour (reinforcing effect), and measure drug-seeking behaviour (Table 3.1). (248,249) Another example of an experimental model that is used to investigate drug addiction is conditioned place preference (CPP) paradigm, where animals are exposed to two different chambers, of which one is paired with the rewarding effect of the drug. However, CPP does not directly resemble human addiction as the drug is administered passively by the experimenter, and therefore, the animal does not have a choice of the drug as it would be possible when using the self-administration approach. In addition, the CPP test is deemed as a learning phenomenon based on the effects of various stimuli on associative learning. (250) Therefore, CPP alone is insufficient to explain the instrumental nature of drug-seeking and drug-taking behaviour, which a drug self-administration model might better explain. (251) The self-administration model has excellent face validity towards human behaviour and experiences. In other words, it has a better translational potential for human behaviour. (248,249) In addition, it can provide the most direct point-to-point correspondence

with addictive behaviour, which may occur in the natural environment compared to other addictive models. Consequently, animal studies of drug addiction rely on drug self-administration models as the gold standard. (248,249) For these reasons, the self-administration model was selected in this current study.

Addiction	A chronic, relapsing brain disorder that is characterised by compulsive drug-seeking and use, despite harmful consequences.
Reinforcement	The process whereby the event strengthens behaviour follows the behaviour and a procedure by which the contingencies between the reinforcers and behaviour are arranged within a paradigm.
Reinforcer	A stimulus event strengthens the behaviour that follows it.
Reinforcing efficacy	The likelihood that a drug will serve as a reinforcer under various experiment conditions (also termed reinforcing strength). For example, a drug that is only self-administered when work required to obtain a delivery is low (that is, fix-ratio 1) would be considered a weak reinforcer. In contrast, a drug that is self-diminished under various experimental conditions and when the work requirement is high would be deemed a strong reinforcer.
Reinstatement paradigm	A model of relapse whereby the animal is tested on responding on a lever that was formerly associated with the drug following re-exposure to a small priming dose of the drug or the environment stimulus associated with the drug.
Self-administration	Operant responding that directly produces administration of the drug.

Table 3-1. *A glossary of some terms used in the self-administration experiment. Adapted with permission from National Institute on Drug Abuse.* (252)

Self-administration procedures can be classified according to different criteria. (248) From a pharmacokinetic aspect, it can be classified by the route of administration by which the medication is delivered to the animals. (248) For example, some studies have used oral self-administration methods to model human opioid-taking behaviour, while most addictive drug abusers inject the drug intravenously. (253) Moreover, the oral and intravenous (IV) routes of administration give completely different pharmacokinetic and pharmacodynamic profiles which pose a challenge for the animal models and their alignment with human behaviour. Not surprisingly, the most common method of administration is IV since this route of administration provides rapid uptake and near-immediate induction of reward. Thus, in summary, the route of administration plays a significant role in modelling human behaviour, and IV route was selected in this current study. (254)

From a behavioural aspect, drug self-administration can be categorised as an operant and non-operant procedure. The non-operant procedure is restricted to oral administration and is mainly used in alcohol research. In 1962, Weeks developed self-administration paradigms confirming that animals voluntarily self-administer addictive medications when placed inside an operant chamber. Inside the chamber, any response to an active lever automatically delivers a specific amount of drug (infusion) through an implanted catheter. This operant self-administration paradigm shows high predictive validity in assessing the reinforcing properties of the drug, which are related to its abuse liability potential. (255,256) For these reasons, the operant procedure was selected in this current study.

In order to evaluate the drug reinforcement, it is necessary to assess the reinforcing efficacy of the drug. The reinforcing efficacy is the degree to which a drug sustains the tested behaviour (*e.g.,* drug-seeking behaviour), as defined in table 3.1. The concept of reinforcing efficacy cannot be discussed as an absolute value. The reinforcement is instead discussed in terms of relative reinforcing efficacy value as compared to the reinforcement provoked by other stimuli, various doses of the drug, or the same drug in different circumstances. (257,258) Within the context of self-administration studies, reinforcing effects of drugs are typically measured in terms of: (1) the amount of drug animals consume, (2) the rate of responding to receive the drug, and (3) the rate of times drug is preferred over a placebo or a non-drug alternative reinforcer. (259)

Schjerning *et al.* conducted a systematic review of the abuse potential of pregabalin and found that seven preclinical studies exist, of which five used the CPP test, and two studies focused

on self-administration experiments. (129) The CPP studies, where animals were exposed to two different chambers, of which one was paired with the rewarding effect of the drug (as mentioned above), reported that pregabalin did not induce CPP regardless of dose. (260,261) This outcome may indicate that pregabalin did not induce rewarding effect in these animals. While this may suggest that the exposure to the drug may require a development of pain in animals, there is one study conducted by Rutten *et al.* showed that pregabalin did not induce CPP in either *naïve* or pain model animals. (262) However, there are challenges with this test, as explained above, that may be directly linked to the lack of the effect observed in this experimental approach. The self-administration studies are less aligned with the outcomes and were conducted and reported by Pfizer. (261) According to one of these studies, pregabalin at 3.2 mg/kg and at 10 mg/kg produced significant reinforcing effects, whereas the other studies conducted by Pfizer found that pregabalin did not show reinforcing properties. (261) According to the published evidence referring to pregabalin abusive potential, there is an association between abuse and misuse of pregabalin and opioid use disorders. (98,132) Additionally, pregabalin has been reported to be more commonly abused by patients who have a history of substance abuse. (103) The fact that those patients prefer pregabalin may suggest a higher abuse potential. Interestingly, however, no studies to date investigated the effects of the presence of opioid on pregabalin reinforcing efficacy in an animal model. While the evidence from humans suggests an association between previous opioid exposure and the abusive use of gabapentinoids, studies that would address this in animal models may help to better understand the abusive potential of pregabalin. Therefore, the reinforcing efficacy of pregabalin was examined in this study compared to the established reinforcing efficacy of morphine.

Thus, in the light of understanding the animal behavioural models (248,263) and the increased reports of pregabalin misuse among individuals with histories of opioid dependence (132), the primary aim of the present study was to investigate the abuse potential of pregabalin when used in conjunction with morphine in *naïve* rats (healthy controls; not subjected to any surgical interventions that may result in the development of a disease model). The reason for starting with *naïve* animals was based on establishing a protocol for self-administration and understanding whether or not previous exposure to opioids would affect the reinforcing effects of pregabalin. This was considered as an important methodological step before employing a model of chronic neuropathic pain. Also, a consideration of animals' welfare to

avoid exposing the animals to unnecessary pain was taken on board. With successfully establishing the self-administration protocol in *naïve* animals, the next step planned was conducting a similar study in rats subjected to an experimental model of neuropathic pain induced by sciatic nerve injury. Using both *naïve* and neuropathic pain animals would help to determine the impact of morphine self-administration on motivational behaviour that would be studied in combination with pregabalin which is used for the treatment of neuropathic pain. To the best of the authors' knowledge, this study is the first animal study to examine the reinforcing efficacy of pregabalin after being exposed to morphine self-administration. This study was conducted using an operant self-administration paradigm which consisted of three phases: (1) operant self-administration acquisition phase (food and morphine), (2) extinction phase, and (3) reinstatement phase (re-exposure to morphine then pregabalin).

3.3 Materials and Methods

3.3.1 Ethics and husbandry

The animal work protocol reported in this thesis was performed under the UK Home Office license (P6694C943), with the Animal Welfare Ethical Review Body (AWERB) local approval, and in accordance with current UK legislation as defined in the Animals (Scientific Procedures) Act 1986. The Animal Research: Reporting of In Vivo Experiments (ARRIVE) has been followed in reporting this study.

Animals were housed in the Comparative Biology Centre (CBC) at Newcastle University in standard cages (2-3 per cage) with a humidity of 55% ± 10% and controlled temperature (23^{o}C ± 1^{o}C) under a regular 12-h day/night cycle (light from 0700 to 1900 hours). The rats were allowed to acclimatise to the colony room for at least seven days after arrival. Standard laboratory rodent food and water were provided *ad-libitum* for each cage. Cage bedding (sawdust bedding) was changed every week.

3.3.2 Subjects

Twelve *naïve* rats (adult male Sprague Dawley, Charles River, 280-300g) were used and housed as mentioned previously in 3.3.1.

3.3.3 Surgeries

3.3.3.1 Animal preparation

The surgery was performed under general anaesthesia using isoflurane inhalation anaesthesia according to named veterinary surgeon (NVS) advice ((up to 5% isoflurane with oxygen as the carrier gas for induction and 1.5–2.5% for maintenance). Anaesthesia was delivered through a nose mask and carefully monitored to avoid excessive cardiac and respiratory depression. Ophthalmic ointment (Optixcare Eye Lubricant and Hyaluron) was applied prior to starting the surgery on both eyes for protection.

The rat was then transferred to an induction sealed chamber (internal dimensions 23cm x 10cm x 10cm) until the effect of the anaesthesia started (Figure 3.2 (a)). To induce and maintain an appropriate depth of anaesthesia, the rat was immersed in a steady flow of the inhaled anaesthetic (4%) Isoflurane in a sealed induction chamber. Once the rat was asleep (there was no reaction to pinching between toes), it was moved out from the chamber and nose mask anaesthesia was used and maintained at roughly 3% isoflurane (Figure 3.1). Then, the rat's neck (halfway between chin and arm on the left side, look for the pulse of the jugular vein) and head area, as shown in figure 3.2, were shaved and then cleaned with Hibiscrub® (concentrate antiseptic) 5 to 6 times, starting in the centre of the area then outwards.

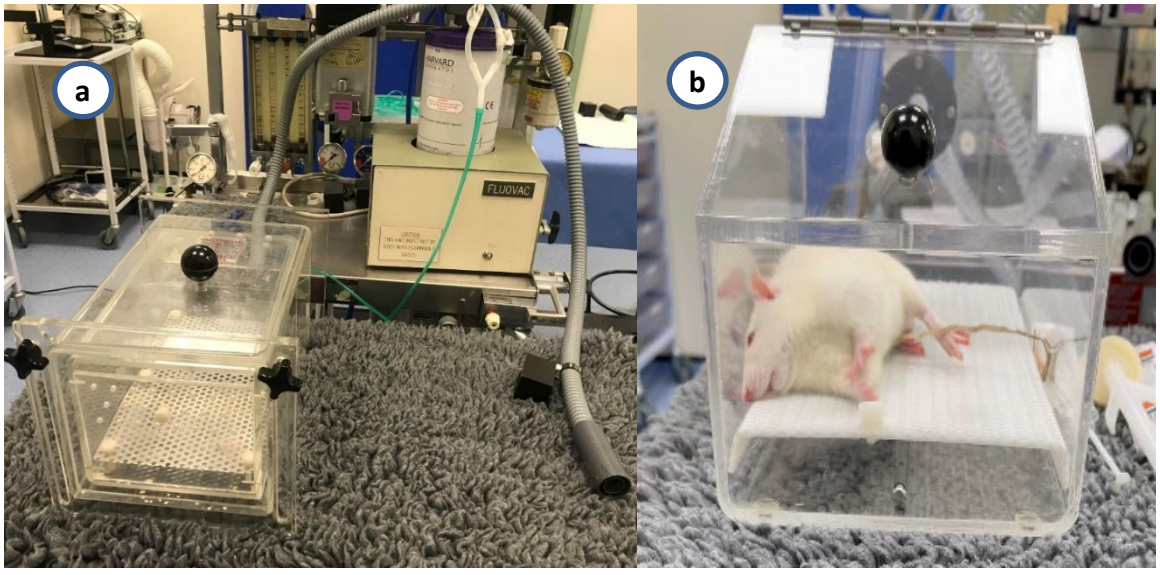


Figure 3-1. *Anaesthesia induction. (a) anaesthesia station; (b) sedated rat inside a sealed induction chamber.*

Figure 3-2. *Shaving rat's neck using a rat fur trimmer and cleaning the shaved area from centre to outward with Hibiscrub®.*

3.3.3.2 Surgeon's preparation

Hands were scrubbed with Hibiscrub® three times. First one, hands and wrists were rinsed, letting water drain down to the elbows. In the second wash, nails only were scrubbed with a brush and rinsed. Third wash, hands and wrists were rinsed. Then, hands were dried with sterile towels or left to dry in the air. During surgery, sterile disposable gloves were worn, but even if such gloves are used, it is necessary to scrub the hands as described above.

3.3.3.3 Catheter implementation

The catheters were prepared before the surgical procedure, as shown in figure 3.3 (home-made IV catheter preparation in Appendix B). The surgery was performed by IO. JA and NVS were surgeon assistants during the catheter implementation surgery.

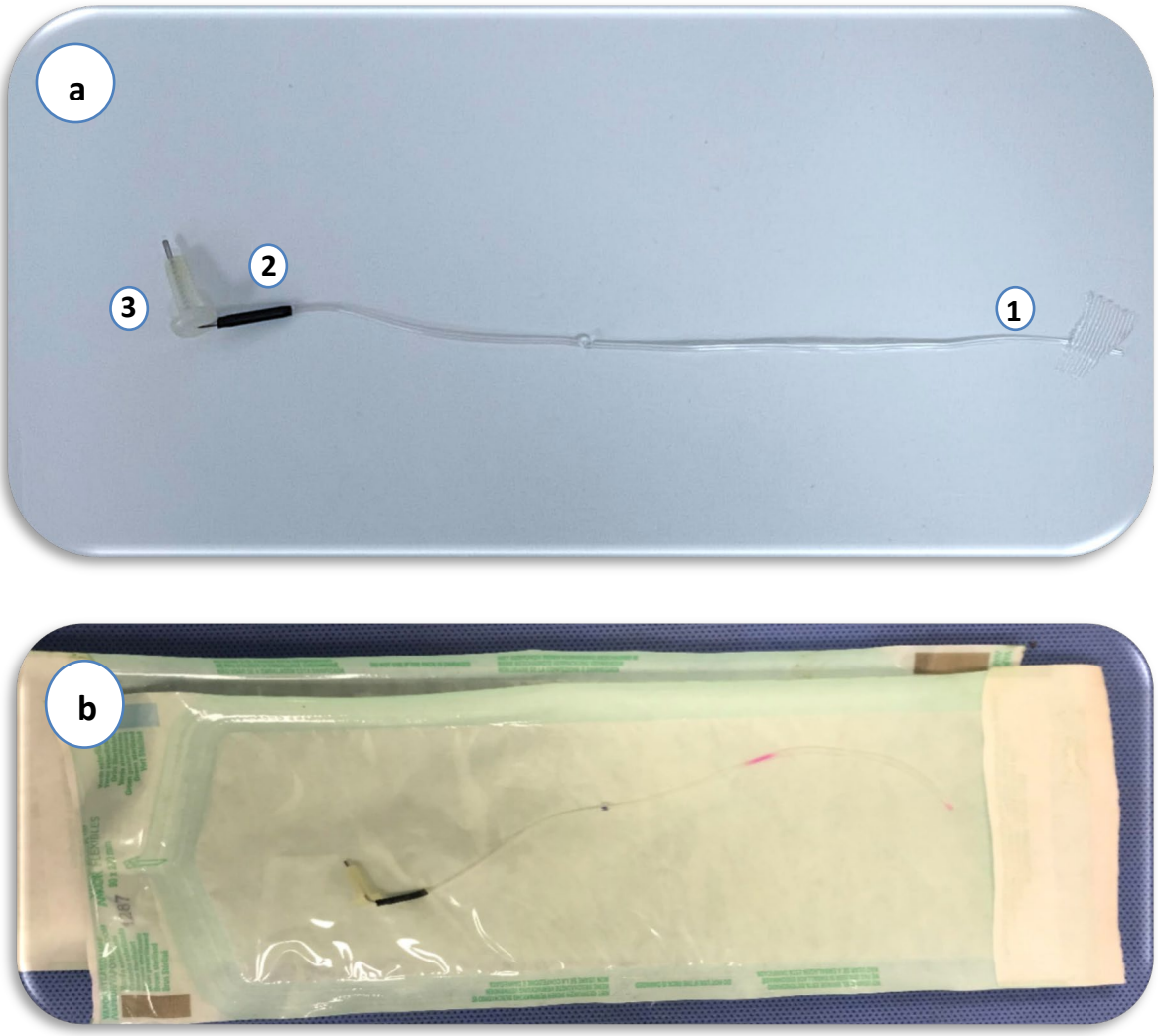


Figure 3-3. *Home-made IV catheter. (a) catheter components: (1) silicone catheter tubing, (2) wire heating element, and (3) external catheter port which included bent cannula covered by a plastic screw, and (b) sterilised catheter.*

After the surgeon scrubbed, the rat was placed on a heated pad throughout the surgical procedure. In order to insert the catheter into the jugular vein, two incisions were made: one on the head for positioning the external catheter port, and the other on the neck for gaining access to the jugular vein. Before making an incision, rats received local anaesthetic around the area of the incision. A local anaesthesia injection included: lidocaine 1% (10mg/ml); and bupivacaine 0.25% (2.5 mg/ml), made up to 1 ml with sterile saline/water, mixed in a vial. The injection was calculated in (mg/kg), and the volume administered was adjusted as and when necessary to keep the dose constant according to NVS advice, as presented in table 3.2.

Rat Weight (*g*)	**Bupivacaine 0.25% (2.5mg/ml)**	**Lidocaine 1% (10mg/ml)**
300	0.3ml	0.48ml
350	0.35ml	0.56ml
400	0.4ml	0.64ml
450	0.45ml	0.72ml

Table 3-2. *Anaesthesia dose according to rat weight.*

As shown in figure 3.4 (a), a straight incision of approximately 3-3.5 cm was made on the lateral shaved neck using a scalpel. In order to expose the vein, a deeper incision was made on the second layer of skin to open the muscle protecting it.

Then, a small incision was made slightly to the side of the pulsing right jugular vein using a scalpel/scissors. Fat and connective tissue were gently teased apart to expose the jugular vein using fine forceps and blunt-ended scissors (Figure 3.4 (b)). Trocar was used to open a subcutaneous tunnel from the neck incision to the head incision, as presented in figure 3.5 (a). Then, the rat was carefully rolled on its stomach, and an incision on the shaved head was done with a scalpel. After that, the rat was returned on its back.

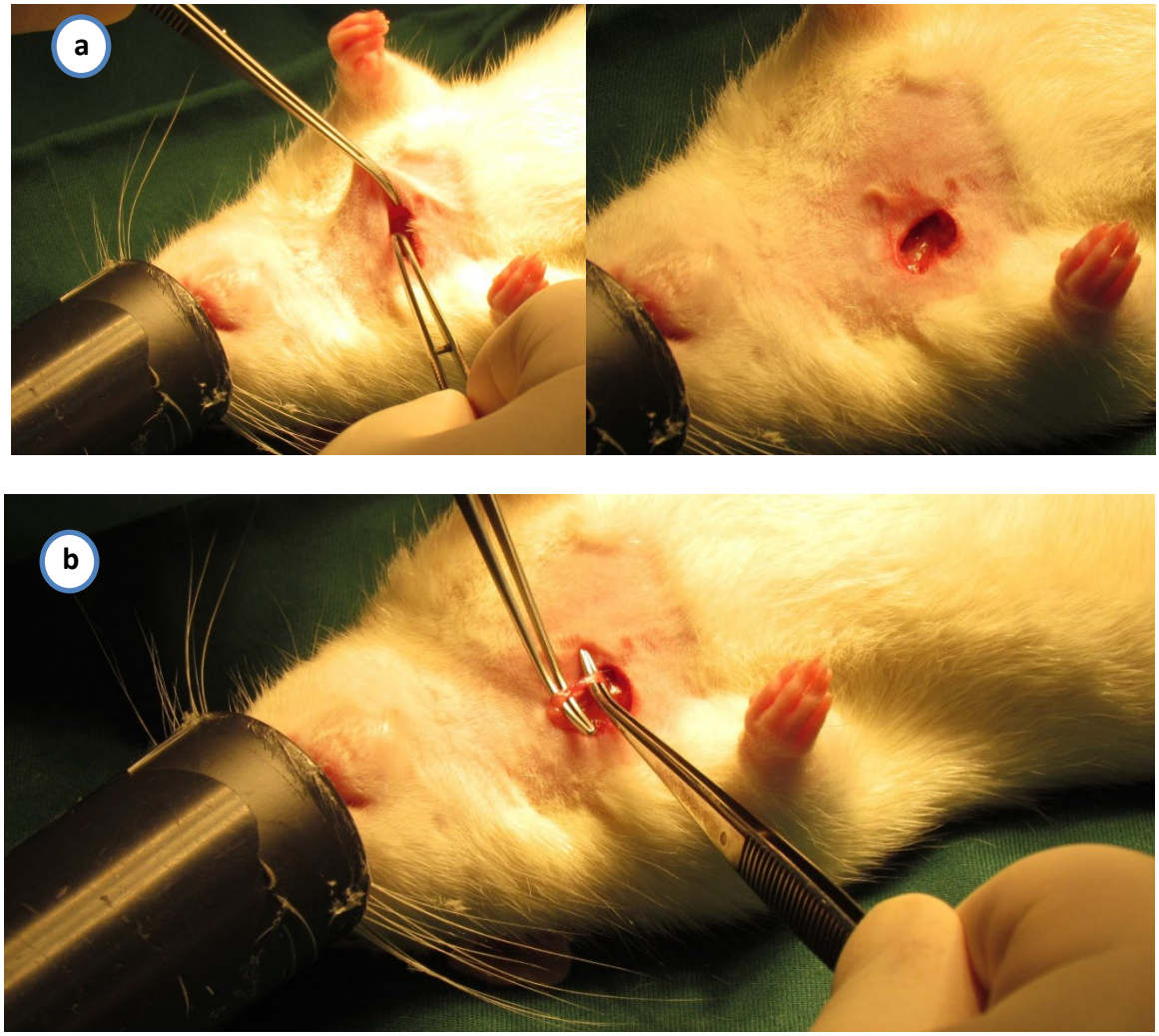


Figure 3-4. *Expose the jugular vein. (a) straight incision was made on the neck of rat, and (b) the jugular vein was separated from the surrounding fat and connective tissue by small movement of the two pairs of fine forceps and blunt-ended scissors.*

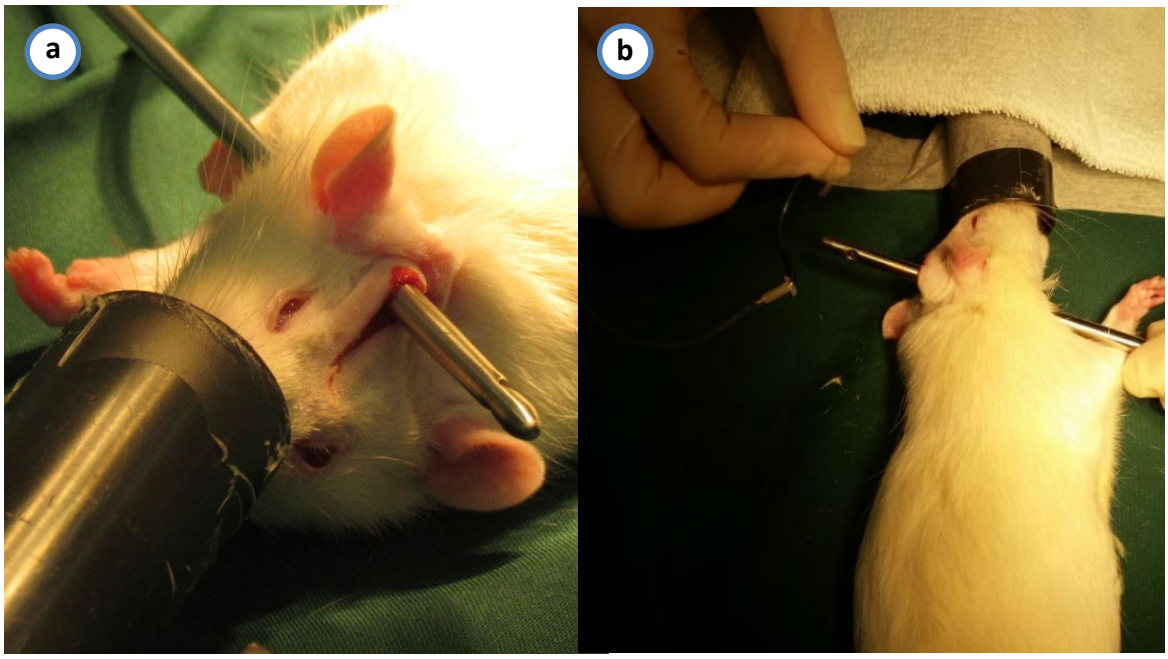


Figure 3-5. *Catheter insertion from the head incision to the neck incision. (a) using trocar to open a subcutaneous tunnel from the neck incision to the head incision, and (b) thread the catheter tubing through the trocar hole.*

The bag containing the sterilised catheter was cut (Figure 3.3). Then, the tubing below the silicon glue was cut to the correct length depending on the weight of the animal (*e.g.,* 300g = 3cm, 350g = 3.5cm). The catheter tubing was threaded through the hole in the trocar, and the trocar was pulled back to pass a catheter through a subcutaneous channel and out of the neck incision (Figure 3.5 (b)).

Then, saline was flushed through the tubing. As shown in figure 3.6 (a), closed hemostat forceps were inserted underneath the jugular vein; then, the forceps were gently opened. A small incision was made on the surface of the vein, and tubing was inserted up to the silicon (Figure 3.6 (b, c)). After positioning the catheter subcutaneously, it was checked if there was a blockage by drawing blood back through the tubing. If the flow was smooth, the catheter was secured in place with a 4/0 Ethilon suture (Figure 3.6 (d)). The knot was checked to be not too tight by drawing blood back through the tubing. The knot was glued with 3M Vetbond™ tissue adhesive and allowed to dry before closing the wound. The wound was sutured using 4-0 absorbable Vicryl and cleaned with Videne® Surgical Scrub (Iodinated povidone 7.5%, Ecolab Ltd, UK) before transferring the rat to the head stage station (Figure 3.6 (f, *g*)).

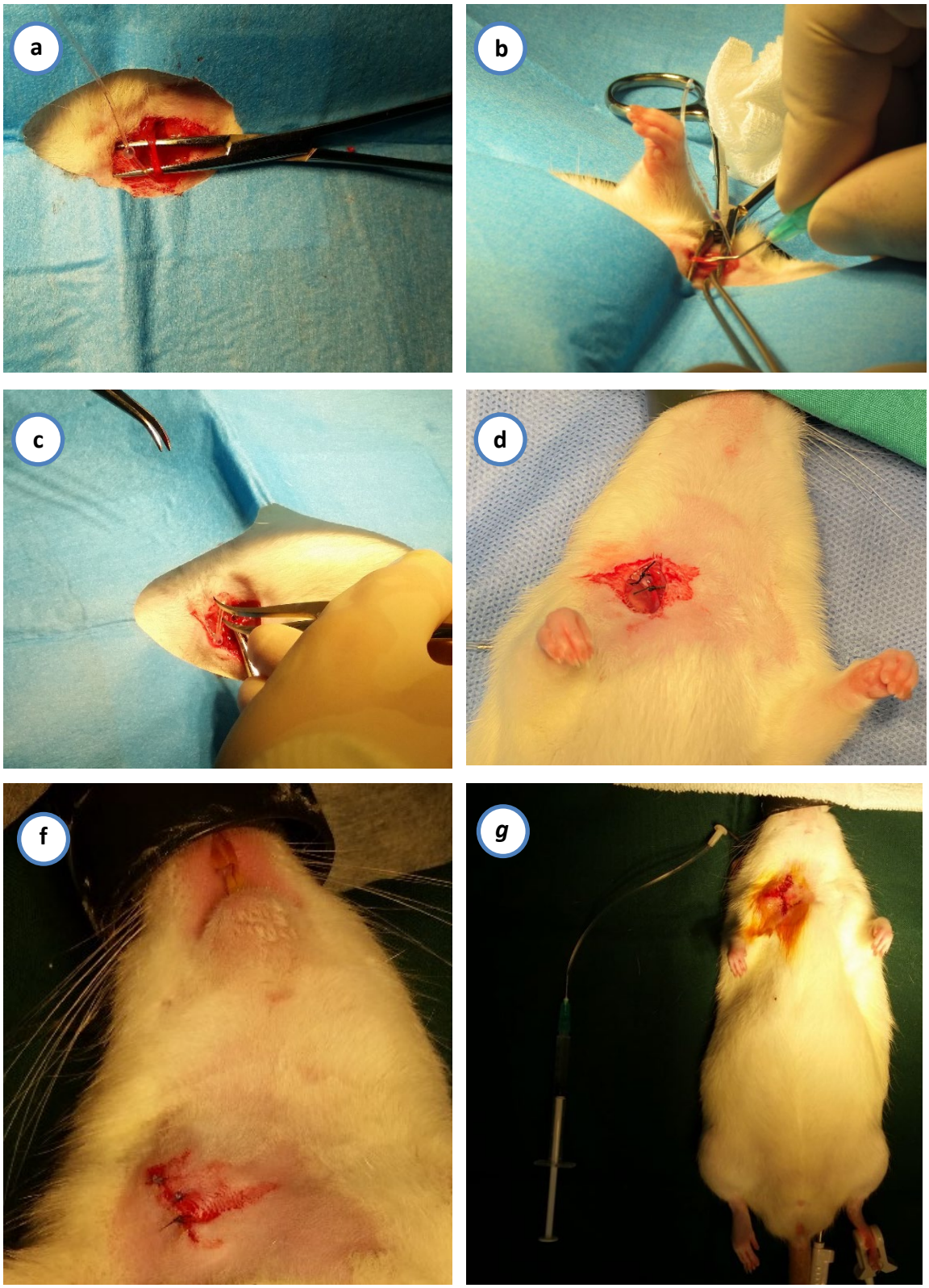


Figure 3-6. *Surgical procedure to implement a catheter into the jugular vein. (a) dissected jugular vein using the haemostat, (b) a hole in the jugular vein was made using a needle, (c) insertion of catheter tubing, (d) anchoring of catheter to the vein by suture, (f and g) wound cleaned with Videne®.*

The rat was transferred to a stereotactic table (Figure 3.7) and appropriately fixed in the apparatus. The external catheter port was checked if it was correctly positioned, and the tubing was not blocked or kinked by drawing blood back through the tubing. Then, the head stage was built using five screws, and dental cement was used to hold the end of the catheter in place (Figure 3.8). In the end, the catheter was checked for the last time by drawing blood back through tubing and flushing through 0.2ml saline; then, the flusher was removed, and the catheter port was sealed with sealed tubing and a screw cap. Finally, the wound was closed using a 4-0 absorbable Vicryl (Figure 3.8). In order to prevent contamination, the catheter port was immediately capped with a home-made plug made of polyvinylchloride tube (PVC), which had one end closed with a monofilament fishing line (Figure 3.9).

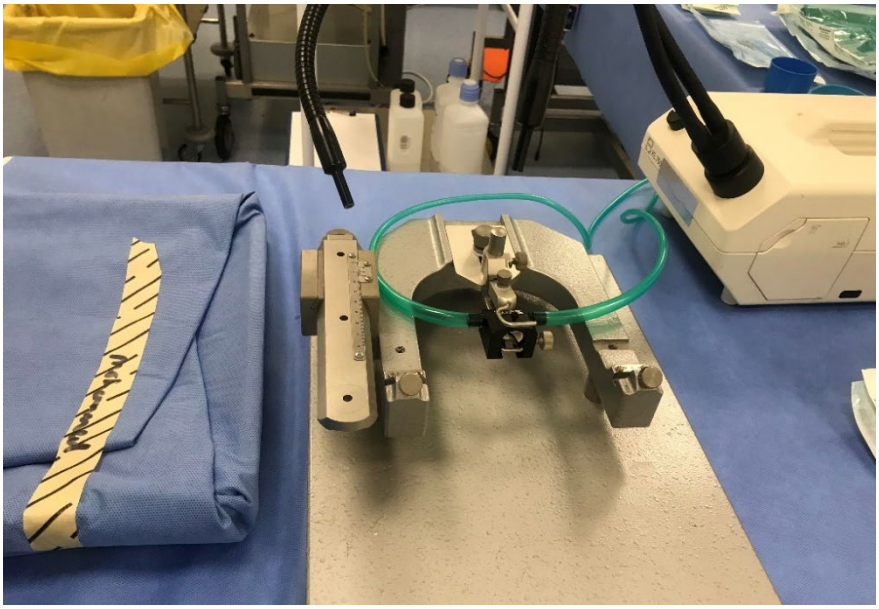


Figure 3-7. *Stereotactic apparatus.*

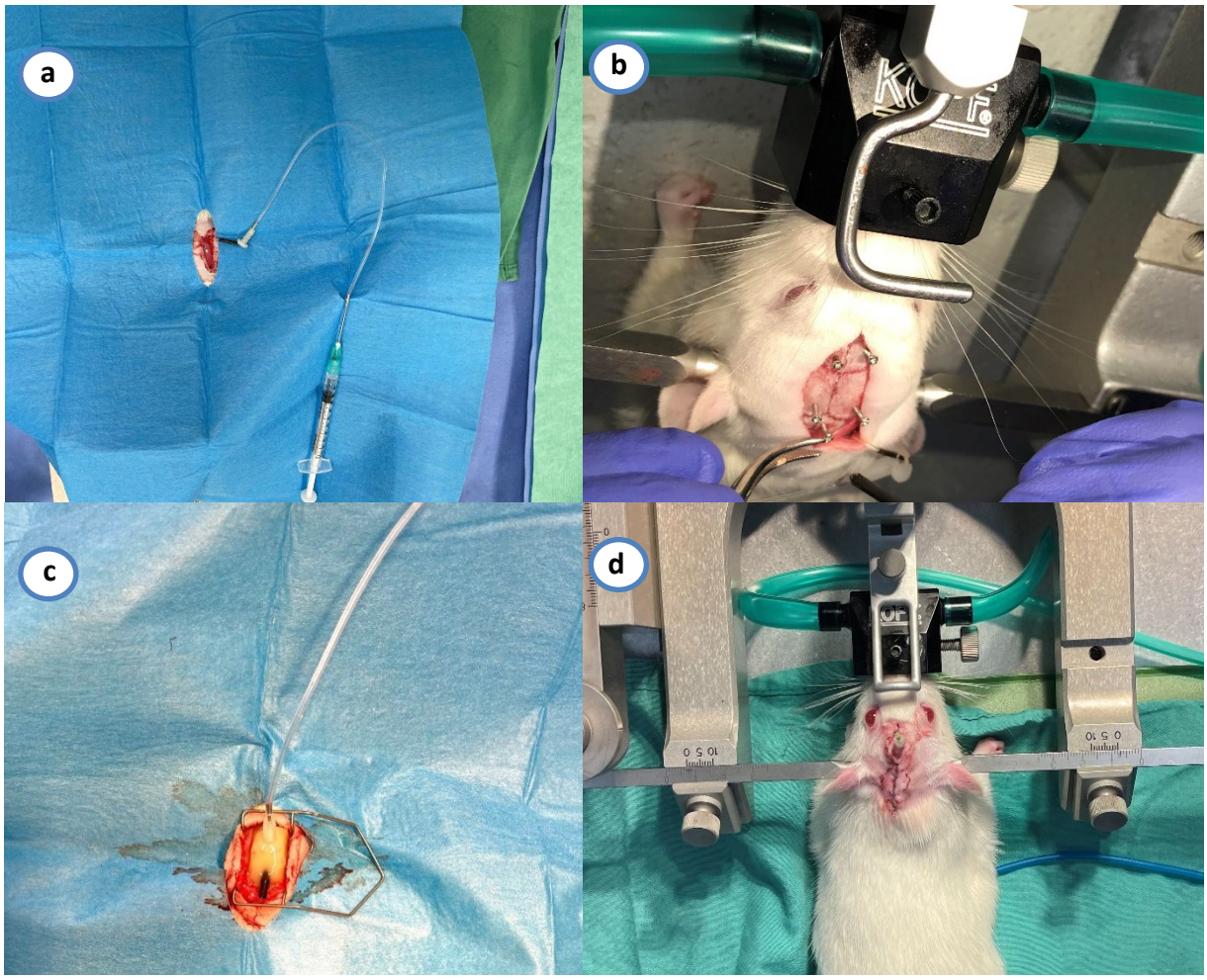


Figure 3-8. *Steps of building a head stage. (a) fixed the rat head on the stereotactic, (b) positioned screws on the rat's skull, (c) the external catheter port fixation by dental cement, and (d) closure of the head wound.*

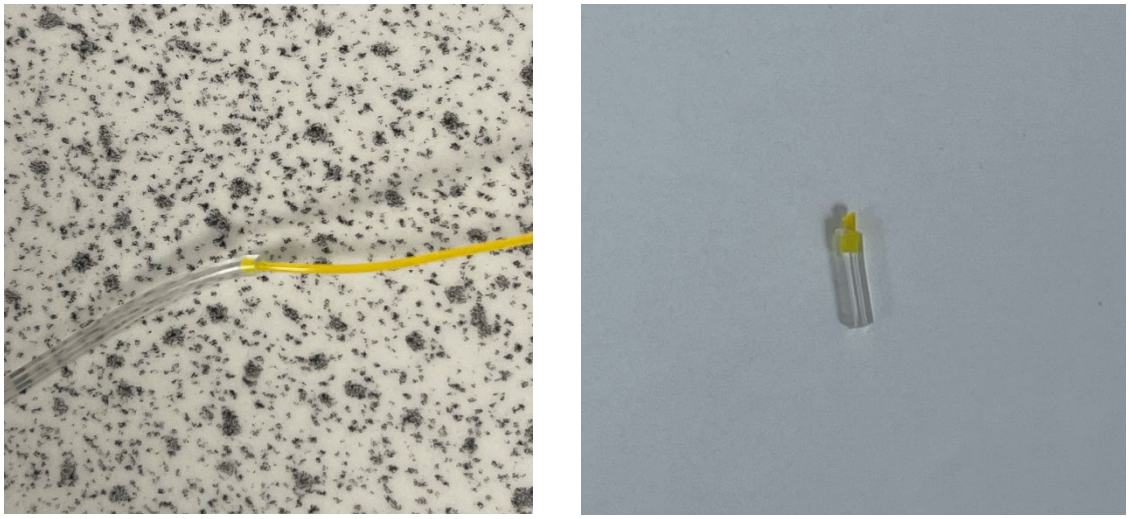


Figure 3-9. *Home-made plug to close the external catheter port. (a) a monofilament fishing line (60lb) was inserted inside a polyvinylchloride (PVC) round tube (bore: 0.50mm and wall: 0.50mm).*

3.3.3.4 Recovery steps

The rat was placed in a cage with absorbable paper on the floor and administered 5 ml warmed glucose-saline (40°C, subcutaneous (SC)) to replace the intra-operative fluid loss. The cage was placed on a heated mat in the recovery area until the rat recovered (awake). Once the rat was awake, water and moistened food were placed in low bowls on the cage floor. During the recovery, changes in general behaviour were monitored. Rats were observed for three hours after the surgery, and pain was scored using the agreed system (Appendix B). Soft bedding, wet mash, chew blocks, and supplementary heat were provided to help to mitigate post-operative pain if observed. Painkillers were not used to reduce the pain as the use of both NSAIDs and opioids might interfere with experimental outcomes, which could prevent achieving the objectives of the study. However, local anaesthetics (*e.g.,* EMLA cream) were used to reduce local pain for a short time and therefore were implemented during surgery. During the last three days of post-operative care, catheters were flushed daily or twice daily with 0.1 ml sterile saline/Heparin/Baytril solution (1% w/v Heparin and 5% w/v Baytril in 100 ml saline). Then, the flushing of the catheters was done daily.

On the next day of surgery, rats were transferred back to the holding room and rehoused as groups with sawdust bedding, solid food, and water *ad libitum*. Whenever rats were not receiving infusions or attached to the self-administration chamber, catheters were continuously capped with a PVC tube and then screwed using a metal cap (Figure 3.10). A metal cap was used to prevent rats from chewing and damaging the external catheter port.

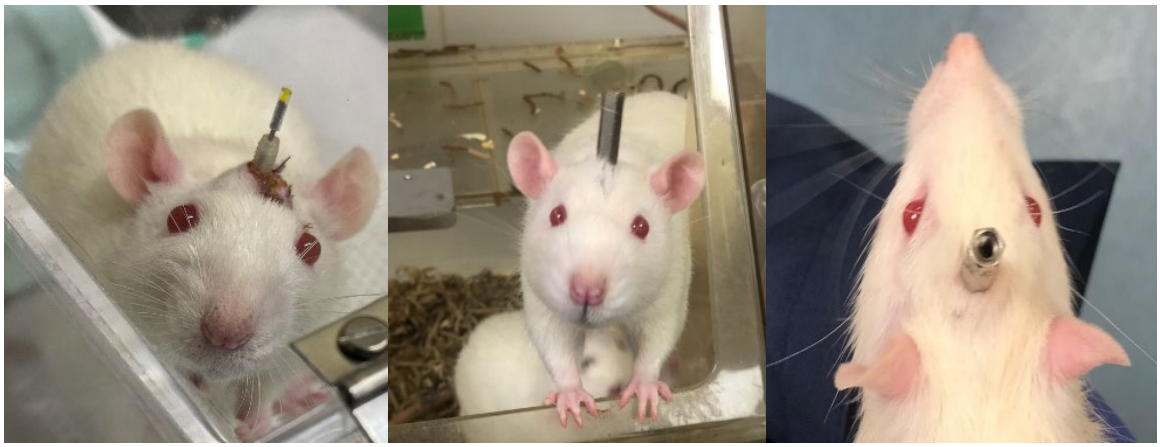


Figure 3-10. *Capping the external catheter port.*

3.3.4 Drugs

Morphine

Morphine (morphine sulphate; Macarthys Laboratories Ltd, t/a Martindale Pharma, UK) was dissolved in saline (Sodium chloride 0.9% solution NaCl; Fresenius Kabi Ltd, UK) immediately prior to running the self-administration experiment. Rats were weighed daily in order to calculate the morphine dose. The dose of morphine used was 0.56 mg/kg/infusion (120 µL /infusion over 2 seconds (s)), followed by a gap in time of 20 seconds (s). (264–266) This dose was selected based on the available literature (264–266)

Pregabalin

Pregabalin (pregabalin; Bio-Techne Ltd., UK) was dissolved in saline immediately before running the experiment. The dose of pregabalin used was 2 mg/kg IV per infusion. This dose was used based on previous studies reporting behavioral effects of pregabalin. (17,25)

3.3.5 Self-Administration Chamber

Twelve standard operant conditioning boxes were prepared for use that consisted of a Plexiglas™ enclosure with one visual stimulus light, one tether and a fluid swivel, fan-ventilated, and two standard fixed levers. Specifically, the box included an extra wall sound attenuating cubicle measuring 59.69 x 55.88 x 40.64 cm and was housed in a custom-built 63.5 x 60.96 x 42.55 cm and modular test chamber (interior dimension; 53.34 x 34.93 x 1.27 cm, exterior dimension; 53.34 x 34.93 x 27.31 cm) had one transport wall and a stainless-steel grid floor (ENV-005 GF Grid Flour, Med Associates, St Albans, VT, USA). One lever was defined as an active lever (deliver a drug; reinforcer) and another one as an inactive lever (no infusion received when pressed on). The catheter was connected to an infusion pump through a tether and a freely rotating fluid swivel (Figure 3.11). Through the use of swivels, rats were able to rotate freely during drug operant sessions, preventing the drug line from becoming tangled. The operant boxes were controlled by a microcomputer using the Med-PC® (Behavioral Software) software package.

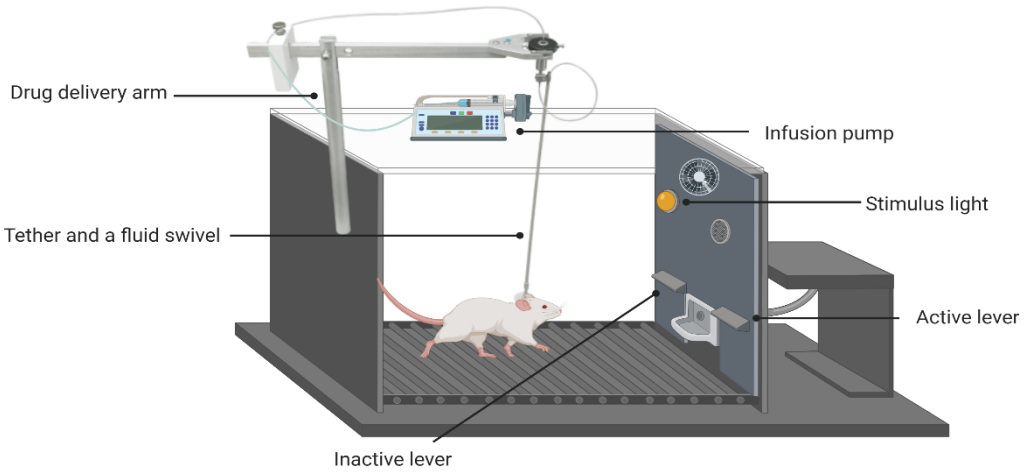


***Figure 3-11**. Schematic illustration of a modular test chamber. Rats were implanted with catheters in the jugular vein. The catheter was connected to a tether-and-tubing system that was attached to a drug-loaded syringe. Created with BioRender.com.*

3.3.5.1 Chamber maintenance protocol

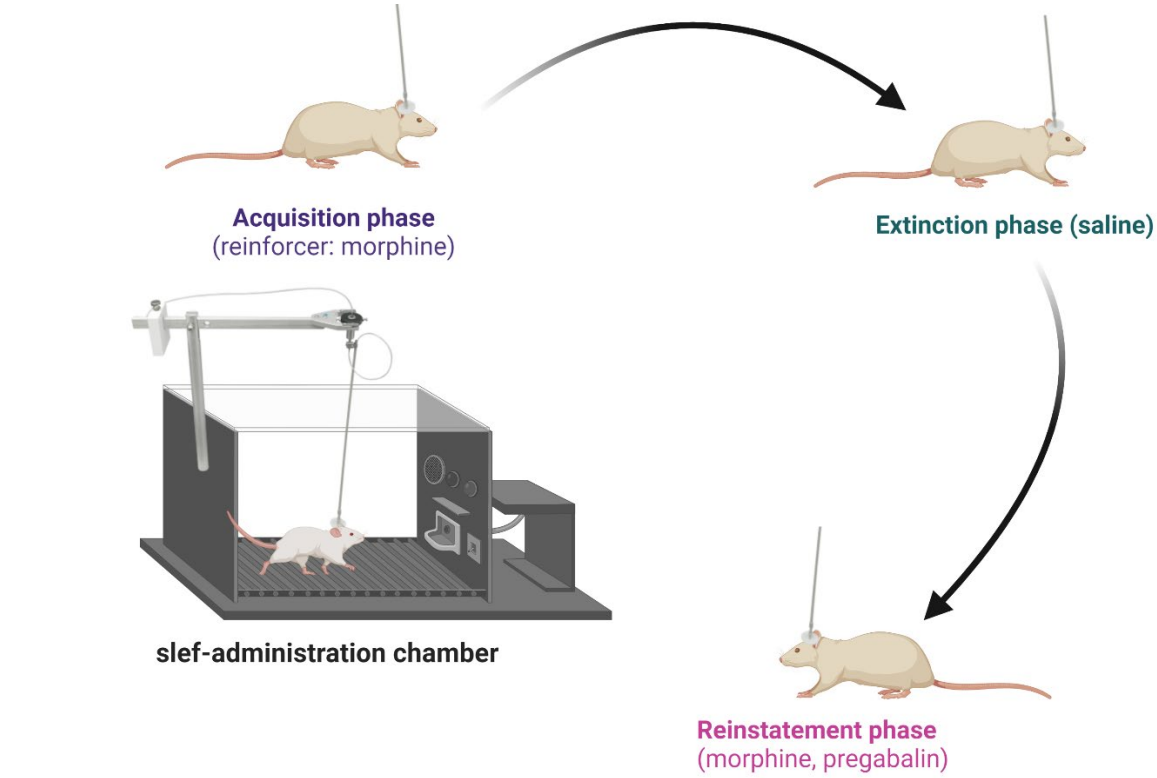
- Before and after the experiment, the chambers were maintained in a clean state free of dust and dirt by regular (at least weekly) cleaning with ethanol followed by rinsing.
- Trays were cleaned after each training session, and at the end of the day, all IV lines and syringe tubing were flushed with sterile water.
- Flushers were left connected to tubing whilst the box was not in use, and the end of the IV line stopped with a sealed needle containing Milton sterilising fluid (1% sodium hypochlorite and 16.5% NaCl).
- IV lines were changed once a week, and upper tubing at least once a month. All tubing were sterilised before installation (soak overnight in full strength Cidex, then flush with sterile water). Sealed needles and flushers were stored in Cidex whilst boxes were in use.
- Rats were flushed with 0.1ml saline containing Baytril before and after training sessions. Whilst the rat was in the test chamber, catheter plugs and the metal screw caps were stored Milton (0.5%; 5ml in 1L saline) in the 6-well containers (separate well for each animal). The same cap was used for each animal all the time.

3.3.6 Behavioural procedure

As mentioned above, the self-administration model is deemed to be the "gold standard" preclinical model for the study of drug reinforcement. (267) Using the self-administration model would be helpful in predictive validity for abuse liability of the drug. (268) Several species of animals have been used to evaluate the reinforcing efficacy using self-administration experiments, including rats, mice, and rhesus monkeys. (269–274) In most of these studies, rats were the species of animal used, particularly Sprague-Dawley rats. Therefore, Sprague-Dawley rats were selected for this experiment because this strain has demonstrated robust drug self-administration and required a few training sessions. (271,275)

In line with previous observations, *naïve* rats subjected to self-administration of morphine showed that morphine serves as a reinforcer and maintains drug-seeking behaviour. (276) The design of the current study was based on two previous studies that reported self-administering effects in rats after administration of morphine at a dose of 0.3-0.56 mg/kg/infusion. This resulted in acquiring between 2.5-5 mg/kg of morphine in one session, on average, which exhibited self-administration behaviour. (264,266) Thus, in the current experiment morphine dose was used as a positive reinforcer at a dose of 0.56 mg/kg per session lasting 60 minutes.

The duration of the study postoperatively was 16 weeks. Rats were given at least ten days to recover from the surgery (catheter implementation procedure) prior to running the behavioural procedure. The behavioural procedure included three phases: acquisition phase, extinction phase and reinstatement phase. Figure 3.12 demonstrates the experimental phases' timeline.



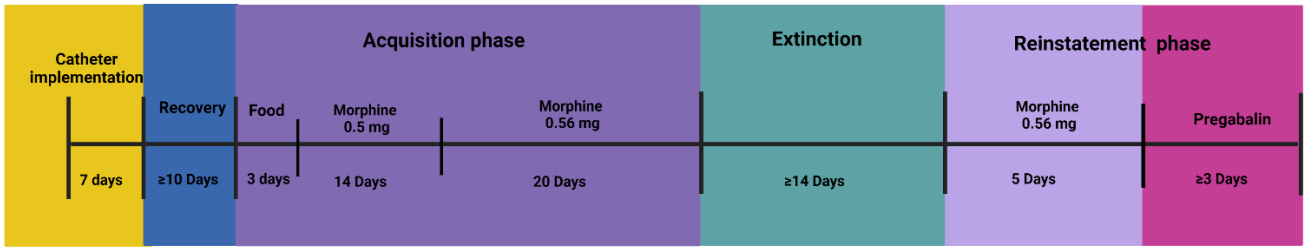


Figure 3-12. *Experimental timeline demonstrating the behavioural procedure used for pregabalin self-administration. Created with BioRender.com.*

3.3.6.1 Acquisition phase

Food restriction was used one day before commencing the experiment to facilitate the acquisition of behaviour. The use of food restriction is common in self-administration studies due to the fact that it increases motivational behaviour of the animal and therefore the sensitivity of the self-administration model to identify drug reinforcement. (256) Doing so facilitates the acquisition phase, decreases the threshold reinforcing dose, increases the total amount of drugs consumed, and boosts the effort rats are willing to make to obtain drugs. (256,277)

After experimentation in the operant chamber, rats were provided with 20g of food per day. At the beginning of each session, rats have been automatically delivered a morphine priming infusion as a trigger (0.56 mg/kg IV per infusion; 120 µl per 2s, for 2 weeks then increased to 0.56). (278) The priming infusion was administered in both the acquisition and reinstatement phases.

Rats underwent three days of food training. During the food training, a diluted honey solution was added on the active lever, as shown in figure 3.13, in order to train rats for pressing behaviour. The food training was done on a fixed ratio 1 (FR1) schedule of reinforcement (by one press (a fixed number of times) on an active lever delivered one infusion of a reinforcer (morphine)) for 60 minutes per day. Concurrent with the start of each injection, the stimulus light consisting of the white light was illuminated between the active and inactive lever will turn off. Each infusion was followed by a 20s time-out period when the responses were recorded but failed to produce any programmed consequences. After the 20s, the stimulus light was re-illuminated, and morphine was available for self-administration. Responses made on an inactive lever were recorded but not rewarded with morphine administration.

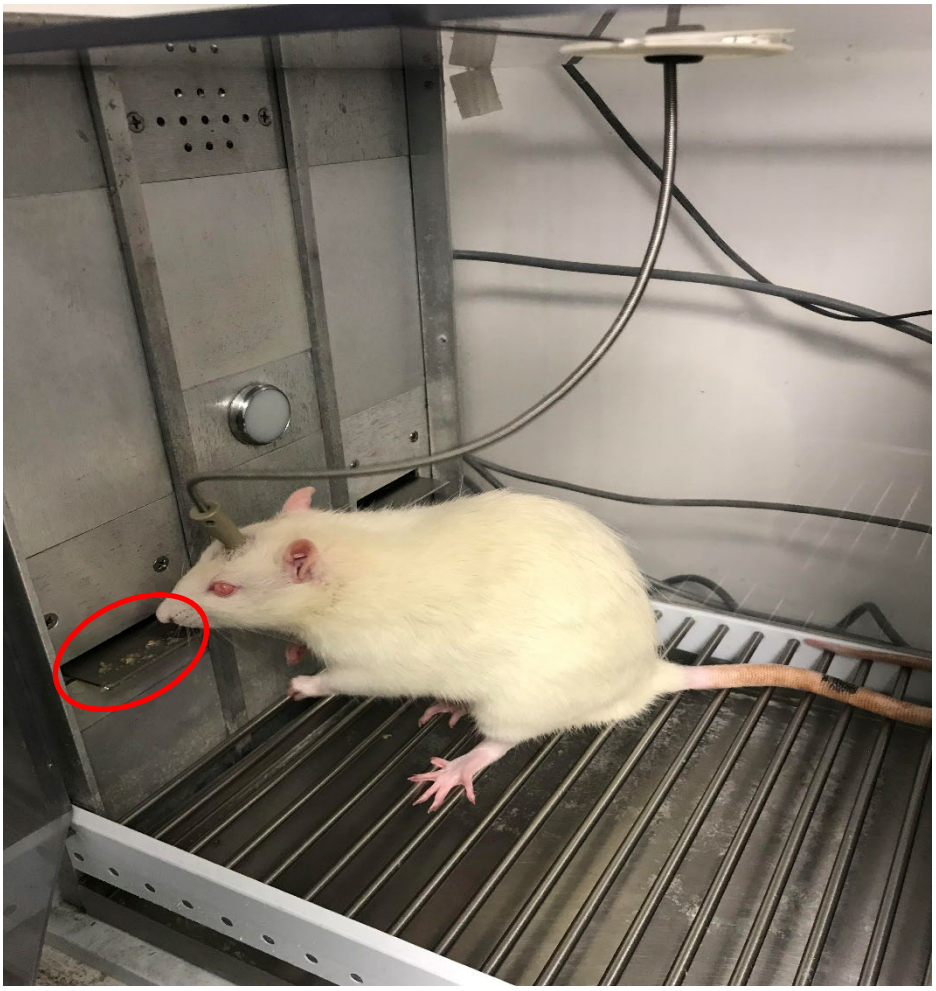


Figure 3-13. *Food training session with a diluted honey solution on the active lever.*

After three days, the use of honey solution on the lever was stopped completely. After this, morphine reinforcement was used until the performance was stabilised. The rats were subjected to two weeks of titration phase (0.5 mg/kg). (278) By day 15, the dose was increased to 0.56 mg/kg. As soon as rats showed stable performance (at least 80% of active lever pressing *versus* 20% inactive lever response) and a stable level of morphine infusion over three consecutive sessions, the fixed ratio was increased up to FR3 (3 presses on the active lever). (258,272) Once a stabilised performance on FR3 was achieved for three consecutive days; the morphine was substituted by saline for ≥14 days.

3.3.6.2 Extinction phase

After the acquisition, morphine-self-administering rats were subjected to 1-hour extinction session in which lever presses resulted in saline infusion until the extinction criterion was met.

The extinction criterion was defined as the total presses per session being ≤ 20% of the average total pressing reached during the last three sessions of acquisition. (270,272)

3.3.6.3 Reinstatement phase

After the extinction and drug abstinence, rats underwent reinstatement (relapse) phase morphine with FR3. A priming infusion of morphine was administered immediately prior to the self-administration session. The morphine reinstatement was continued until the performance was stabilised, as described previously in section 3.2.6.1. After that, pregabalin was substituted for morphine for five days.

3.3.7 Statistical analyses

GraphPad Prism 9 software was used for all data analyses, version is 9.4.1 for Windows (GraphPad Software, San Diego, CA). Gaussian distribution, also known as the (Normal distribution) was applied using Shapiro-Wilk normality test. (279) According to the nature of the data, parametric data were analysed using two-way ANOVA for (effects between active and inactive lever pressing, effects between sessions/phases, interaction between levers responding and phases), and *post-hoc* Tukey's *t*-test comparisons were performed to reveal differences between group means when appropriate. Tukey's t-test was used instead of a paired t-test because the t-test makes a single comparison, while Tukey's deals with all possible pairwise comparisons. However, Tukey's test is fundamentally a t-test excluding that it corrects an experiment-wise error rate. i.e. basically, the more pairwise comparisons are made, the greater the likelihood of having a type I error. (279,280) Statistical analyses were performed based on the mean of the last three consecutive sessions of the three phases (extinction, reacquisition, reinstatement). This technique enabled comparisons across self-administration phases with an uneven number of sessions and focused on stable behaviour. (281) Data from the extinction phase (first and last day) were analysed using *t*-tests (paired). Statistical significance was defined as $P < 0.05$. Behavioural data from self-administration are illustrated as mean ± SEMs.

3.4 Results

Of the 12 rats assigned to the self-administration experiment, eight rats were excluded from the final analysis for various reasons. Three rats were excluded because of loss of catheter patency. An additional three rats failed to acquire morphine self-administration, and two rats failed to reacquire morphine self-administration after the extinction phase. Only four rats were trained to self-administer pregabalin, as illustrated in figure 3.14.

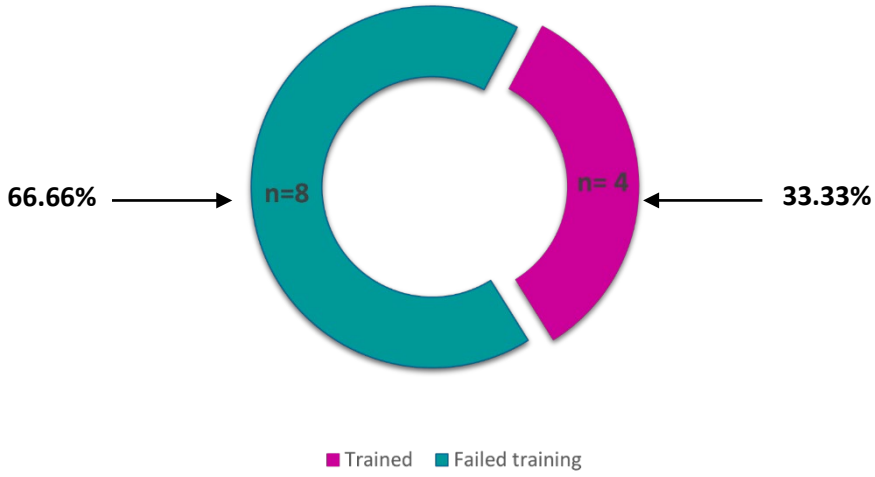


Figure 3-14. *Pregabalin self-administer success rates.*

3.4.1 Acquisition phase

For the data from the acquisition days, the test revealed a significant effect between the active lever and inactive lever responding [F (1, 136) = 78.83, *P*<0.0001] over the whole period.

As presented in figure 3.15, there is a significant interaction between lever responding and the acquisition sessions [F (23, 136) = 3.464, *P*<0.0001]. *Post-hoc* analysis revealed that a significant difference between the active lever and inactive lever responding occurred between sessions 20 and 24 (*P*<0.0001), the active lever pressing increased significantly over the session.

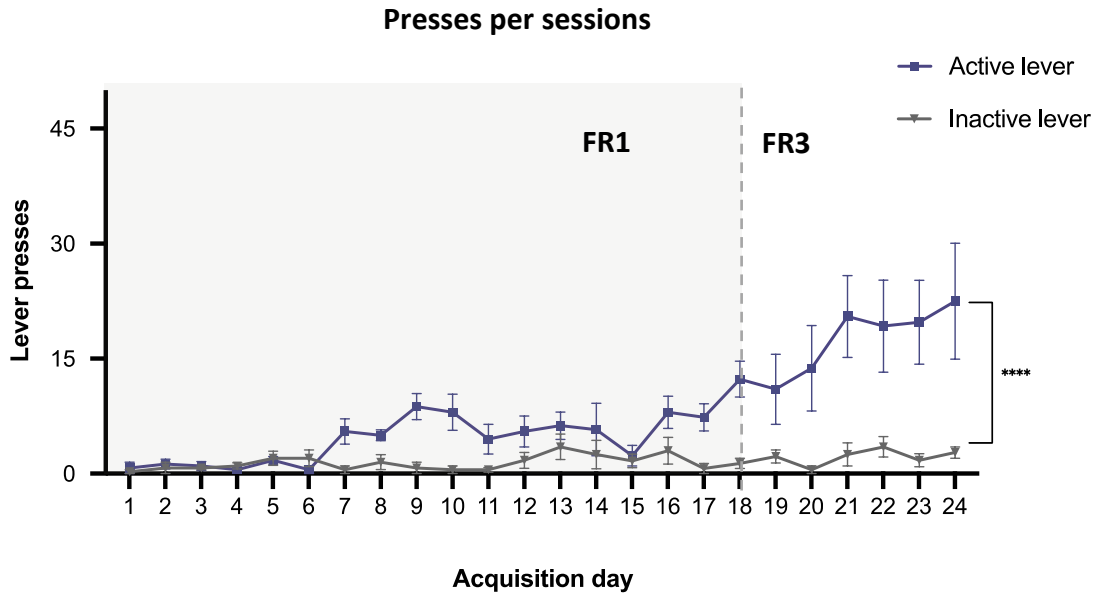


Figure 3-15. *The acquisition phase, morphine self-administration under an FR1 and FR3 schedule of reinforcement in Sprague Dawley rats. The mean (±SEM) number of active and inactive lever pressing are shown (n=4).*

****P*<0.0001; denotes a significant difference between active and inactive lever responding (two-way ANOVA followed by Tukey's t-test).

3.4.2 Extinction phase

Following the acquisition phase, rats underwent at least six days of extinction until the stabilise criteria were met (n=4) (Figure 3.16). The results did not show a significant decrease in active lever responding compared to the first day to the last day of extinction [t (3) = 1.77, *P*=0.17].

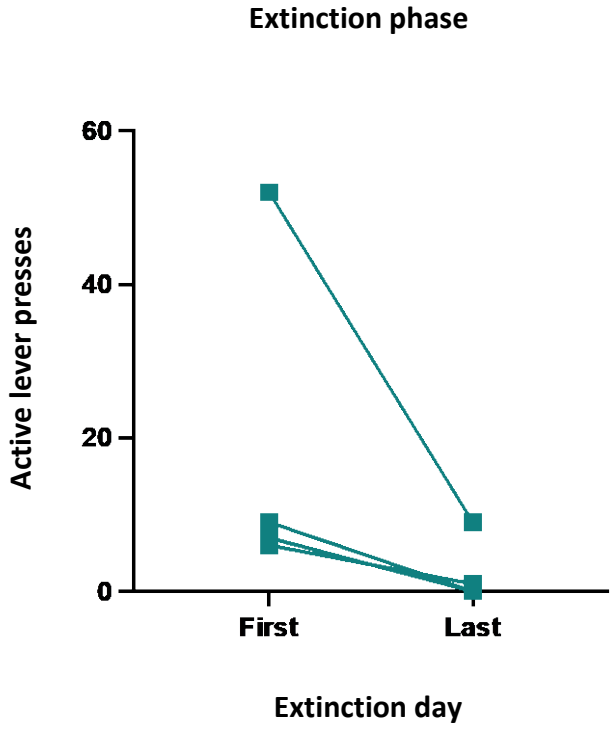


Figure 3-16. *The extinction phase, saline was substituted for morphine in response to the active lever. Morphine self-administering rats did not show a significant difference in active lever pressing from the first day of extinction to the last (P=0.17).*

3.4.3 Reinstatement phase

Following the extinction test, animals were given access to morphine. Substitution of morphine for saline produced a significant change in the rats' responses to the active lever compared to the inactive one [F (1, 22) = 134.5, *P*<0.0001].

A two-way ANOVA for repeated measures indicated that the active lever response rates significantly differed by phases compared to inactive lever responding [F (1, 11) = 210.6, *P*<0.0001]. The effect of phases [F (2, 22) = 5.644, *P*=0.01], as well as the interaction between levers responding and phases [F (2, 21) = 37.30, *P*<0.0001], showed a significant difference. *Post-hoc* analysis revealed that a significant preference for the active lever pressing occurred on morphine sessions compared to extinction sessions (*P*<0.0001) and extinction active lever compared to pregabalin (*P*=0.0038). Substitution of morphine or pregabalin for saline did not produce any significant change in the inactive lever response [F (2, 32) = 0.03878, *P*=0.96].

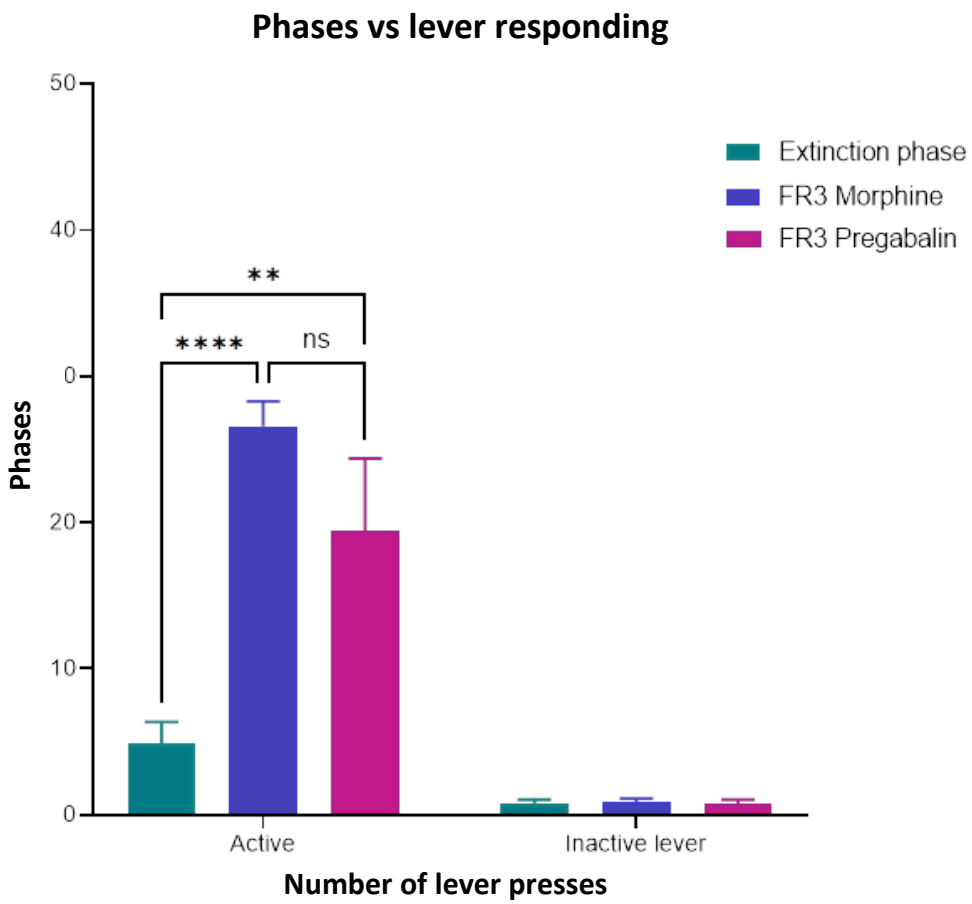


Figure 3-17. *Active and inactive lever responding during extinction, reacquisition, and reinstatement phases.*

**P<0.0001; denotes a significant difference for active lever presses between morphine (reacquisition self-administration) compared to saline (extinction) and pregabalin compared to saline.*

There were two separate self-administration experiments conducted with *naïve* rats. The first experiment had to be repeated due to technical difficulties.

3.5 Discussion

The question of whether pregabalin has abuse potential, especially for patients with neuropathic pain, is still controversial. The findings from Chapter 2 indicate that there was no evidence to confirm the potential for pregabalin abuse and misuse in neuropathic pain patients without previous opioid misuse. Therefore, the primary aim of this operant self-administration study was to investigate the reinforcing efficacy of pregabalin after exposure to morphine self-administration. In this study, pregabalin has been evaluated using self-administration for the first time in preclinical studies to determine its reinforcing properties and abuse potential. A strong correlation exists between the self-administration of drugs by humans and laboratory animals, which makes the self-administration technique helpful in predicting the likelihood of drug abuse. (263) The findings of the current self-administration study, although conducted on a small group size, may indicate that there is a potential for pregabalin misuse, particularly with the preexistence of opioid abuse. While there is a need to increase the experimental group size and confirm statistical effect, these findings may help to understand the mechanism behind the potential abusive effect of pregabalin with previous exposure to morphine. Extending this work to an experimental model of neuropathic pain may lead to the development of more effective treatment strategies for patients suffering from chronic pain.

The reinforcing effects of pregabalin may increase concerns about its potential abuse liability. Several clinical studies have observed an increase in abuse liability cases, particularly in cases where opioids are being used concurrently with pregabalin. (97,134) A limited number of animal models have been used to examine the potential for pregabalin to induce abuse or to reduce pain. Bura *et al.* conducted an operant self-administration experiment to evaluate the reinforcing effects of pregabalin in *naïve* and neuropathic pain models. (255) Both healthy animals and those subjected to neuropathic pain showed a significant self-administration of pregabalin. (255) These results are consistent with our findings, which showed that pregabalin had a reinforcing effect in rats. However, this is the only available evidence indication for an abusive potential of pregabalin in preclinical models. While there is evidence that previous exposure to opioids increases pregabalin abuse in humans, there is a lack of studies demonstrating this effect in animals. A better understanding of the interaction between opioids and pregabalin, particularly in the context of pain, may result in the improvement of

pain management strategies in humans. Therefore, this study aimed to investigate the reinforcing effects of pregabalin in the presence of morphine addiction in *naïve* and neuropathic pain models. The second study (neuropathic pain model) could not be carried out due to the loss of the operant equipment and unavoidable requirement to stop this line of experiments.

Data presented here indicate that in the acquisition phase rats acquired morphine self-administration behaviour, which is defined as the development of a significant difference in the active lever responding, that resulted in morphine infusion, compared to the inactive lever. Specifically, this work shows that significant difference for the active lever pressing was developed at FR3 between session 20 and 24 (P<0.0001). It is consistent with the data obtained by Mierzejewski *et al.* who found that self-administration of morphine was significantly acquired starting from FR3 until the final FR5 schedule of reinforcement (P<0.01). (258)

Following the extinction, rats were given access to morphine for five days at the same previous dose (0.56 mg/kg/infusion) in order to reacquire and reinstate morphine self-administration. As expected, the data showed that morphine substitution for saline produced a significant change in the number of active lever presses. This is consistent with other morphine self-administration studies, which reported that rats reinstated morphine intake immediately after extinction tests which showed a significant effect between active and inactive lever responding. (258,276,282)

The primary goal of the study presented here was to determine whether pregabalin had a reinforced effect and an interesting finding was that the total number of active lever responses maintained by pregabalin (after morphine reacquire) was significantly different when compared to the number of responses by saline in the extinction phase. Therefore, this study provides evidence of pregabalin reinforcing properties, which is shown in its ability to maintain self-administration behaviour when substituted for morphine. This finding aligns with the human observational studies that found an association between pregabalin misuse and opioid use disorder. (283–285)

This study has some limitations, which should be taken into consideration. A potential limitation is that this study was conducted in *naïve* rats only. As a result of the loss of the self-administration equipment which have been transferred to another institution outside the UK before starting the next experiment, pregabalin self-administration with the neuropathic

model was not conducted. However, this study still allowed to shed the light on the understanding of the reinforcing efficacy of pregabalin after exposure to morphine in *naïve* Sprague-Dawley rats. Nevertheless, further studies are needed to determine whether pregabalin abuse is associated with neuropathic pain that may contribute to increased abuse risk. It should be pointed out that, the self-administration study is a complex experiment as well as requires substantial time and effort. (263) Another limitation that should be noted is that there were only a few numbers of rats gained the drug-seeking behaviour. Evidence shows that using a small number of animals in data analysis can confound conclusions drawn from in-*vivo* experiments. (286) The neuroscience literature also reported that using a small number of animals results in low statistical power and less reliable results. (286,287) Consequently, the likelihood of a statistically significant finding reflecting an actual effect is diminished. (286) In this regard, further studies including a larger number of animals are required.

3.6 Conclusion

In conclusion, the key finding of this study indicates that pregabalin may have a reinforcing effect when substituted for self-administering morphine in *naïve* rats. This suggests that further preclinical experiments comparing *naïve* rats *versus* neuropathic pain models are required to investigate the impact of pain on pregabalin-seeking behaviour.

Chapter 4 State-of-the-art review and narrative synthesis of community pharmacist-led interventions to tackle misused analgesia.

4.1 Chapter description

To address analgesia misuse, it was decided to synthesise the existing literature on community pharmacy-led interventions and the role of pharmacists in this area. The findings of this review helped in informing the research questions for the next Chapter.

4.2 Publication

The work of this Chapter has been published as Mills VG, Meaadi J, Nazar H, Obara I. A review and narrative synthesis of community pharmacist-led interventions to tackle medicines for pain that are misused. Int J Pharm Pract. 2022 Aug 9;30(4):305–14. (Appendix C) DOI: 10.1093/ijpp/riac041

Some parts of the study were included in the MPharm thesis submitted by Verity Mills in 2021 entitled: A rapid review of community pharmacist-led interventions to tackle medicines for pain that are misused.

4.3 Introduction

In order to combat gabapentinoid misuse, it is necessary to understand how community pharmacies handle this issue in their daily practice. It is common for pharmacists to be the last healthcare professional that patients interact with before they receive their medications, whether on prescription or when bought over the counter (OTC). This puts pharmacists in a unique position to address and possibly intervene in the case of medicines-related problems such as misuse issues. (288) Furthermore, CPs are among the most accessible healthcare professionals in the UK. (142) For example, in England, 89.2% of the population can access a community pharmacy within 20 minutes of walking distance. (142)

In managing pain medicine misuse, CPs are primarily responsible for decreasing adverse events and identifying inappropriate pain management via early identification, monitoring prescriptions, and educating patients about drug misuse. (155) Furthermore, the role of CPs in substance misuse management focuses on dispensing opioid substitution therapy and providing needle exchange services. Other community pharmacy-led informal interventions undertaken in the UK have included refusing sales, referring patients elsewhere, limiting the number of products sold or moving products out of sight. (152) In recent years, there has been an increased interest in CPs participating in reducing the use of potentially inappropriate medications (PIMs), (158) such as the inappropriate use of analgesia. As no studies have been conducted on the misuse of gabapentinoids and pharmacist-led interventions in the literature, this Chapter focused on evaluating the interventions by CPs to address the misuse of analgesic medications in general.

Implementing changes for identifying and managing analgesia misused in community pharmacies requires behaviour change for pharmacists and patients grounded in a theoretical understanding of behaviour. It is necessary to consider the benefits of the behaviour change theory when considering how to change pharmacists' and patients' behaviour in the context of analgesic misuse. Using theory permits a systematic approach to intervention development and provides an explanation of why, when, and for what reasons a behaviour occurs or does not occur, the reasons an intervention succeeds or fails, and facilitates the replication of interventions. (289) It has been proven that behavioural change can be achieved when interventions are based on and informed by evidence-based concepts and theories of

behavioural change. (290) An understanding of what strategies have been attempted in previous work and their effectiveness can be determined using behaviour change theories and frameworks. The Behaviour Change Wheel (BCW) has been developed by examining and critically integrating 19 behaviour change frameworks. (289) The BCW comprises three various layers; at the core of the wheel is capability (C), opportunity (O), and motivation model of behaviour (COM-B). Each of the three components (C, O and M) can be divided into two subcomponents: capability: psychological and physical; opportunity: physical or social; and motivation: reflective or automatic. The surrounding layer of the BCW is intervention functions which comprise nine intervention functions as potential bases for a behaviour change intervention. The nine intervention functions are defined in table 4.1. By using these intervention functions, any deficit in the behavioural component can be improved. The outer layer is policy categories that facilitate the intervention (Figure 4.1). This Chapter will make the active components of CPs' interventions transparent, which future intervention designers, commissioners and implementers will find helpful in exploring patterns of successes and failures.

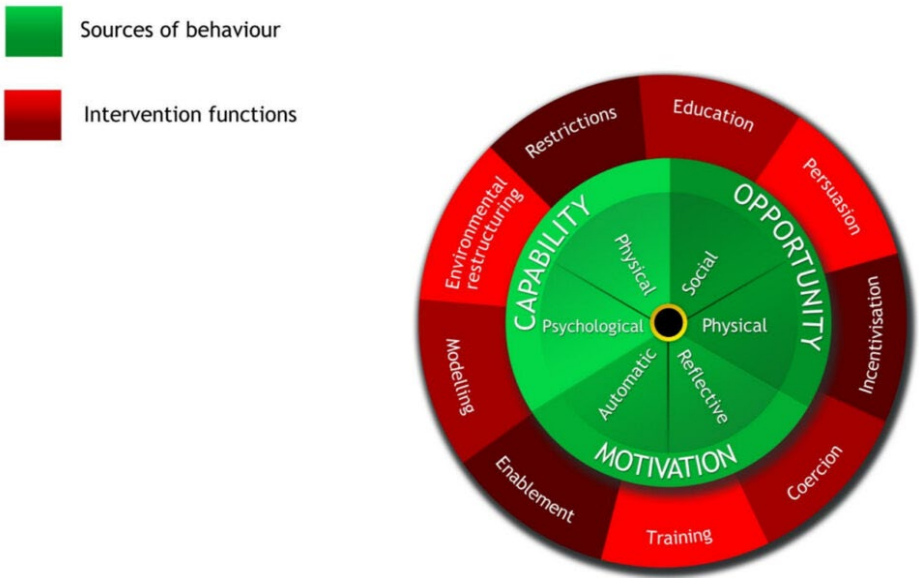


***Figure 4-1**. The Behaviour Change Wheel. Figure used with permission from the publisher.* (289)

Intervention Function	Definition
Education	Enhancing knowledge or understanding
Persuasion	Utilising communication to induce positive or negative feelings or stimulate action
Incentivisation	Creating an expectation of reward
Coercion	Creating an expectation of punishment or cost
Training	Developing skills
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or to increase the target behaviour by reducing the opportunity to engage in competing behaviours)
Environmental restructuring	Changing the physical or social context
Modelling	Providing an example for people to aspire to or imitate
Enablement	Increasing means/reducing barriers to increase capability (beyond education and training) or opportunity (beyond environmental restructuring).

Table 4-1. *BCW intervention function definitions. Adapted with permission from the publisher.* (289)

4.4 Aim

To identify and critically assess the evidence of CP-led interventions to address misuse and/or abuse of analgesic medications.

4.5 Objectives

1. Investigate the roles of CPs have played in addressing the misuse of analgesic drugs.
2. Investigate the intervention components and strategies that impact community pharmacist and patient behaviours.
3. Identify evidence that exists to demonstrate the effectiveness of the interventions to change behaviours.

4.6 Materials and Methods

The review was conducted as stipulated in the PRISMA guidelines, as described previously (2.6.3). (169)

4.6.1 Search strategy

Scoping searches have been conducted to better understand what roles CPs have played in tackling gabapentinoid misuse and abuse. This gives a preliminary estimate of how many studies may be found during the main search. However, there was no evidence in the literature regarding tackling gabapentinoid misuse by CPs. In light of this, the research team decided to examine the role of CPs in addressing the misuse of pain medicine in general. This step was undertaken before the systematic review question was finalised.

Based on several scoping searches, four electronic literature search was performed using EMBASE (Ovid), MEDLINE (Ovid), Web of Science and Scopus. MEDLINE was considered a suitable database for this review because it includes citations from more than 5200 peer-reviewed journals published worldwide and used by healthcare professionals and researchers. (291,292) To expand our search, we included EMBASE, which provides a comprehensive coverage of biomedical literature, including journals not included in other databases. (292) Web of Science and Scopus are multidisciplinary bibliographic databases offering extensive databases covering a wide range of disciplines, (293) so they were deemed adequate for this research. To complete this step, the research team discussed the selected databases and consulted with an expert librarian familiar with searching databases. These electronic databases were searched for published studies until November 2020 (the last search was performed on 17th September 2022). A manual search of the references of key articles was conducted in order to identify additional papers. Additional searches were undertaken on the Internet using the Google and Google Scholar search engines. Strategies were developed through several test searches and discussions of search findings with the librarian and revised by two other researchers (HN and IO). Search filters were also applied to retrieve relevant articles and remove irrelevant ones from the search results. A combination of text words and medical subject headings (MeSH) related to the review question was employed. The search strategy, as outlined in table 4.2, was used in EMBASE (Ovid). The keywords and database-

specific medical subject headings (MeSH) were used for other databases where applicable. Search terms focusing on 'community pharmacy' and 'analgesic medications' were used. Based on draft of NICE guidelines on chronic pain in adults over 16 years of age, keywords and MeSH headings for specific analgesics were developed (Appendix C). (294) There were no date limitations or restrictions on the research setting, and it was limited to the English language.

The following search strategy was used for EMBASE (OVID):

1. analgesic agent/ or gabapentin/ or pregabalin/
2. codeine/ or codeine phosphate/ or morphine/ or morphine sulphate/ or opiate/ or tramadol/
3. gabapentinoid*.mp.
4. opioid*.mp.
5. 1 or 2 or 3 or 4
6. community pharmacist/
7. "pharmacy (shop)"/
8. community pharmac*.mp.
9. 6 or 7 or 8
10. 5 and 9

Table 4-2. *Search terms entered into EMBASE (Ovid).*

4.6.2 Eligibility criteria

In order to evaluate the full-text articles, the following criteria were used:

4.6.2.1 Inclusion criteria

Inclusion criteria were adopted using the PICO, (174) as shown in table 4.3.

Population

All studies aimed to evaluate the effectiveness of the interventions delivered by CPs to identify the misuse of analgesic medications. These studies include patients who are at risk of analgesic misuse or who actively misuse analgesia. Moreover, those studies reported 'drug misuse' and/or 'drug abuse' of analgesics. Analgesic medications were included, particularly prescribed analgesia for chronic pain. Some misuse of analgesia were reported by draft NICE guidelines on chronic pain in over 16's consisting of opioids (such as morphine) and gabapentinoids (*e.g.*, pregabalin and gabapentin). (294)

Intervention

All peer-reviewed studies using CP-led interventions to identify misuse of analgesia were included. Any multidisciplinary interventions involving direct interventions by CPs were considered.

Comparison

There was no limitation for the comparator group applied in the included studies.

Outcomes

Included studies had to have reported either qualitative results, such as CPs' perceptions of intervention feasibility and acceptability or quantitative results, including clinical outcomes.

For this review, any study design was included. Published protocols, conference papers or in-progress research were excluded. Grey literature was excluded due to a lack of peer-review of unpublished literature. (295) In addition, data from unpublished studies in grey literature can itself produce bias. (295)

Inclusion criteria	
Participants (P)	CP-led interventions to identify analgesic "misuse" or "abuse." The study population contained patients at risk of misusing or who experienced analgesia misuse. Analgesic drugs especially those used for chronic pain, are commonly misused, *e.g.,* opioids (such as morphine) and gabapentinoids (*e.g.,* pregabalin and gabapentin).
Intervention (I)	Peer-reviewed studies that evaluate the interventions of CPs to identify the misuse of analgesic medications.
Comparison (C)	No comparator groups were specified.
Outcomes (O)	*Qualitative outcomes:* Pharmacist attitudes towards feasibility and acceptability of the intervention *Quantitative outcomes:* Effectiveness outcomes.

Table 4-3. *The PICO elements that framed the inclusion criteria. CPs: community pharmacists.*

4.6.2.2 Exclusion criteria

Any study focused on the following interventions was excluded:

- Investigating interventions addressing analgesic misuse by healthcare providers other than CPs.
- Any intervention including the supply/dispensation of pharmacy-based naloxone for the prevention of opioid overdose without counselling to address analgesic misuse.
- Interventions involving opioid substitution therapy, if the study included participants using analgesics for illegal purposes or if the purpose of misuse was unclear.

4.6.3 Study selection

Using Mendeley (reference manager software) as a bibliographic library, studies were retrieved from electronic databases and entered into the software. The Mendeley de-duplication tool was used to identify duplicate studies that were then removed and placed in a separate library. After the initial systematic search and removal of duplicates, titles and abstracts of all potentially related references were evaluated against the inclusion and exclusion criteria by one of the authors Verity Mills (VM) for relevance. VM has completed her Undergraduate Masters in Pharmacy (MPharm Degree) at Newcastle university and used part of the extracted data in her MPharm project. The second researcher (JA) selected a random sample to screen abstracts and assess for eligibility according to the pre-specified criteria. Any disagreements were resolved by consensus. Full-text papers from those abstracts considered relevant were independently assessed for their suitability for inclusion by two researchers (VM and JA). When a decision could not be reached solely based on the abstract, discussion took place between the research team to gain consensus. (JA, VM, HN, and IO).

4.6.4 Data extraction

Cochrane Consumers and Communication Review Groups' data extraction template was used to extract the raw data as a basis, as described previously in section 2.6.5. (296) Two researchers (VM and JA) extracted data independently and checked for agreement or discrepancies. PhD supervisors (HN and IO) were consulted for additional review where necessary.

Data components

Data were extracted and arranged as follows:

1. Bibliometric data (*e.g.,* authors, year of publication, and region of study);
2. Study characteristics (*e.g.,* study design);
3. Participants (*e.g.*, CPs or patients who received the intervention);
4. Analgesic medications misused (comprising drug name and the measure of misuse/abuse);
5. Type of intervention delivered by pharmacists;
6. Type of outcome (*e.g.,* qualitative, and quantitative findings); and
7. Key findings (*e.g.,* qualitative, and quantitative results).

Identified studies were recorded using Mendeley Reference Manager, and the extracted data were entered into a table using Word Microsoft Office 365.

4.6.5 Data collection and analysis

Various types of meta-synthesis, such as meta-ethnography, Grounded Theory, and narrative synthesis, have been described in the literature. Meta-ethnography and Grounded Theory were excluded because they focus only on qualitative data and do not draw from quantitative evidence. The systematic review included a wide range of very different studies, including both quantitative and qualitative data; it was decided that a narrative synthesis would be the most effective approach to synthesise the results of the included studies to address Thesis Objective 4.

The narrative synthesis approach and tables were used to summarise the findings of the included studies. Narrative synthesis is a common method used to synthesise research in systematic reviews whose distinguishing feature is the use of words and text (rather than statistical) to summarise the findings of the synthesis. (297) In 2006, Popay *et al.* developed a guideline for conducting narrative synthesis, which enables researchers to adapt the approach to synthesise the data and focus on transparency and rigour within the review. (297) The guideline provides a set of suggestions as to which tools or techniques are appropriate for narrative synthesis. Table 4-4 presents tools and techniques for developing a synthesis. (297) As mentioned previously, the tabulation technique was used to report the findings from the included studies. Typically, tables are used to provide details about study designs, quality assessments, outcome measures, and other findings. (297) They are deemed to be useful at any stage of the synthesis process. (297)

Tools and techniques	Description
Textual descriptions of studies	It produce a descriptive paragraph on each included study.
Groupings and clusters	It starts to group the included studies based on their variation.
Tabulation	It is a common method used to represent both quantitative and/or qualitative data.
Transforming data into a common rubric across quantitative studies	The findings of the included studies may take different numerical and/or statistical forms; therefore, results need to be transformed into a common numerical/statistical rubric, if possible.
Vote counting as a descriptive tool	It is a complex task based on a number of positive studies is compared with the negative studies to synthesise evidence from multiple evaluations.
Translating data; thematic analysis	Findings are presented in the form of themes.
Translating data: content analysis	Findings are reported in the form of concepts.

Table 4-4.*Tools and techniques for developing a preliminary synthesis. Adapted from reference. (17)*

Next, data were categorised according to whether they contained interventions or outcomes. The extracted interventions were classified based on whether they comprised components of patient identification, patient education, long-term management, active intervention to deter misuse, onward referral or additional services provided. In accordance with the study descriptions, the components were interpreted or directly understood.

4.6.5.1 Coding process using BCW

Narrative reviews have become increasingly common to be systematic, resulting in a wide range of methods and terms used to describe them. (298) There are several ways in which narrative synthesis can be used. According to the methodological literature, numerous methods exist for synthesising both quantitative and qualitative evidence. Those methods include content analysis, critical interpretive, thematic, and framework synthesis. Framework synthesis was selected as a suitable approach for synthesising qualitative and quantitative data with the aim of learning about behaviour change. After tabulating the extracted data, the

framework synthesis was applied inductively using the BCW. The reason for the exclusion of other methods is shown in Table 4.5.

Method	Exclusion reason
Content analysis	Extremely time consuming and subject to increased error
Critical interpretive synthesis	Its flexibility: make its application and reporting in research ambiguous (affecting its trustworthiness)
Thematic synthesis	Having diverse approaches: uncertainty in synthesis.

Table 4-5. *Exclusion reasons for some narrative synthesis methods.*

Many theories have been applied to the development of behaviour change intervention (BCI), such as: Social Cognitive Theory (SCT), (299) Theory of Planned Behaviour, (300) and Stages of Change (Transtheoretical Model). (301) Table 4.6 compares the characteristics of BCI theories.

This Chapter did not apply these classic theories since they do not provide a systematic approach to comprehensively explaining behaviour and selecting appropriate intervention components. (302) However, the BCW theory was developed to help intervention developers move from a behavioural analysis of the target problem to an evidence-based intervention method. Consequently, the BCW was used to map the extracted intervention onto it. It has been recommended to use BCW in this context by NICE as it provides a comprehensive approach to addressing behavioural factors within nine intervention functions. (303) The interventions were scrutinised for their component parts and coded using the COM-B and the intervention functions. The extracted interventions were coded in light of changing the behaviours of pharmacists and patients. This mapping process was undertaken by two researchers independently (JA and HN). Disagreements between the researchers were resolved through consensus. In this coding process, two aspects have been explored:

1. Engaging CPs in the implementation and provision of patient interventions.
2. Determine which patient behavioural aspects the intervention targeted.

All identified outcomes were grouped according to three main measures: (1) process outcomes, (2) satisfaction and attitudinal outcomes and (3) effectiveness outcomes.

Theory	**Social Cognitive Theory**	**Theory of Planned Behaviour**	**Stages of Change**
Establishment	It started in the 1960s by Albert Bandura as a Social Learning Theory and developed in 1986 into SCT as the learning process occurs in a social context. It explains human behaviour based on a three-way, dynamic, reciprocal model in which individual factors, environmental influences, and behaviour continually interact.	It was developed in 1980 as the Theory of Reasoned Action to predict an individual's intention to act at a specific time and place. The theory aims to explain self-controllable behaviours.	In the late 1970s, Prochaska and DiClemente developed the program to understand why some people can do something independently and others require additional interventions.
Elements	1. Observational learning 2. Reinforcement 3. Self-control 4. Self-efficacy	1. Attitudes 2. Behavioural intention 3. Subjective norms 4. Social norms 5. Perceived power 6. Perceived behavioural control	1. Precontemplation 2. Contemplation 3. Preparation 4. Action 5. Maintenance
Limitations	It often is overly general and lacks a cohesive framework.	It does not contain other behavioural factors, *e.g.,* emotions.	It is only useful as an enhancement for thinking about changing behaviour.

Table 4-6. *Characteristics of behaviour change intervention theories. Adapted from references. (10–12)*

4.6.6 Risk of bias assessment

Considering the various designs of the included studies, it was decided to use Joanna Briggs tools, which have tools specific to each design. (304) The JBI tool is preferred over other tools, (304) *e.g.,* the Critical Appraisal Skills Programme (CASP), since the CASP is considered less sensitive to aspects of validity. (305) The JBI tools have been designed to help assess published papers' trustworthiness, validity, and findings. (305)

The methodological risk of bias of the included studies was assessed by Joanna Briggs tools for cross-sectional studies, case reports, and RCTs checklists. (304) There were four possible answers for each question: “Yes”, “No”, “Not applicable”, and “Unclear”. In order to determine the risk of bias in individual studies, the following cut-off score were used:

- ≤49% = high risk of bias
- 50%-69% = moderate risk of bias
- ≥70%= low risk of bias.

The studies were assessed independently by the same two authors who conducted the data extraction (JA and VM). Any disagreements between assessors were resolved by discussion within the research team (JA, MV, IO and HN). Meta-analysis was not possible due to the included studies differing in their designs and outcomes.

4.7 Results

4.7.1 Literature search

The initial search of databases retrieved 2712 published articles, which decreased to 1511 publications after removing duplicates. Following the process of reviewing the title and abstract of each article, 1479 articles were excluded from consideration. Based on the assessment of the 32 remaining studies, only five studies were selected for inclusion. (306–310) One further study was identified for inclusion when the research was re-run on 17th September 2022. (311) The search and screening results were presented using a PRISMA flow chart as presented in figure 4.2.

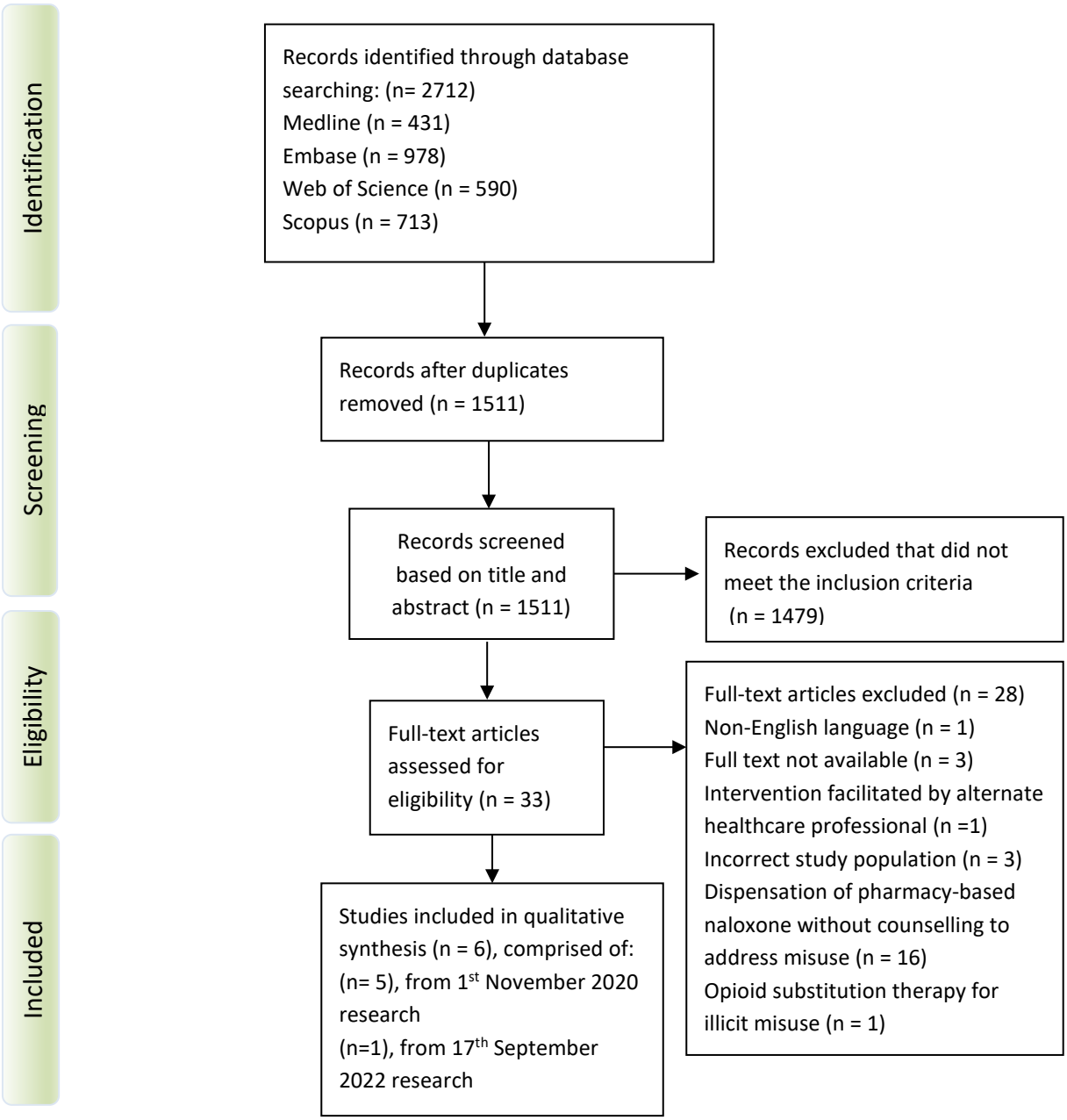


Figure 4-2. *PRISMA flow diagram depicting the search strategy of the included studies.*

4.7.2 Characteristics of included studies

The main characteristics of the included studies are summarised in table 4.7. One study was from Northern Ireland, (20) and five were from the USA. (306–309,311) Among the included studies, there were four cross-sectional, (308–311) one case report, (307) and one small-scale RCT. (306)

4.7.3 Participants

A total of 1174 pharmacists who worked in community pharmacies were included. The number of pharmacists included in these studies ranged from 2 to 852.

In total, 10361 patients were involved in the included studies. Those patients were either misusing or had misused prescribed opioids, (306) suspected misuse or abuse of OTC medications, (310) at risk of misusing prescribed opioids and accidentally overdosing on opioids, (307,309,311) or receiving treatment for substance misuse/abuse at a specialised institution. (308) The included patients in these studies ranged from 32 to 8,217.

study details (Authors, publication year, country)	**Study characteristics** (Study design and methods)	**Analgesic(s) misused and measures of misuse**	**Intervention(s)**	**Outcomes measured**	**Key findings**
Skoy *et al.* 2022 US (North Dakota)	Cross-sectional study (32 months). ONE-Rx programme using Opioid Misuse Risk Prevention toolkit (ORT) tool to provide universal preventive screening for opioid misuse patients. ONE-Rx was implemented in 41 community pharmacies, and 240 pharmacists participated.	**Analgesic(s) misused:** prescription opioids. **Measure of misuse:** ORT.	ONE-Rx: Each patient was screened for risk of accidental overdose and opioid misuse using the ORT. Pharmacists provided (1) *risk-dependent intervention*; these interventions include discussing the patient's potential for opioid misuse, discussing the availability and benefits of naloxone, dispensing naloxone, contacting the prescriber with concerns, providing information on community support services, as well as explaining the symptoms of opioid overdose and how to prevent them. (2) *risk-independent interventions:* Providing information regarding proper disposal of opioid medications as well as the option of partially filling opioid prescriptions	**Process outcomes:** Reach	**Process outcomes:** Of all screenings recorded, 3.9% were patients at high risk for opioid misuse (ORT score ≥8) and 18.3% were identified as at risk for accidental opioid overdose. 43.9 % of patients who screened at high risk received education and about opioid use disorder and 14.4% received information on community support services. 41.1% received one or more pharmacist-led interventions. 85% of screened patients received instructions on how to dispose of opioid medications, and 4% decided to partially fill their opioid prescriptions.
Strand *et al.* 2020 USA (North Dakota)	Cross-sectional study (9 months). ONE-Rx was implemented in 63 community pharmacies. Evaluating the ONE-Rx using the 5 domains of the RE-AIM Model.	**Analgesic(s) misused:** prescription opioids. **Measure of misuse:** ORT tool.	One-Rx: Each patient was screened for risk of accidental overdose and opioid misuse using the ORT. According to screening findings, pharmacists provided interventions using a clinical decision-making tool; medication take-back, opioid prescription partially filled, critical interventions for at risk individuals, discussed community support services, explained benefits of or dispensed naloxone, contacted provider, discussed opioid use disorder and accidental overdose.	**Process outcomes:** RE-AIM.	**Process outcomes:** Reach/Efficacy: 16.9% of all patients receiving opioid prescriptions were screened for risk of opioid misuse and/or accidental overdose; 97.1% of eligible patients were delivered the pharmacy interventions. Adoption: 45% of eligible community pharmacies enrolled in ONE-Rx. Implementation: 44.8% of adopting pharmacies successfully implemented One-Rx.

study details (Authors, publication year, country)	**Study characteristics** (Study design and methods)	**Analgesic(s) misused and measures of misuse**	**Intervention(s)**	**Outcomes measured**	**Key findings**
					Maintenance: 80% of implementing pharmacies achieved maintenance by completing at least one screening 3 months after the initial provision.
Cochran *et al.* 2019 US (Western Pennsylvania)	Single blinded RCT (15 months). Population: ≥ 18-year-old who speak English. 32 participants randomly assigned on a 1:1 ratio to a Brief Motivational Intervention-Medication Therapy Management (BMI-MTM) (n = 15) or standard medication counselling (SMC) (n = 17) conditions. A baseline assessment was conducted two and three months after patient navigation (PN) was completed by BMI-MTM recipients.	**Analgesic(s) misused:** Prescription Opioids **Measure of misuse:** Prescription Opioid Misuse Index (POMI), urine toxicology and Short Form (SF)-36.	BMI-MTM: Integrated model pharmacist-led medication brief motivational interviewing session, along with 8 patient navigation sessions. The practice includes: (1) medication therapy management (MTM), (2) brief motivational interviewing (BMI), (3) PN, and (4) naloxone training and referral. SMC (control): (1) offer medication counselling, (2) document counselling has been offered, (3) document patient refusal of counselling, (4) discuss possible generic substitutions (5) provide information about the medication.	**Process outcomes:** Reach. **Satisfaction and attitudinal outcomes:** Feasibility and patient acceptability of BMI-MTM. **Clinical outcomes:** Mitigation of opioid medication misuse, opiate toxicology (pain and depression by SF-36).	**Process outcomes:** 100% of BMI-MTM recipients received the pharmacist intervention. **Satisfaction and attitudinal outcomes:** 13 BMI-MTM recipients agreed/strongly agreed that the pharmacist actively listened to their concerns, increased their confidence when managing medications and ensured safety. Only one patient would not recommend the pharmacist to family/friends. **Clinical outcomes:** BMI-MTM recipients were less likely than SMC patients to report continued opioid misuse at 3 months. For BMI-MTM recipients, there was a non-significant decrease in positive opiate toxicology screens during the study. Greater improvements in BMI-MTM recipients' mean scores for pain and depression were demonstrated over time compared with SMC recipients. There was a non-significant improvement in pain compared with SMC recipients.
Riley and Alemagno 2019 US (Ohio)	Cross-sectional study. Online surveys were administered to Ohio pharmacists and patients	**Analgesic(s) misused:** Prescription	Five pharmacy-based opioid misuse interventions: 1. pharmacists providing patients with counselling on the risk of misuse, abuse,	**Satisfaction and attitudinal outcomes:**	**Satisfaction and attitudinal outcomes:** The use of PDMP and patient counselling were the most acceptable interventions among pharmacists with 85.8% of

study details (Authors, publication year, country)	**Study characteristics** (Study design and methods)	**Analgesic(s) misused and measures of misuse**	**Intervention(s)**	**Outcomes measured**	**Key findings**
	in treatment for substance use disorders examining five specific pharmacy-interventions using a Likert scale to measure acceptability.	Opioids, illegal Opiates **Measure of misuse:** Patients in treatment for substance misuse disorder	addiction, and overdose associated with opioid prescriptions; 2. referring patients suspected of misuse to local treatment services; 3. use of Prescription Drug Monitoring Programs (PDMP) to identify illegitimate prescriptions; 4. Providing naloxone with opioid prescriptions; 5. Selling naloxone OTC.	Acceptability of interventions among pharmacists and patients, level of agreement or disagreement when comparing the opinions of each group.	pharmacists supporting counselling and 97.9% supporting PDMP use. PDMP use and OTC availability of naloxone were the most acceptable interventions among patients, with 71% of patients supporting PDMP use and 83.7% supporting OTC naloxone.
Strand *et al.* (2019) US (North Dakota)	Case report study (6 weeks). Pharmacists trained for 3 hours sessions to use the ORT. Following each encounter, pharmacists completed a summary of the care provided worksheet. After 6-weeks, each pharmacist completed a pilot project process evaluation survey and a focus group.	**Analgesic(s) misused:** Prescription opioids **Measure of misuse:** ORT.	ORT: Pharmacists assigned a score to the patient's screening questionnaire. If the ORT score was ≥4, the pharmacist evaluated the patient for red flags indicative of misuse via a review of PDMP or professional judgment. If red flags were raised, pharmacists contacted the prescriber. Patients then offered all/some of the following services: prescribe, dispense, and counsel on naloxone; counsel patient on substance misuse and community support services available; counsel patient on partial fills and safe disposal of unused medication.	**Process outcomes:** Reach. **Satisfaction and attitudinal outcomes:** Feasibility of using ORT by pharmacist feedback.	**Process outcomes:** All patients with ORT ≥ 4 received all the pharmacy services. **Satisfaction and attitudinal outcomes:** Pharmacists valued having an objective measurement of opioid misuse rather than relying exclusively on professional judgement. Using the ORT, pharmacists reported an increased capacity to identify eligible misuse patients.
Wazaify *et al.* 2006 Northern Ireland (Greater Belfast)	Cross-sectional study (6 months) Six pharmacists volunteered to participate in the study and implement the	**Analgesic(s) misused:** OTC opioid-containing products. Ibuprofen	Harm minimisation model (HMM): Client identification and recruitment (cases of misuse/abuse), treatment and referrals, data collection and outcome measurement. Treatment is determined by the type of product involved and	**Process outcomes:** Reach. **Satisfaction and attitudinal outcomes:**	**Process outcomes:** Of the 196 identified patients, the subject of inappropriate OTC use was raised with 70 (27 misuse/43 abuse cases). **Satisfaction and attitudinal outcomes:** Some pharmacists thought the training was

study details (Authors, publication year, country)	**Study characteristics** (Study design and methods)	**Analgesic(s) misused and measures of misuse**	**Intervention(s)**	**Outcomes measured**	**Key findings**
	intervention model. All pharmacists participated in semi-structured interviews to explore their views and experiences of the study. No client proceeded to completion of the follow-up phase (*e.g.,* health-related QoL).	codeine combination product was the 3rd highest product associated with misuse/abuse (n = 22). **Measure of misuse:** Professional judgement	whether the product is being abused or misused. Treatment by pharmacists alone (information provided on management of the condition, alternative products suggested, follow-up visits arranged) or referrals to GPs or community addiction team (CAT) is outlined in the treatment algorithm.	Pharmacist perceptions of the intervention. **Clinical outcomes:** Success of the intervention.	difficult and non-relevant. Pharmacists agreed that time pressures made data collection difficult. All pharmacists agreed that the study positively impacted their practice; however, further training and greater participation by all pharmacies in a geographical area were advocated. **Clinical outcomes:** Success was achieved with 12 misuse and two abuse cases.

Table 4-7. *Characteristics of included studies.*

**Presented in chronological order.*

ONE-Rx: Opioid and Naloxone Education programme, ORT: Opioid Misuse Risk Prevention Toolkit, RE-AIM outcomes: Reach, Effectiveness, Adoption, Implementation, and Maintenance, PDMP: Prescription Drug Monitoring Programme, OTC: over the counter, SMC: Standard Medication Counselling, GP: General Practitioner, CAT: community addiction team, PN: Patient Navigation, POMI: Prescription Opioid Misuse Index, HMM: Harm Minimisation Model, QoL: quality of life, and SF-36: 36-Item Short Form Survey.

4.7.4 Interventions

A total of six studies examined complex and multi-component interventions delivered by community pharmacies, which include the following interventions:

1. Harm Minimisation Model (HMM) for the treatment of OTC drug abuse, (310)
2. Standard Medication Counselling (SMC) and Brief Motivational Interviewing and Medication Therapy Management (BMI-MTM), (306)
3. Opioid Misuse Risk Prevention Toolkit (ORT), (307)
4. The Opioid and Naloxone Education (ONE-Rx) programme, (309,311)
5. Acceptability of five single-component interventions for prescribed opioid misuse was assessed in the Riley *et al.* study (308), which includes:
    - Pharmacist-led counselling about the risk of misuse, abuse, addiction and overdose associated with prescription opioids,
    - Pharmacist referral of patients with suspected medication misuse, abuse and addiction to local treatment services,
    - The use of prescription drug monitoring programs (PDMP) to identify illegitimate prescriptions,
    - Naloxone provision by pharmacists with opioid prescriptions, and
    - Pharmacists selling OTC naloxone.

Two of the included studies reported that 100% of screened patients received pharmacist-led interventions. (306,307) While, one study mentioned that the interventions were provided to 97.1% of eligible patients. (309) Skoy *et al.* found that pharmacist-led interventions were delivered to 41.1% of the patients screened. (311) However, the number of screened patients declined at the peak of COVID-19-related restrictions and during the COVID-19 pandemic. According to a study conducted by Wazaify *et al.* 36% of clients suspected of abuse/misuse received interventions. (310)

Only Cochran *et al.* study used a control group that incorporated participants receiving standard medication counselling (SMC) compared to BMI-MTM. (306)

4.7.4.1 Coding extracted interventions to BCW

In table 4.8, the components of the COM-B system are linked to the extracted interventions, followed by the intervention function of the BCW to which they were mapped.

As shown in table 4.8, two of community pharmacy-led interventions were coded into intervention functions: environmental restructuring, education, training, and enablement to address pharmacists' behaviour. (306,310) Three studies incorporated education, training and enablement, (307,309,311) and one study by Riley and Alemagno did not outline any strategies for targeting the behaviour of pharmacists. (308)

In order to identify patient behaviour, the BMI-MTM intervention was linked to more intervention functions, including education, training, environmental restructuring and enablement. (306) The HMM intervention mapped to education, environmental restructuring, and enablement. (310) The intervention of One-Rx involved two intervention functions (education and restrictions). (307,309,311) While each of the five interventions reported by Riley and Alemagno's study included a maximum of one intervention function, mostly environmental restructuring (Table 4.8). (308)

Study	Intervention name	Intervention functions to change pharmacist behaviour (components of COM-B targeted)	Interventions aim	Intervention components	Intervention functions to change patient behaviour (components of COM-B targeted)
Skoy *et al.* 2022	ONE-Rx	***COM-B:*** Capability (physical, psychological) Opportunity (physical, social) Motivation (reflective, automatic) ***Intervention function:*** Education Training Enablement	1. Identification 2. Education 3. Long-term management 4. Prevention	ORT screening tool: Based on the risk, the intervention includes: - Discussing the patient's risk of opioid misuse; - Discussing the availability and the benefit of naloxone; - Contacting the prescriber with concerns; - Discussing available community support services, and - Discussing the signs and risks of opioid overdose.	***COM-B:*** Capability (physical) Opportunity (physical, social) Motivation (reflective) ***Intervention function:*** Education Restrictions
Strand *et al.* 2020 Strand *et al.* 2019	ONE-Rx	***COM-B:*** Capability (physical, psychological) Opportunity (physical, social) Motivation (reflective, automatic) ***Intervention function:*** Education Training Enablement	1. Identification 2. Education 3. Long-term management 4. Prevention	ORT screening tools and pathways include: - Prescribe, dispense, and counsel on naloxone - Counsel patient on the potential for substance use disorder and community support - Counsel on opioid prescription pearls, such as the possibility of a partial fill and safe disposal of unused medication.	***COM-B:*** Capability (physical) Opportunity (physical, social) Motivation (reflective) ***Intervention function:*** Education Restrictions
Cochran *et al.* 2019	BMI-MTM	***COM-B:*** Capability (physical, psychological) Opportunity (physical, social) Motivation (reflective, automatic)	1. Identification 2. Education 3. Long-term management 4. Prevention 5. Referral	POMI 1. Medication therapy management: - improving adherence to opioid medication as prescribed and resolving barriers - Review opioids and identify interactions - Speak about the misuse and how to identify	***COM-B:*** Capability (physical, psychological) Opportunity (physical) Motivation (reflective, automatic)

Study	Intervention name	Intervention functions to change pharmacist behaviour (components of COM-B targeted)	Interventions aim	Intervention components	Intervention functions to change patient behaviour (components of COM-B targeted)
		Intervention function: Education Training Environmental restructuring Enablement		- Identify targets for adherence improvement 2. Brief motivational interviewing; 3. Patient navigation around holistic care; 4. Naloxone training and referral.	***Intervention function:*** Education Training Environmental restructuring Enablement
Riley *et al.* 2019	5 individual interventions		1. Identification 2. Education	Pharmacists provide patients with counselling on the risk of misuse, abuse, addiction, and overdose associated with prescription opioids	***COM-B:*** Capability (physical) Motivation (reflective)
					Intervention function: Education
			1. Identification 2. Referral	Pharmacists referring patients suspected of misuse, abuse, and addiction to local treatment services	***COM-B:*** Opportunity (physical) Motivation (automatic)
					Intervention function: Environmental restructuring
			1. Identification	The use of prescription drug monitoring programs to identify illegitimate prescriptions	
			1. Identification 2. Prevention	Pharmacists providing naloxone with opioid prescriptions	***COM-B:*** Opportunity (physical, social) Motivation (automatic)
					Intervention function: Environmental restructuring
			1. Prevention	Pharmacists selling naloxone OTC.	***COM-B:*** Opportunity (physical, social) Motivation (automatic)
					Intervention function: Environmental restructuring

Study	Intervention name	Intervention functions to change pharmacist behaviour (components of COM-B targeted)	Interventions aim	Intervention components	Intervention functions to change patient behaviour (components of COM-B targeted)
Wazaify *et al.* 2006	HMM	***COM-B:*** Capability (physical, psychological) Opportunity (physical, social) Motivation (reflective, automatic)	1. Identification 2. Education 3. Long-term management 4. Prevention 5. Referral	Based on the Transtheoretical change model: 1. Client identification and recruitment (non-standardised or validated) 2. Treatment and referral to GP or CAT 3. Follow-up data collection and outcome measurements	***COM-B:*** Capability (physical) Opportunity (physical) Motivation (reflective, automatic)
		Intervention function: Education Training Environmental restructuring Enablement			***Intervention function:*** Education Environmental restructuring Enablement

Table 4-8. *The intervention aim, components and how they are coded using the BCW.*
BCW: Behaviour Change Wheel, ONE-Rx: Opioid and Naloxone Education programme, BMI-MTM: Brief Motivational Intervention-Medication Therapy Management, POMI: Prescription Opioid Misuse Index, and HMM: Harm Minimisation Model.

4.7.5 Outcomes

4.7.5.1 Process outcomes

Data measuring the process outcomes were extracted using RE-AIM (reach, effectiveness, adoption, implementation, maintenance) dimensions. (312) The RE-AIM model was published by Glasgow *et al.* in order to evaluate public health intervention. Strand *et al.* used the RE-AIM model to assess the ONE Rx programme in the community pharmacy sector. (309)

The reach dimension refers to an individual-level measure (for example, a patient). (312) It was defined as the proportion of individuals receiving opioid prescriptions who completed community pharmacy-based patient screening. Five included studies evaluated the reach of CP-led interventions to patients. (306,309–311) Across those studies, the reach of pharmacists-led interventions ranged from 16.9% to 100%.

Adoption, implementation and maintenance are organisational-level measures. (312) Adoption was defined as "the proportion of eligible community pharmacies that participated in delivering the intervention". (309) Implementation was defined as "the proportion of pharmacies participating in ONE-Rx with at least five patient screenings". (309) Maintenance was defined as "a measure of the proportion of pharmacies that adopted ONE-Rx and completed a screening three months after the initial provision". (309) One study assessing One-Rx reported those three dimensions. (309) Approximately 45 % (n=67) of eligible community pharmacies participated in the ONE-Rx programme. Only 44.8% (n=30) of the enrolled community pharmacies achieved implementation of the programme. The maintenance of the One-Rx programme was achieved in 80% (n=24) of participating pharmacies.

4.7.5.2 Satisfaction and attitudinal outcomes

These outcome measures were extracted from four included studies. (306–308,310) The satisfaction and attitudinal outcomes incorporated the feasibility of pharmacists using the ORT, (307) perceptions of pharmacists regarding HMM patients, (310) acceptability and feasibility of BMI-MTM, (306) and pharmacists and patients' acceptance of five specific pharmacy-based interventions for opioid misuse. (308)

In the case report, (307) it was reported that pharmacists valued using the ORT toolkit as an objective measurement of potential opioid misuse instead of depending entirely on professional judgement to determine whether opioids may be misused. Additionally, pharmacists reported that the screening tools improved their ability to identify patients at risk of opioid misuse. This improved conversation with patients, resulting in more effective patient care and education. Using the ORT tool was perceived as easy to integrate into the workflow and required a minimum of time for information collection.

Wazaify *et al.* found that the two full days of training for the HMM provided pharmacists with an opportunity to improve their communication skills with patients as well as fulfil their own needs for continuing professional development (CPD). (310) As a result of participation in the HMM, pharmacists were better able to communicate with neighbouring pharmacies, and there was increased awareness of OTC medicine misuse within the pharmacy teams. Nevertheless, pharmacists shared that patients were generally unwilling to discuss misuse and unresponsive to advice.

Cochran *et al.* reported that most of BMI-MTM participants were highly satisfied with the pharmacist-led session. (306) In particular, 13 participants in the BMI-MTM group strongly agreed that the pharmacist listened carefully to their concerns, enhanced their confidence in managing their medications, and ensured medication safety.

Riley and Alemagno reported that pharmacists were generally favourable to using PDMP to identify illegitimate prescriptions (98%), deliver counselling regarding the potential for addiction to prescription opioids (86%) and refer patients to local drug treatment services (67%). (308) In terms of patient acceptability, most patients agreed that pharmacists should provide these interventions. Most patients reported some level of support for pharmacist counselling (66.2%) and referrals to local drug treatment services (63.7%). There was significant disagreement about two interventions (sale of naloxone OTC and paired prescription of naloxone). Patients (62.7%) expressed strong support for selling naloxone OTC, whereas pharmacists (33.7%) expressed moderate support. Approximately 41% of pharmacists opposed the intervention by the provision of naloxone with opioid prescriptions, but there is significant support among patients with around 61% reporting moderate or strong support.

4.7.5.3 Effectiveness outcomes

Effectiveness outcomes was defined by Strand *et el.* as "the proportion of individuals at elevated risk for a poor outcome(s) who received the appropriate services". (309) Wazaify *et al*. documented that 70 identified patients (27 misuse and 43 abuse cases) were using inappropriate OTC. The HMM intervention was achieved successfully with 12 misuse cases and two abuse cases. Approximately 44.4% of misusers and 4.7% of abusers agreed to stop using the misused/abused medication and/or to try a safer alternative.

In the RCT study, participants who received the BMI-MTM intervention experienced more significant improvements than those who received the SMC intervention. (306) There was a lower rate of continued misuse among participants who received BMI-MTM intervention than patients who received SMC intervention at 2-months and 3-months. There was a promising decrease in positive opiate toxicology screens among BMI-MTM recipients, but the reduction was not significant. Furthermore, this RCT showed that both groups improved in terms of mean pain and depression scores during the study period, with BMI-MTM recipients showing more significant improvements than SMC recipients.

4.7.6 Risk of bias assessment

A summary of the risk of bias associated with the six studies included in this review is provided in tables 4.6, 4.7, and 4.7. Three studies were classified as having a high risk of bias, (308–310) 2 studies were considered to have a moderate risk, (306,307) and only one study was graded as having a low risk of bias. (311)

The validity and reliability of exposure measures were an issue in the cross-sectional studies. (308–311) Throughout all studies, pharmacists had the option of participating in the study. There is a possibility that those who participated were more positive regarding the intervention. Thus, this bias would be reduced if a larger sample of pharmacists were recruited without being included by self-selection. (155)

Author	Study type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes %	Risk
Soky *et al.* 2022	cross-sectional	Yes	Yes	Yes	Yes	No	No	Yes	Yes	75%	Low
Strand *et al.* 2020	cross-sectional	Yes	No	unclear	Yes	No	No	unclear	Yes	37.5%	High
Riley and Alemagno	cross-sectional	Yes	Yes	No	Yes	No	No	Yes	Yes	37.5%	High
Wazaify *et al.* 2006	cross-sectional	Yes	Yes	No	No	No	No	Yes	No	37.5%	High

***Table 4-9**. Assessment of the risk of bias for cross-sectional studies using Joanna Briggs checklist.*

Q1: were the criteria for inclusion in the sample clearly defined? Q2: were study subjects and the setting described in detail? Q3: was the exposure measured in a valid and reliable way? Q4: were objective, standard criteria used for the measurement of the condition? Q5: were confounding factors identified? Q6: were strategies to deal with confounding factors stated? Q7: were outcomes measured in a valid and reliable way? Q8: was appropriate statistical analysis used?

Author	Study type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Yes %	Risk
Strand *et al.* 2019	Case report	No	No	Yes	Yes	Yes	N/A	N/A	Yes	50%	Moderate

***Table 4-10.** Assessment of the risk of bias for the case report using Joanna Briggs checklist.*

Q1: were patient's demographic characteristics clearly described? Q2: was the patient's history clearly described and presented as a timeline? Q2: was the current clinical condition of the patient on presentation clearly described? Q3: were diagnostic tests or assessment methods and the results clearly described? Q4: was the intervention(s) or treatment procedure(s) clearly described?, Q5: was the postintervention clinical condition clearly described? Q6: were adverse events (harms) or unanticipated events identified and described? Q7: does the case report provide takeaway lessons? N/A: not applicable.

Author	Study type	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q12	Yes %	Risk
Cochran *et al.* 2019	RCT	Unclear	Unclear	Yes	Yes	N/A	Yes	unclear	No	Yes	Yes	Yes	Yes	Yes	61.5%	Moderate

***Table 4-11.** Assessment of the risk of bias for the RCT using Joanna Briggs checklist.*

Q1: was true randomisation used? Q2: Was allocation to treatment groups concealed? Q3: were treatment groups similar at baseline? Q4: Were participants blinded? Q5: Were those delivering treatment blinded? Q6: were outcomes assessors blinded? Q7: were treatment groups treated identically other than the intervention of interest? Q8: was follow up complete? Q9: were participants analysed in the groups to which they were randomised? Q10: were outcomes measured in the same way? Q11: were outcomes measured in a reliable way? Q12: was appropriate statistical analysis used? Q13: was trial design appropriate? N/A: not applicable.

4.8 Discussion

This is the first systematic review to conduct a theoretical analysis of pharmacist-led interventions to tackle the misuse and abuse of analgesic medications in the community sector. A total of six articles were identified as eligible for inclusion in the review. The inclusion criteria were restricted to study populations at risk of analgesic misuse or actively misusing analgesics; studies with interventions for patients prescribed analgesic medications with abuse potential were not considered. As all of the included studies were conducted in the USA or Northern Ireland, the findings may not be applicable elsewhere. Even so, it is important to note that the identification and coding of intervention components within the BCW give researchers and decision-makers some evidence and strategies regarding the design and implementation of interventions that can be tailored for use in other healthcare settings.

In this review, the COM-B model was applied to determine what changes need to be made to facilitate pharmacist and patient behaviour change, and the BCW to determine how this may be achieved. It is common for behaviour change literature to focus on healthcare professionals' behaviour and patients' behaviour separately. (313) A separate model is often utilised to analyse the behaviour of healthcare professionals and patients. This research implies that analgesic medication misuse/abuse is a complex behavioural issue which may be influenced by collaborative behaviours between patients and pharmacists, indicating that it is a key area that should be studied in the future. Significantly, most reported interventions incorporated education aspects: for the pharmacists to prepare them to engage and for the patients to learn about the misuse of analgesics. Functions of environmental restructuring also featured highly across the interventions which aim to change pharmacists' behaviour and/or the patients' behaviour.

All the reviewed studies aimed to identify patients who may be misusing or abusing analgesics and provide patient education, long-term management, prevention, and referrals. As a practical first step in addressing the issue, understanding the unique role that CPs can play may be helpful. A qualitative study by Murphy *et al.* examined pharmacy experiences in addiction care, which revealed a need for improved relationships and better communication and collaboration between healthcare professionals. (314) It has been shown in another study that CPs' silo working challenges their ability to provide clinical services. (147) This situation

could be improved, as recommended previously, through formal referral pathways and integrated working. (147)

There is no doubt that more integration with other support and care services is important. In future interventions, it would be more appropriate to consider the local healthcare system rather than the isolated setting of community pharmacies. The intervention can be designed by involving all stakeholders, including pharmacists, patients and doctors, in order to create a more pragmatic, feasible and suitable role for the pharmacist. In order to facilitate this multidisciplinary approach, appropriate implementation strategies and theories must be used. An example of using the Theoretical Domains Framework (TDF) and Behaviour Change Techniques (BCTs) was demonstrated by Cadogan *et al.* These studies sought to design an intervention to develop appropriate polypharmacy in the elderly. (315,316) In the design of this intervention, both doctors and pharmacists were involved. In another study using the TDF, Hatton *et al.* looked at barriers to pharmacists integrating into multidisciplinary teams. (317) The main barriers that challenge pharmacists include lack of awareness of the role of the pharmacist, poor interdisciplinary communication, and workload. Those barriers hampered pharmacists from integrating into the multidisciplinary team. (317) The authors suggested that pharmacist responsibilities and working patterns must be restructured in order to facilitate multidisciplinary integration. (317)

Furthermore, in Germany, researchers engaged GPs, CPs, and specialist providers to design an electronically supported deprescribing intervention. (318,319) As a result of this project, researchers provided a new electronic decision tool “MediQuit”, which aims to guide doctors and facilitate patient-shared decision-making during the deprescribing consultation of polypharmacy drugs. (320)

Future studies should consider this multidisciplinary approach alongside assessing the experiences of pharmacists in implementing interventions. In order to determine the capability of CPs to provide interventions, validated objective outcome measures should be used when possible. In addition, it is imperative to conduct service evaluations that monitor pharmacists’ performance. (321) Additionally, assessments must be conducted simultaneously to identify potential substance relapses and their consequences (*e.g.,* hospital admissions or incidence of opioid use disorder). A detailed study of relapse after substance

misuse treatment by Ramo and Brown showed that (n=160) 100% of adults experienced a relapse in the 18 months after initial treatment. (322)

More evidence must be conducted in this area, which may also need a thorough consideration of how interventions will be evaluated to determine their effectiveness. The Health Foundation proposes a "balanced scorecard" approach to understand the changes in health service quality. (323) The balanced scorecard approach is a mixture of measures which include: process measures and clinical outcomes as well as patient experience and resource use. (323) Among the included studies, two studies successfully assessed the process, attitudinal and clinical outcomes. (306,310)

Currently, the Institute for Primary Care and Health Sciences at Keele University is conducting relevant research aiming to improve patients' outcomes using opioid medicines for chronic pain. (324) In 2019, the research team commenced developing PROMPPT, a Proactive clinical Review of patients taking Opioid Medicines long-term for persistent Pain led by clinical Pharmacists in primary care Teams. The PROMPPT search consists of three phases: intervention development, feasibility study, and the main trial. The research investigates whether these clinical pharmacists can help identify overprescribing opioid analgesics to reduce the risk of addiction and overdose. It may be beneficial to extend proactive measures within general practices to target the source of the issue if this research findings prove successful. Also, the need for measures that address the opioid medication misuse issue in community pharmacies setting would decline. Proactive and reactive measures will be necessary to combat the opioid epidemic and improve the health outcomes of chronic pain patients who use opioids, particularly those who misuse them.

4.8.1 Strengths and limitations

A strength of this study is that it applied a robust theoretical framework to conduct this review. (289) Using COM-B coding allows linking the extracted intervention to the BCW intervention function, which is helpful in finding mediators of change. In this review, the COM-B model and BCW were utilised in accordance with the guidelines of the UK NICE and the Medical Research Council Framework for intervention development and evaluation. (325) This suggests that interventions focusing on improving community pharmacy-led interventions using the COM-

B model and BCW may be more effective than existing approaches. Further research is required to examine this hypothesis.

There are some limitations to this review. Firstly, the pharmacist-led interventions are not adequately described, and experimental research designs have little use. Consequently, there is a limitation in the evaluability of those interventions, their contribution to the evidence base, and their potential future adoption within a practice. Despite the small number of included studies, there were considerable interventions provided among community pharmacies to manage analgesic medication misuse/abuse. Some of those obtained studies had a low response rate, between 4.1 % and 5.9 %. (308,310) This could be related to COVID-19's impact on the services delivered by community pharmacy sectors when the included studies were conducted. (311) Moreover, no studies about pharmacist-led interventions in the UK were identified. Additionally, this review included only articles published in English, so studies in non-English languages may have been missed.

4.9 Conclusion

Evidence of CP-led interventions to address medication misuse for pain is limited. There is a growing interest in studying the roles of CPs; however, their interventions vary and are not fully described or assessed. Therefore, it is impossible to draw any significant conclusions or recommendations that might contribute to the design or implementation of future interventions.

Nevertheless, interventions to address this problem should be a multifaceted approach to target the behaviours of pharmacists and patients. Owing to the complexity of the problem, which is not limited to community pharmacies as well as the challenges posed by siloed work practices, developing a framework that can facilitate the design of evidence-based, theoretically based interventions is essential to address the issue more effectively. In order to significantly contribute to the evidence base, further studies should be conducted using experimental designs that comprise larger populations and have a sufficiently long evaluation period.

Chapter 5 Community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia: A qualitative study.

5.1 Chapter description

Chapter 4 illustrated that there was limited evidence about pharmacist-led interventions to tackle pain medication misuse and a lack of a clear description of the role of CPs. Therefore, in this Chapter, the perspectives, and experiences of CPs in identifying and addressing inappropriate prescribing, particularly analgesics, were explored.

5.2 Publication

The work of this Chapter has been published as Meaadi J, Obara I, Nazar H. A qualitative study to investigate community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia. Int J Pharm Pract. 2023 March.

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5.3 Introduction

Once started treatment, medications can be difficult to stop. It takes time for healthcare professionals (*e.g.,* physicians, nurses, or pharmacists) to reassess the use of prescribed medications for patients with multi-morbidities who receive potentially inappropriate medications. (326) Inappropriate medications can be defined as medications which are used when their risks outweigh their benefits. (327) Therefore, the inappropriate use of medications (IUM) refers to (1) use of medication without indication (misuse), and (2) incorrect choice of medication, incorrect dose or duration (326,327). The IUM is often associated with adverse events, mortality, hospitalisation, and death. (327) A recent report from the Office for National Statistics revealed that the death rate related to drug misuse in England and Wales was 52.3 deaths per million people. (328) However, the issue of inappropriately prescribed medications can be addressed by examining the prescribing process and reviewing and optimising the patient medication regimen.

In March 2017, the WHO launched the third global patient safety challenge: Medications without harm, which aims to decrease severe avoidable medication-related harm by 50% over a five year period. (329) Identifying and determining inappropriately prescribed medications is the first step to improve the use of medications and thereby reduce harm. This can be considered a multistep process that includes assessing the treatment plan for the needs to stop medications, agreeing on a plan between healthcare professionals and patients which could include decreasing or stopping medications, and monitoring the outcomes. Many studies have shown that interventions by CPs, physicians, and other healthcare professionals can reduce the use of inappropriate medications. These reductions tend to be safe, but the evidence on benefits remains mixed. (326) A meta-analysis showed that interventions to reduce inappropriate medications particularly hazardous prescribing, might be expected to save money, however, these savings must be offset against the cost of these interventions. (330)

In a systematic review of RCTs and observational studies about stopping inappropriate prescribing, the authors focused on specific drugs and drug classes rather than the interventions. (331) Most of the studies showed that medications could be successfully withdrawn with little to no harm to the patients. Another systematic review of RCTs about

stopping inappropriate prescribing through pharmacist-led medication reviews found that discontinuing unnecessary or harmful medications led to reductions in medication usage and cost, though only a few trials investigated clinical outcomes. (332)

The IUM is a widespread problem among patients with chronic pain because of insufficient pain management. (308) Therefore, healthcare professionals are faced with the most significant challenge of distinguishing legitimate prescriptions for analgesics from illicit prescriptions. (333) Since many analgesic abusers obtain inappropriate drugs directly from healthcare professionals in different ways, *e.g.,* fabricating pain symptoms, forging prescriptions, and engaging in doctor and pharmacy shopping. Ultimately, they have multiple prescriptions from multiple providers or pharmacies. (334) In the USA, opioid analgesics alone or in combination with other analgesic drugs (*e.g.,* gabapentinoids or benzodiazepine) accounted for nearly half of the drug overdose deaths and more than 75% of prescription drug-related emergency department visits in 2009. (334) In the UK, 13% of adults had one or more opioid analgesic prescriptions dispensed from 2017 to 2018. (335,336) In 2018, the death rate due to opioid misuse increased from 34.9 to 38.7 deaths per million people. (337)

Pharmacists are the last defence before a patient receives a supply of medication which means they are in an excellent position to address medicines-related problems such as IUM (misuse). (335) In addition, community pharmacies are among the most accessible healthcare professionals in the UK. (338) Chapter 4 identified that the evidence of CPs interventions to tackle painkiller misuse is limited. Moreover, pharmacist-led interventions were not completely described, which indicates that the specific role played by CPs in reducing IPA remains unclear. (338)

To change traditional practice and design an intervention; it is essential to understand the process underlying a target behaviour (*e.g.,* identifying IPA in community pharmacies). Thus, it is fundamental to understand the determinants (barriers and facilitators) for the involvement of CPs in addressing IPA. It has been demonstrated that theory-based approaches to identifying barriers to behaviour change and designing targeted interventions to address those barriers are more effective than non-theory-based approaches in changing behaviour. (339–341) Taylor's meta-analysis found that studies that used theory explicitly for intervention design were more likely to be successful in changing behaviour than studies that

did not use theory. (342) In the absence of theory-driven behaviour change strategies that address IPA in community pharmacies, this Chapter applied the BCW and TDF to address this gap.

5.4 Aim

To understand community pharmacists perceived barriers and facilitators to identify inappropriately prescribed analgesia.

5.5 Objectives

1- Describe the barriers and facilitators for identifying inappropriately prescribed analgesia.
2- Apply theory-driven behaviour change strategies to map identified barriers and facilitators onto the domains of the Theoretical Domains Framework.
3- Find appropriate Behaviour Change Techniques to incorporate in a theoretically informed intervention to facilitate community pharmacists involvement in addressing inappropriately prescribed analgesia.

5.6 Methodology

5.6.1 Qualitative research

Qualitative research is a superordinate term that includes many techniques and methods used to collect and analyse data in language data (words) rather than numerical data. (343,344) Qualitative research is defined as a "*naturalistic, interpretive approach, concerned with exploring phenomena from the interior and taking the perspectives and accounts of research participants as a starting point*". (345) One of the most essential characteristics of qualitative research is that the aims and objectives pursue to answer questions of "what", "how", and "why" of specific behaviours or experiences. Therefore, researchers adopt qualitative research approaches to understand human behaviour, and gain in-depth knowledge of how research participants interpret their experience and stand-point. (343,346) In pharmacy practice research, qualitative research approaches are usually used to identify, improve, and develop current practices. Those approaches are a helpful way of understanding existing

practices and beliefs. (347) For developing our research process we followed the “research onion” by Saunders. (348) Saunders presents the research onion framework to help and guide the researcher through each necessary step to develop a research study. (348) The research onion is divided into three different decisions the researcher needs to consider when developing the methodology: (1) research philosophy and research approach, (2) research design, and (3) data collection and analysis aspects. (349)

5.6.2 Research philosophy and research approach

Conventionally, researchers develop and structure their qualitative research on an underpinning philosophical framework. This informs their research design, data collection, and analysis process. (350,351) Various philosophical frameworks can give a lens for the qualitative research being undertaken; following a framework will help researchers conduct their research in a rigorous way. (345)

Researchers will intentionally or unintentionally make many philosophical assumptions while starting on research. (352) Philosophy (also called a paradigm) means beliefs about using different ways to abstract ideas and beliefs about a phenomenon. (353) Guba defined philosophy as a “*basic set of beliefs that guides action*“. (354) Research philosophy creates philosophical assumptions that justify how the research will be conducted. (355) The philosophical assumptions are defined as “*the first ideas and beliefs in developing a study*”. (356) Thus, different frameworks are underpinned by philosophical assumptions (*e.g.,* ontological assumption, epistemological assumption). (356) The ontological assumption is the assumption that relates to the nature of reality which seeks answers (reality) to the research questions. While the epistemological assumption is the assumption related to the nature of knowledge; how the knowledge of a phenomenon can be acquired. (345) As it relates to this Chapter's objectives the epistemological question is concerned with how the knowledge of a phenomenon (addressing IPA) can be acquired from the perspective of the agents (CPs) in daily practice.

The literature discusses a variety of theoretical paradigms, including positivism, interpretivism/constructivism, transformative, and pragmatism paradigms. Various research methods and tools have been advised in the literature to be used for each paradigm, as shown in table 5.1. (357) However, there are two prominent epistemological positions: positivism

and interpretivism/constructivism. (358) According to Ritchie *et al.* positivism, which is knowledge the researchers derive from their research, will be only "fact", which means it cannot include personal viewpoints. (345) Whilst interpretivism seeks to understand the meaning from what people say and understand as their world views. (356) Positivism tends to be associated with quantitative research, while interpretive paradigms relate to qualitative research. (357) Since Thesis Objective 5 focuses on exploring the barriers and facilitators facing the CPs for identifying IPA, the best approach was interpretive epistemological philosophy. (357) This considered exploring addressing IPA from the perspective of CPs involved in the context (primary care) of interest.

Paradigm	**Methods**	**Tools**
Positivism	Quantitative (predominate)	Experiments Quasi-experiments Tests
Interpretivism /constructivism	Qualitative (predominate)	Interviews Observations Document reviews
Transformative	Qualitative methods Quantitative Mixed methods	There is a need for a variety of tools to prevent discrimination
Pragmatism	Qualitative and/or quantitative methods	Interviews Observations Test Experiments

Table 5-1. *A comparison of the methods and tools used by each paradigm. Adapted from references. (26,27,29)*

5.6.2.1 Using theory to explain the participants' perspective

Behaviour change science provides several theories, frameworks, or models that underpin the development and evaluation of interventions. BCW theory, as mentioned previously (section 4.3), was used in this thesis to explore the participants' behaviour towards identifying IPA according to their experiences (Figure 5.1). (289) The BCW theory is a recent development in the behavioural change field that provides a structured approach for identifying and understanding the nature of the behaviour and develops strategies for modifying the target behaviour. (289) In a comparative study investigating the effectiveness of existing frameworks of behaviour change by Michie *et al.* it was shown that the BCW framework has met three

fundamental criteria: coherence (selecting relevant options is based on a systematic approach), comprehensiveness (considering all the options available to change the behaviour), and explicit link to a model of behaviour that incorporates context. (359)

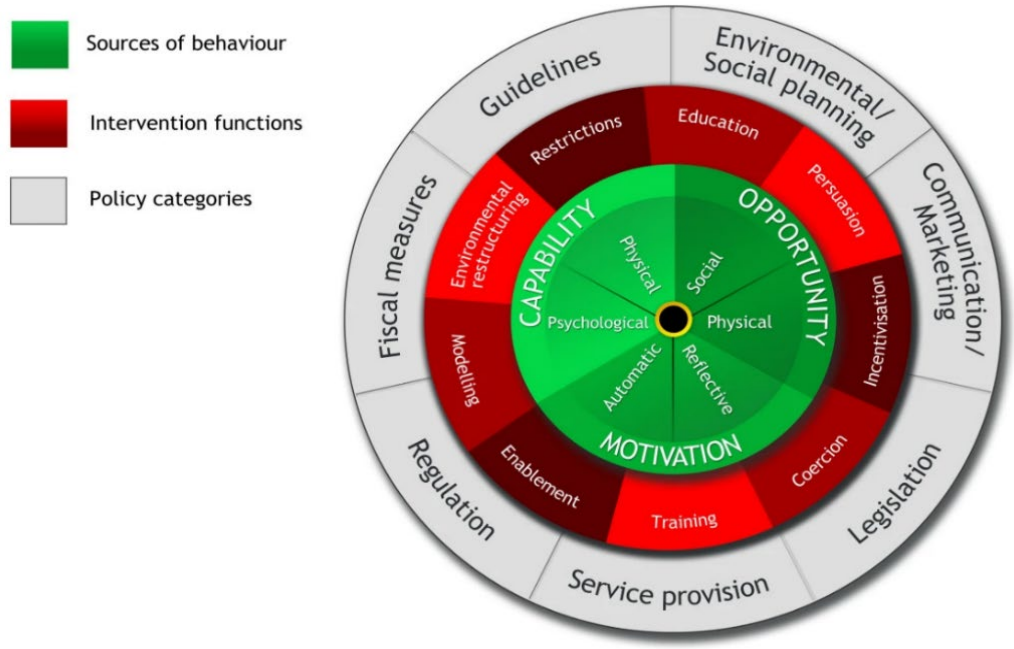

Figure 5-1 *The Behaviour Change Wheel. Figure reproduced with permission from the publisher.* (289)

The BCW comprises of three various layers; at the core of the wheel is COM-B model, the surrounding layer is intervention functions, and the outer layer is policy categories. (289) The starting point for selecting target behaviour and designing an intervention is the COM-B model. (289) The COM-B model was used to understand capabilities (how CPs' capabilities to engage in addressing IPA as behavioural modification), opportunity (factors in the environment that impact community pharmacy practice), and motivation (the readiness to change) of CPs to identify and address IPA. (289)

The TDF was also used to explore the barriers and facilitators that CPs are experiencing with identifying and addressing IPA. (302,360) The TDF is an "integrative framework" which was developed through a consensus approach between psychologists and implementation scientists. (289) Thirty-two international experts in behaviour change addressed TDF and identified 128 constructs from 33 behaviour change theories. (302) Then, the TDF was simplified into 14 domains and has been validated by an international consensus of 36 experts. (360) The TDF works as a ''theoretical lens'' through which specific determinants of the target

behaviour (*e.g.,* addressing IPA in community pharmacies) can be recognised for targeting with a behaviour change intervention. (361)

The TDF expands the COM-B system into 14 domains, and each of these domains is recognised as a determinant of the target behaviour (Table 5.2). For example, the 'Skills' domain refers to "an ability or proficiency acquired through practice" and 'Social Influence' refers to "those interpersonal processes that cause an individual to change their behaviour, views, and feelings". (362)

COM-B component		**TDF domain**
Capability	Psychological	Knowledge Skills Memory, attention, and decision process Behavioural regulation
	Physical	Skills
Opportunity	Social	Social influences
	Physical	Environmental and context resources
Motivation	Reflective	Social/professional role & identity Beliefs about capabilities Beliefs about consequences Optimism Intentions Goals
	Automatic	Social/professional role & identity Optimism Reinforcement Emotion

Table 5-2*. Mapping of the COM-B model to the TDF domains. Adapted with permission.* (302,360)

The TDF has been successfully used for identifying the determinants of different health behaviours investigated through interviews and focus groups. (363,364) A number of recent studies have used the TDF to understand factors related to decreasing potentially inappropriate prescribing at the organisational or individual level. (158,365) The TDF framework has a unique advantage which is mapping the TDF domains into the BCT taxonomy version 1 (BCTTv1), helping researchers propel from a theoretical understanding of the behaviour to develop an evidence-based intervention. The BCTTv1 is synthesised to specify an "active ingredient" of interventions with regard to their component BCTs. (366) Michie *et al.*

and Cane *et al.* provided a linking table that explains the mapping process between identified TDF and BCTs. (367,368) This linking can determine the target behaviour by specifying the significant domains that give the theoretical understanding needed to develop an intervention.

Utilising the COM-B model and TDF frameworks in this thesis offers a guide to collecting data on CPs' perspectives about inappropriate analgesia for chronic pain patients and facilitates the identification of barriers and enablers for tackling this issue. This approach is helpful to find which specific component needs to change for the target behaviour to happen and offers guided techniques and strategies that can be employed in the future to modify the behaviour.

5.6.3 Study design

Research design is an overall research structure including: methodological choices, research strategy, and time horizon. (348) In contrast, the research method is a process and procedure that is used to analyse or collect data. (369) The inductive approach was used which aims to generate theories from research rather than starting research with a *priori* assumptions or theories. Knowledge about a specific community or phenomenon is gained by observations of the participants' world and understanding their thoughts and interpretations. (345) Therefore, an individual interview was chosen as the appropriate method to address the study aim through the understanding of participants' thoughts, feelings, opinions, and knowledge. (370) Further discussion of other methods of data collection is provided in section 5.7.4.

Qualitative strategies most commonly used in health research include narrative research, Grounded Theory, Ethnography, and phenomenology. (371) Deciding which qualitative strategy to apply can be challenging. After reviewing the focus of each qualitative strategy and meeting iteratively with the research team, phenomenology was decided as the appropriate strategy for this study. To address Thesis Objective 5, phenomenology was used as the strategy to capture CPs' perceptions of their involvement in addressing IPA. Narrative research is primarily focused on the stories that participants recount rather than their perceptions related their lived experiences, (372). Grounded theory attempts to study a certain phenomenon to discover a novel theory rather than describe it. (373) Therefore, the research team decided to exclude this approach, as inadequate for this research. The ethnographic strategy was unsuitable since it involves observing or interacting with CPs in their natural

environment and then generating data to explain the phenomenon being studied. (374) Consequently, it would have been impossible to capture participants' individual opinions and viewpoints about the barriers and facilitators they encountered when tackling the IPA issue without explicit accounts from participants.

A phenomenological strategy seeks to understand the nature of a phenomenon through an in-depth exploration of participant's experiences and perspectives. Moustakas described some characteristics of phenomenological approach as making them appropriate for human science research. (375) The phenomenological strategy considers the whole nature of a phenomenon, free from preconceptions, and develops an understanding based on the information provided by the data. (375) The phenomenological strategy would, therefore, contribute significantly to the literature by providing a comprehensive description of the phenomenon (tackling IPA), so that practitioners, policymakers, and academics can better understand barriers and facilitators about CPs' involvement for addressing this issue. For these reasons, the phenomenological qualitative strategy was adopted to explore the “lived experiences” of community pharmacies in addressing inappropriate prescribed analgesia. Welman and Kruger noted that phenomenology is concerned with understanding a specific phenomenon from the perspectives of participants who have experience with it. (376) Phenomenology can be categorised into two categories: interpretive (hermeneutic) and descriptive (transcendental). An interpretative phenomenology involves interpreting personal experiences as the source of knowledge, which is influenced by the researcher's prior knowledge or experience of the phenomenon being studied. (375) In contrast, transcendental phenomenology focuses on describing personal experiences as the source of knowledge and is not affected by researcher experience. (375) Generally, hermeneutic phenomenology differs from Transcendental phenomenology in that it is not concerned with "what we can know about the world (epistemology)" but instead with what it means to be in the world (ontology). (377)

As this study is underpinned by epistemological assumption, transcendental phenomenology was used as the appropriate approach to focus on describing "what" the participants experienced about a phenomenon and “how” they experienced it in their world rather than illustrating interpretative representations. (378) The consolidated criteria for reporting qualitative research (COREQ) 32 checklist was used for reporting this qualitative study. (379)

5.7 Methods

5.7.1 Ethical approval

Ethical approval was obtained from Faculty of Medical Sciences Research Ethics Committee, part of Newcastle University's Research Ethics Committee (Reference number 2116/11765). NHS Research Ethics Committee (REC) approval was not required for this research using the NHS REC tool (Appendix D).

Data protection and confidentiality

All research team members endeavoured to protect the rights of the study's participants to privacy and informed consent. This aligns with Newcastle University policies and the recent General Data Protection Regulation. Electronic data, including database records and digital recordings, were held securely on a password-protected computer and backed up regularly to remote media in an encrypted format. Access was secured by user identifiers and passwords and was limited to the research team only.

The information obtained from individual participants in this study was considered confidential and cannot be disclosed to third parties. In addition to ensuring participant confidentiality, identification code numbers were used in the electronic database computer files to ensure participant confidentiality.

5.7.2 Sample

Sampling is a strategy that enables researchers to obtain information about a population from a representative sample without investigating every single person. (380) Sampling methods can be categorised into two types: probability sampling and non-probability sampling. (380) The probability sampling method is used primarily in quantitative research and means that each individual has an equal chance of being chosen (randomly selected). Non-probability sampling, on the other hand, is often employed in qualitative research to enable rich data collection related to the study topic by ensuring participants have adequate experience. There are different non-probability sampling techniques such as purposive sampling (also known as judgment sampling), snowball sampling, and convenience sampling. (381–383) Table 5.3 presents advantages and disadvantages of each technique. (381–383)

Sampling techniques	**Pros**	**Cons**
Purposive sampling: choosing participants according to specific criteria pertinent to the research objective.	Time and cost efficiency Ideal for exploratory design	Subjective Easily influenced by researcher bias Lacks clear generalisability
Snowball sampling: participants helping in recruiting other participants.	Can estimate rare traits Access hard-to-reach populations	Time-consuming Lack of cooperation Sample bias
Convenience sampling: choosing participants according to their ease of access.	Efficient and easier process Least time-consuming Least expensive Collect data quickly	Selection bias Lack of representative

Table 5-3. *A comparison of non-probability sampling techniques and their pros and cons. Adapted from references. (48–50)*

The most common technique used in qualitative research is convenience sampling. The Convenience sampling technique can be defined as a sample of research participants who are chosen based on the ease of accessibility and availability. (384) This study used convenience sampling instead of other sampling methods due to its flexibility in recruiting participants during the pandemic restrictions (COVID-19), as many community pharmacists were extremely busy during that time.

For qualitative studies, sample sizes are not stipulated. It has been argued that there is no clear answer to the question of "how many" in qualitative research. (385,386) Sandelowski advises that qualitative research sample sizes need to be large enough to facilitate a deeper understanding of the phenomenon. (387) However, at the same time, they need to be small enough to make qualitative data "in-depth, case-oriented analysis" possible. (387) Morse argues that fewer participants will be needed if more usable data is collected from each individual. (388)

There are some qualitative scholars who predetermine sample size based on information power. In 2016, Malterud *et al.* proposed information power concept which means selecting a proper sample size according to the study objectives. (389) To put it another way, the more useful information a sample contains about the study, the fewer participants are required. (389) This concept was provided to guide adequate sample size for qualitative studies. (389)

Information power is influenced by the sampling technique. (390) This concept is suitable for purposive sampling since selecting participants with rich and diverse experiences enhances the information power of the research. (389,390)

On the other hand, some qualitative researchers do not predetermine a sample size in advance. They collect data until no additional issues or insights are identified, which is known as data saturation. Guest *et al*. revealed that saturation has become "the gold standard" to determine the sample size in health science research. (391) Nevertheless, as per reported recommendations for studies that aim to describe a shared perception, belief, or behaviour; the sample of 12 will likely be sufficient. (391) However, we aimed to collect data until we reached inductive thematic saturation (when there were no further emergence of codes or themes) as described by Francis *et al*. (392) This approach was selected based on the Chapter objectives and sampling technique in order to obtain a comprehensive and deep understanding of CPs' perspective on their involvement in addressing IPA.

5.7.3 Recruitment

It was planned to collect data from CPs who had worked in community pharmacies for more than one year. (393) Gatekeepers are essential to gaining access to study settings and potential participants within their authorities. (394) They have the power to grant or refuse the needed access. (394) There is evidence in the literature that gatekeepers play an important role in recruitment processes, as those who support research initiatives can play a positive role in recruitment. (395,396) Consequently, the Local Pharmaceutical Committee chair was contacted as a gatekeeper to the CPs in the region in order to facilitate recruiting these participants. It was explained to the volunteer members the purpose and background of the research as well as their role in recruiting participants and circulating consent forms (a legal document signed by participants to confirm that they agree to take part in the study) and participant information sheet (a file including fundamental information about the study) (Appendix D). The gatekeeper were asked to distribute participant information sheet and consent form electronically to CPs. Due to poor recruitment using this strategy, social media platforms Twitter and LinkedIn were used to widen recruitment of UK-based CPs. The participants, who expressed interest to take part, were sent a formal email including a participant information sheet, consent form and demographic survey, which requested the

following information: gender, years of experience, qualification (Table 5.4 for a brief summary of the participants).

The participant information sheet provided an overview of this study that included aim and objectives, benefits of participating, adverse events, method of data collection. Within this information sheet, it was clearly stated that participants were able to withdraw up until the conclusion of the interview and were provided with an opportunity to do so if they wished. Interested participants were asked to complete and sign a consent form and return it directly to the primary researcher (JA) within 5-7 days of receipt of the documentation.

5.7.4 Data collection

Data collection in qualitative research can take many forms, such as observations, textual or visual analysis (*e.g.,* from books or videos) and interviews (with individuals or groups). (397) However, data collection methods used in healthcare research commonly include focus groups and interviews. (345,380) A focus group is a method of conducting research through group discussion on a specific topic. (397) In contrast, an interview (one-to-one) is a way to obtain one participant's opinion, experience or perspective about a particular topic. (397) Interviews have been used widely in healthcare and pharmacy research to understand participants' perspectives better. (344,398)

In terms of research interviews, there are three basic types: structured, semi-structured and unstructured. (397) In structured interviews, standardised and premeditated questions are asked to gather information without allowing follow-up questions on responses requiring further explanation. Therefore, this approach, which allows for limited participant responses, cannot be used to answer the Chapter objectives, which seek to gain a deeper understanding of the experiences and opinions of the CPs. Conversely, an unstructured interview is one without pre-planned questions. Typically, the unstructured interviews take several hours to complete (time-consuming), are difficult to manage, and participants struggle with what to say. (397)

The semi-structured approach relies on a predetermined agenda, derived from the research questions, and permits the participants to choose which type of information is produced according to their interests and experiences. (397) It was difficult to conduct a focus group or unstructured interview during the COVID-19 pandemic, where this research was conducted,

due to the busy schedules of the CPs. Therefore, the research team decided that one-to-one, semi-structured interviews was the most appropriate method to address the thesis objective (5): explore CPs' perceived barriers and facilitators to identify IPA.

Semi-structured interviews were conducted with consenting CPs in the UK. This type of interview is a popular data collection method, as it allows a researcher to improvise follow-up questions based on interviewees' responses. (399) In this study, participants were offered to undertake the interview at a convenient time and in a convenient way (*e.g.,* virtually, telephone, or face-to-face where the pharmacists work). Interviews were conducted between March and June 2021, and the signed consent form was obtained prior to starting each interview from the participants. The interviews were recorded with an audio recorder, and then recordings were coded anonymously and transcribed. The contact details for the interview participants were not included in the transcripts.

5.7.5 Interview topic guide

The COM-B model and TDF framework were used to develop the topic guide to investigate the addressing and identifying of IPA in community pharmacies. (359) The COM-B and TDF are proven to be helpful to design topic guides for health science research. (339,400,401) Each component of COM-B fits well with one or more TDF domains as outlined by Michie *et al*. (289) In 2012, Cane *et al.* revealed that TDF domains linked into COM-B segments would help identify the potential barrier and facilitators of tackling inappropriate prescribing of analgesics. (360) Moreover, the interview topic guide was refined through consultation with the research team who have academic and community pharmacy practice backgrounds. The interviews were initiated with general questions to elicit participants' general views and thoughts about determining inappropriate prescribing, and then their perceived barriers and facilitators to identifying this issue in community pharmacies (Appendix D).

5.7.6 Data analysis

Once data collection begins, qualitative data analysis begins. By doing so, the interviewer will be able to refine questions and explore new avenues of inquiry during the interview, review previous interviews, and identify new themes or ideas. (345) The interview data was subject to thematic analysis in a way consistent with recent theory-based intervention development

research. (364,402,403) As this research explores the CPs' perspective on their involvement in addressing IPA, a thematic analysis was considered as the most applicable method because of its flexibility to use inductive and deductive analyses. This would facilitate the identification of barriers and facilitators that faced CPs.

The thematic analysis can be combined approaches using inductively "bottom-up" and deductively "top-down". (404,405) Inductive approach means the insights and patterns are derived from raw data. (404) Unlike deductive analysis, or a *priori*, which uses predetermined codes to the data set. (404) The inductive way was used to identify the barriers and facilitators related to address IPA (stage 1). The inductive approach was used to ensure the themes that resulted were not confined to the predefined TDF domains. Then, the deductive approach was used in the secondary analysis to map the themes generated to the TDF domains and identified appropriate BCTs (stage 2 and 3).

Analysis process

A primary researcher transcribed verbatim the interview recordings, which were double-checked for accuracy. Data analysis was conducted using QSR NVivo® Version 12 Pro software. In order to ensure anonymity, all identifiable information within the transcript has been eliminated, and each participant has been assigned a distinct reference number (*e.g.,* CP_1, CP_2, etc). Data analysis went through the following three stages:

Stages 1. Thematic analysis for each transcript as defined by Braun and Clarke to identify the determinants (barriers, facilitators) of addressing inappropriate analgesia. (405,406)

Stages 2. Mapping identified determinants from stage 1 to the TDF domains.

Stages 3. Mapping the identified TDF domains to appropriate BCTs.

5.7.6.1 Stage.1 Thematic analysis

Collected data was initially analysed using thematic analysis as defined by Braun and Clarke through five phases: (1) data familiarisation, (2) coding, (3) generating initial themes, (4) developing and reviewing themes, and (5) refining, defining and naming themes. (407)

Phase 1: Data familiarisation

JA read and re-read each transcript many times to become immersed and familiar with the details and content of transcripts. In this process, JA gained an overview of beliefs within the data and noted the initial ideas and beliefs.

Phase 2: Coding

In this phase, each transcript was coded inductively by JA, and categorised the data into barriers and facilitators of addressing IPA. The coding phase went through three rounds to ensure resultant codes and associated data extracts were coded comprehensively. The codes and relevant data extracts were reviewed and refined over discussions by the research team.

Phase 3, 4, and 5: Generating initial themes, developing, and Refining themes

Herein, codes and similar excerpts were investigated and combined to the potential themes by JA. All initial themes were discussed among the research team (JA, HN, and IO). After that, themes were reviewed to ensure that the collected data in each theme fit well together to produce a distinctive and coherent analysis. These themes needed to provide a compelling story from the data and reflect the interviewees' perspectives. Therefore, themes were revised several times to ensure a 'true' interpretation of data. Despite these phases being an arduous process, each round of revision provided new meaning and understanding of the beliefs and perceptions of CPs about identifying and tackling IPA. Illustrative quotes were captured alongside the themes to ensure the interpretative themes could be later supported.

5.7.6.2 Stage.2 Mapping identified determinants to the TDF

The definitions of TDF domains defined by Cane *et al.* were used to guide this mapping. (360) All inductive codes from stage 1 were mapped into the TDF domains independently by two researchers (JA and HN). Next, the mapping codes relating to determinants (barriers and facilitators) were compared, and any disagreement was discussed by the research team (JA, HN, and IO) until consensus was achieved.

5.7.6.3 Stages.3 Mapping the identified TDF domains to appropriate BCTs

In order to link BCTs to the identified determinants in stage 2, the mapping table developed by Cane *et al.* was used. (367) Each TDF domain was mapped onto an appropriate BCT

independently by two researchers (JA and HN). After that, the mapping domains with BCTs were compared, and any queries about the mapping process were resolved by discussion between the research team (JA, HN, and IO). The researchers completed online training in BCTTv1 before the mapping process.

5.8 Trustworthiness

Quality assessment of research is important if findings are to be used in clinical practice. In order to evaluate qualitative research's quality, Guba and Lincoln developed four principles for trustworthiness: credibility, transferability, dependability, and confirmability. (408) These trustworthiness principles are associated with the conventional quantitative assessment criteria of generalisability, validity, and reliability. These criteria were used in this study as described below.

5.8.1 Credibility

Lincoln and Guba described credibility as the confidence that can be added in the "truth" of the research data and interpretations of these findings. (408) The credibility of the study determines the "fit" between participants' thoughts and "how" researchers represent them (409). This research followed the 32-item consolidated criteria for reporting qualitative research (COREQ-32) checklist for systematic and transparent reporting to enhance the research credibility. (379) The COREQ-32 checklist was developed to include essential components of study design that need to be reported. The ingredients contained in the checklist play an important role to help researchers reporting key aspects of study methods, the context of the research, results, data analysis and interpretations. Moreover, the interview topic guide was developed using COM-B model and TDF. The COM-B and TDF are well-known tools for identifying key determinants (barriers and enablers) that are perceived to affect identifying behaviour and afford a theoretically robust evidence base to inform intervention design. (302,360)

5.8.2 Transferability

Transferability is analogous to external validity/generalisability in quantitative research. Transferability refers to the applicability of qualitative research to which findings can be

applied to other settings and different contexts. (408) Therefore, it is the researcher's responsibility to provide a comprehensive description in the report to permit the reader to evaluate which findings can be transferable to other settings, situations, and other contexts. (408,410) The details of this study are documented throughout including details such as the community pharmacies' location, the location of each interview, the demographics of CPs who took part, data collection methods that were adopted, the time period over which the data was collected, the duration of data collection sessions. These comprehensive details provide a reader with information about context so that they best able to determine the transferability to different settings, situations, and population.

5.8.3 Dependability

Dependability refers to reliability of the findings which can be repeated in the future if the inquiry were replicated in a similar research context. It is akin to reliability in quantitative research, but with the understanding reliability of conditions depends on the nature of the study question, theoretical framework, research philosophy (*e.g.,* positivism, interpretivism, etc), chosen methodology (*e.g.,* phenomenology, semi-structured interviews), research approach (*e.g.,* inductive or deductive), and data analysis (thematic analysis, content analysis, etc.). (411)

As noted by qualitative researchers, this concept is difficult to address considering the changing nature of the phenomena scrutinised. Therefore, to address the dependability concept more directly, the methods within the study need be reported in detail, enabling future investigators to replicate the work that is not necessary to gain the same results. The in-depth documentation of the methods employed in this research allows for readers to assess the extent to which theoretical framework and appropriate research methodology have been followed, provide an understanding of the methods, and identify their effectiveness to produce reliable findings.

5.8.4 Confirmability

Confirmability is a criterion that refers to objectivity. Confirmability should be taken to help ensure as far as possible that the data generated from the participants' experiences and ideas are not affected by the characteristics and preferences of the researcher. (408,410) It was

recommended that researchers should mention justifications for using theoretical, methodological, and analytical choices throughout the entire study, so that readers are able to understand how and why decisions were made. (410) For instance, the decision to use the convenient sampling technique instead of the purposive one was due to poor recruitment and COVID-19's impact and not the researcher's preference. Confirmability can be assessed through reflexivity and the researcher being transparent about their perspective and experiences that may have influenced the findings. The strategy that was considered in this study is reflexivity in order to decrease the effect of researcher bias.

5.8.4.1 Reflexivity

Researchers in qualitative study play a role as data collecting tools that create the process of analysis and interpretation of findings. Thus, researchers' experiences and qualifications are pertinent to establishing confidence in the data. It has been argued that the trustworthiness of the research is enriched if the report includes information about the researchers and their backgrounds. (412)

It is crucial that the researchers who conduct qualitative research investigate their own perceptions and assumptions in the study to aid the quality control of the research. (413) This means each researcher will add their own background, perspectives, and beliefs to the study, influencing why they chose the topic, the approach of the study and how the collected data will be analysed and interpreted. The reflexivity will help the readers to understand the researcher's perspective and aid them to consider this when they are reading and understanding the study.

I, the primary researcher (JA), am a pharmacist with experience working in hospital settings. According to my professional life, I worked amongst different pharmaceutical sectors (*e.g.,* drug information centre and ward clinical pharmacist). My primary role as a pharmacist was ensuring patient safety by providing medicines management. This role starts from how medicines are selected to how they are used by the patients. Through this process, I review patients' medications to help them get the desired care outcomes. I believe that many chronic pain patients are receiving potentially inappropriately prescribed medicines, particularly patients with neuropathic pain.

My personal and professional experiences have made me aware of the complexity of treatment for chronic pain and the issues raised when chronic patients use analgesia long term. I believe that the decision to continue using analgesic drugs for pain patients is limited between doctors and patients. Involving the CP who sees patients regularly is key to addressing IPA.

This statement aimed to provide transparency and illustrate the impact of my personal attitudes and beliefs in relation to addressing IPA as a subject of my study. Acknowledging this is important to enhance quality in the conduction and reporting of the work, so readers can understand how the researchers' experience and background could influence the reporting findings.

5.9 Results

Twelve CPs were recruited into this study. Interviews were conducted in a four-month period from March to June 2021. After ten interviews, data saturation was achieved, and two more interviews were conducted to verify that no new themes had emerged. The mean (±SD) interview duration was 25 (±10) minutes. Table 5.2 presents an overview of the participants' characteristics.

The IPA was a well-known term to CPs and they provided definitions that included: (1) any prescribed medication that is not suitable for a patient's condition, (2) does not have beneficial effects, (3) has a negative impact on patient's QoL, (4) has a negative effect on a patient, (5) prescribed analgesia for longer than indicated, (6) long-term use of medication without review, and (7) overuse/misuse by patients.

ID Code	Gender	Age	Years of Experience (Y)	Qualification(s)	Interview format	City
CP_1	Male	25-30	1-5	Master degree	Video-call	Cardiff
CP_2	Female	25-30	6-10	Master degree; Postgraduate diploma	Video-call	Newcastle
CP_3	Female	25-30	1-5	PhD; Master degree	Video-call	Glasgow
CP_4	Male	> 45	> 10	Bachelor degree	Video-call	Middlesbrough
CP_5	Male	41-45	> 10	Master degree	Video-call	Sunderland
CP_6	Male	41-45	> 10	Bachelor degree	Telephone	Kent
CP_7	Male	31-35	6-10	Bachelor degree; Postgraduate diploma	Face-to-face	Glasgow
CP_8	Male	36-40	> 10	Master degree	Face-to-face	Leeds
CP_9	Male	25-30	1-5	Master degree	Face-to-face	Newcastle
CP_10	Female	31-35	6-10	Master degree	Face-to-face	Newcastle
CP_11	Male	41-45	> 10	Master degree	Face-to-face	Newcastle
CP_12	Male	> 45	> 10	Bachelor degree	Face-to-face	Newcastle

Table 5-4. *Interview participants' characteristics. CP: community pharmacists.*

Participants reported that they usually identified IPA through speaking to patients. All participants mentioned that having a conversation with patients would be the most effective way to address this problem. In most cases (n=10), participants would notify the GPs when they identified an inappropriate prescription for an analgesic (Figure 5.2 (A)). Only one participant described a systematic process for addressing the inappropriateness, as illustrated in figure 5.2 (B).

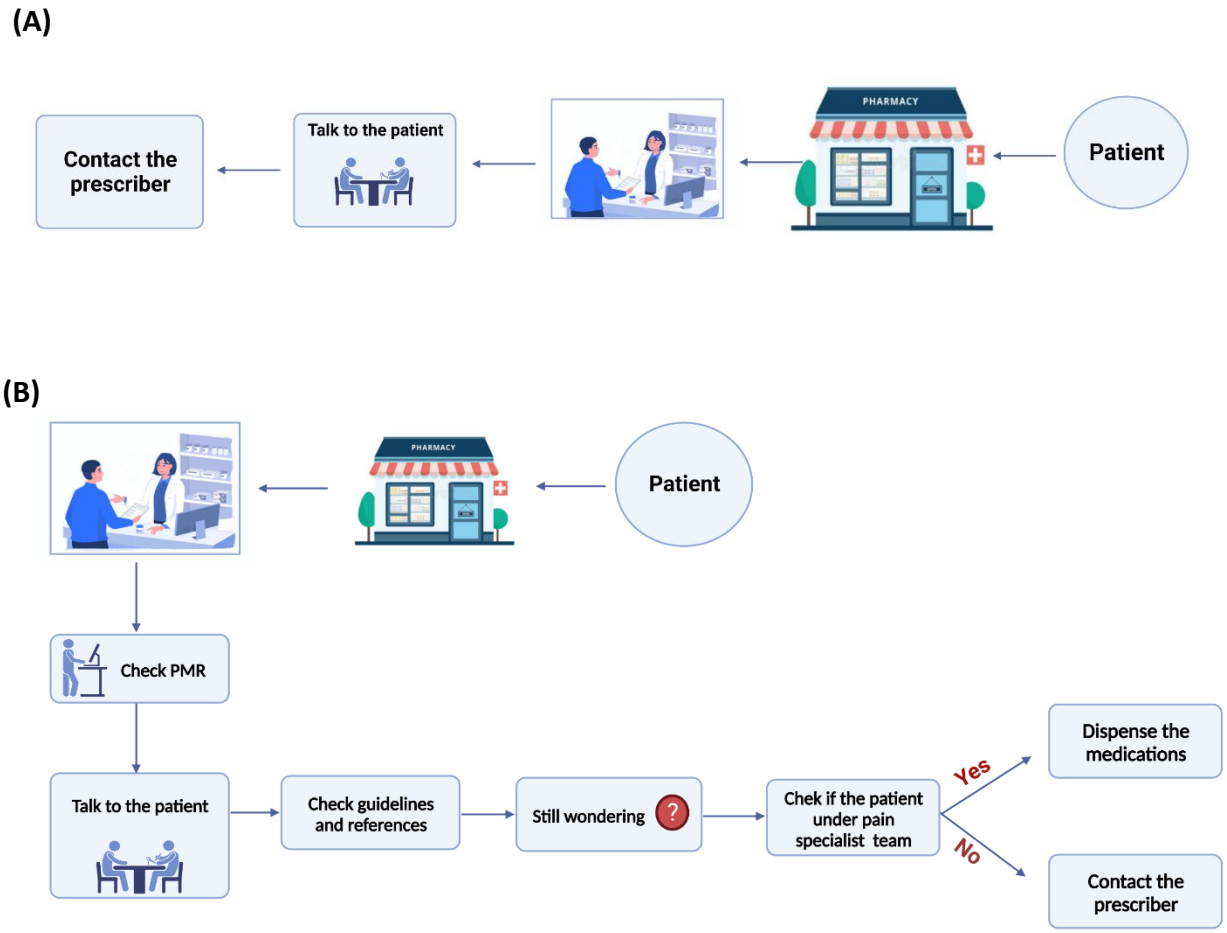

Figure 5-2. *(A, B) Participants' approaches for handling inappropriate prescriptions. Created with BioRender.com. PMR: patient's medical records, CP: community pharmacists.*

5.9.1 Stage.1 Thematic analysis

Two key themes were identified that highlighted the barriers and facilitators of addressing IPA (Figure 5.3).

1- **Environmental factors**

2- **Capability of CPs**

Each theme and subtheme is described below with illustrative quotes from the interviews as appropriate.

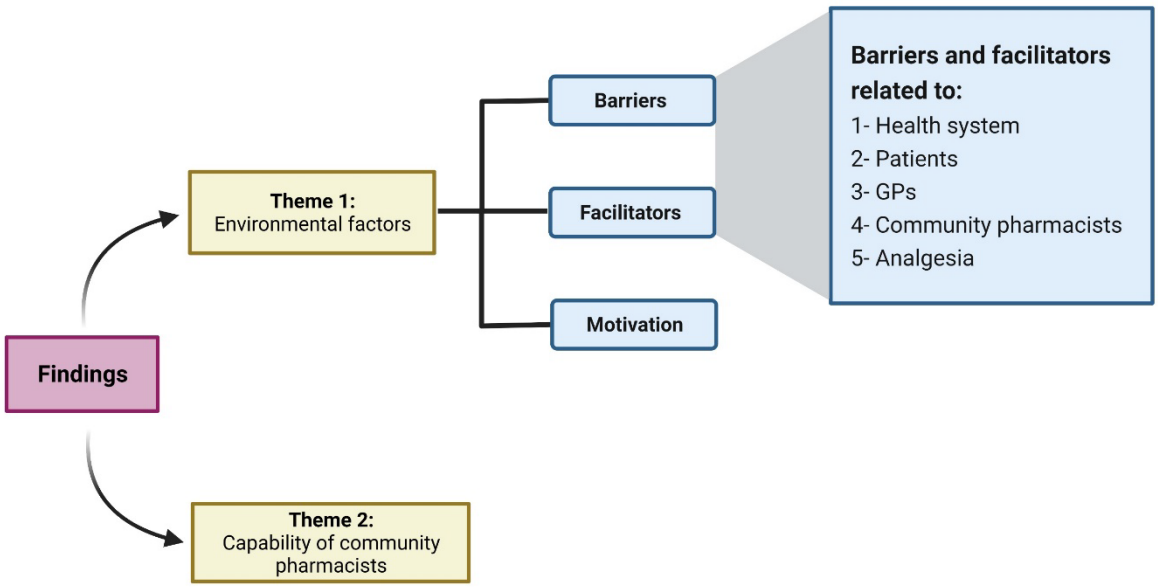

Figure 5-3. *Themes identified from the interviews with community pharmacists. Created with BioRender.com.*

5.9.1.1 Theme 1: Environmental factors

Barriers

Participants pointed out barriers that can be categorised as: the health system; patients; GPs; CPs, and the analgesic drug (Figure 5.3).

Health system barriers

All participants agreed that the main barrier preventing them from identifying IPA is the lack of access to patients' medical records. This lack of patient information (*e.g.,* medication indications, duration of treatment), caused CPs to be unable to decide whether or not the analgesia was appropriate. These factors affected CPs' confidence in decision-making and making intervention recommendations.

> *"I guess that's some of the challenges that community pharmacist has in that you don't have access to patient records. So, in the initial review of a prescription that comes to you, you don't have any background information that would help you make a determination as to is this appropriate? … you can only go based on what is the normal prescribing pattern for this drug?" (CP_1)*
>
> *"We don't have access to the patient file, so we have no complete picture of the patient's case" (CP_3)*

"…more obviously you haven't got access to the patient record" (CP_4)

Some of the participants mentioned that there was confusion as to who is responsible for determining IPA. Some CPs believed that detecting and stopping IPA should be the doctor's responsibility due to having the patient's full history.

"A lot of community pharmacists assume that the doctor will do that. So, there's that kind of wee bit of confusion about whose role ever, which is a shame" (CP_5)

Conversely, some participants stated that addressing IPA is part of the CPs' job. Participants described that they collected any relevant information from patients, usually by asking patients to describe what their prescriber had told them, but they stated that they could not always gather all the required information by following this method. Thus, access to the patient's medical records was described as a facilitator for CPs to have a clear picture about drug use and determine the appropriateness of analgesia for that patient.

"...access to medical records would be fantastic and it would certainly help and facilitate addressing inappropriately prescribed analgesia, but I don't think it's outside the realms of possibility" (CP_1)

Patient barriers

There was an agreed perception among the participants that some patients have fears about interventions relating to their pain medications. Participants further explained that they think this attitude is based on the patient's personal experiences with pain. For example, there was a belief that patients with chronic pain would be reluctant to change their medications or stop using painkillers because they were scared of experiencing increased pain.

"Patients might be a little bit scared about you moving their medicines around because they rely on them for pain relief" (CP_5)

There was an expressed reservation to confront these patient fears in the community pharmacies.

GPs barriers

Participants reported that contacting the doctors to notify them about the identification of IPA was a barrier. Pharmacists described their experience that doctors tended to be unreceptive to interference with patients' medications. In addition, participants voiced concerns regarding the GP refusing to have a conversation with them about addressing IPA.

"…the challenge is that the GP are not receptive. They respond quite defensively in quite negatively…" (CP_2)

"If you constantly get almost refused that sort of conversation with GP, then you just give up trying, because it is very hard to sort of to keep making those interventions in isolation, without the support of the whole healthcare team" (CP_2)

As described by participants, contacting GPs would be their first step after identifying IPA. Participants mentioned several modes of communication to reach GPs such as telephone or NHS email. They asserted that the absence of a clear way (one method) to contact the prescriber is also an obstacle to tackling inappropriate prescribed analgesia.

"I guess the second point is actually what's best with the surgery isn't a phone call. Is it your email by NHS mail? understanding the way of working out the GP and with the background of how urgent is this to resolve for the patient? So a lot of factors that play into some of the communication ways" (CP_6)

Participants related that they have had difficulty identifying who prescribed an inappropriate medication. Due to the limited access to patients' medical records, CPs struggled to contact the right person to discuss the inappropriateness of medication for certain patients. CPs generally tried to contact the GPs through second-hand communication (a receptionist), who then forwarded the message to the doctors. Most participants reported that receptionists are often not aware of the urgency of the situation and a pharmacist may be needing to decide what to do before supplying the medication on a prescription.

"…so I think finding the person who initiated the prescription is going to be really difficult that's like a huge barrier" (CP_3)

"How do you speak through the surgery that you call the surgery and you got to speak to the receptionist who may or may not like you to speak to a prescriber. And again, if you don't have that relationship with the receptionist, you'll be leaving a message." (CP_6)

Furthermore, participants believed that having a good relationship with GPs helped them to solve the issue of IPA. They claimed that CPs need to invest time building a good relationship with GPs to facilitate contact with them when needed.

"A lot of it in terms of how you work with general practice will be about relationships. So, if you haven't invested time in those relationships, that can make things difficult, everyone's busy" (CP_6)

CPs barriers

Participants relayed feeling uncomfortable deciding whether a prescription is appropriate since they don't have a patient's full history. As mentioned earlier, limited access to patients' profiles restricted the CPs' confidence in identifying IPA. Participants believed that CPs are not involved in decision making with prescribers about therapeutic plans. As a result of this isolation, participants lacked the confidence to address the inappropriate use of analgesics.

"Perhaps you wouldn't feel as comfortable having those conversations without having a full history of the patient" (CP_1)

"I think confidence is a big issue, and I think that's it's a challenge, especially in community pharmacies when you're quite isolated from the healthcare system to be confident to make interventions and a patient's care and you kind of lonely assume that things have been considered in full detail when perhaps they haven't" (CP_1)

"It is very hard to sort of to keep making those interventions in isolation, without the support of the whole healthcare team." (CP_2)

One participant reported that in community pharmacies, the inappropriateness of analgesia is usually recognised by noticing the patient's suffering from side effects. However, not all patients will suffer from, or report side effects, so CPs will have a limited opportunity to identify and tackle IPA in this way. Therefore, alternative triggers for the action need to be identified, such as: initiating a conversation with a patient, checking the patients' medical record, and contacting the prescriber.

"I think the usual trigger that would initiate a conversation would be if a pharmacist observes a side effect of a medicine, which leads them to think this is not right (...) So I guess the problem that community pharmacists confront is that by utilising the side effect as the trigger, they will only be tackling a few number of the patients they have this problems (...) if I was to try and tackle I would maybe just start by asking them and I would spend a bit of time listening to them and

understanding about their situation, reviewing the patient's medical record, and phone the GP." (CP_4)

Some participants expressed their concern about the liability for interfering with a patient's pain medications in an isolated environment. They justified that CPs are not involved in the communications between the doctor and patient about the rationale for using these medications. CPs, therefore, were wary of taking responsibility for changing a patient's pain medicine.

"I think the biggest problem or biggest kind of barrier it is a liability; I don't want to be liable for stuff in someone's pain medicines or changing them" (CP_2)

"…some community pharmacists and myself are quite a lot bit reluctant to interfere with the pain medications" (CP_5)

Another barrier that prevents CPs from addressing IPA is lack of time. One participant expressed that CPs do not have enough time to review all medications for each patient, and more staff resource is required to manage this in the pharmacy.

"…to get quite busy. It's very hard to find your time. If necessary to be part of our job, we need more staff" (CP_12)

Participants illustrated they are facing competing priorities within the pharmacy: business responsibilities and championing the patients' best interests. Most participants linked patients' best interests to activities associated with delivering patient care through reviewing and checking the safety of medications before dispensing them, while business responsibilities in community pharmacies was connected to revenue generation. Therefore, participants believed that the involvement of community pharmacies in addressing inappropriate prescriptions resulted in a conflict between clinical responsibilities and business tasks.

"I think it may because, in community pharmacy, there's always been the sort of contradiction between the business and the sort of patient's best interest, especially when it comes to deprescribing that there's actually a disincentive to deprescribing community pharmacy because you'd get less payment prescriptions." (CP_1)

Analgesia barriers

The main problem with analgesia is that it is not well documented in the patient's medical record. In discussing long-term treatment with analgesia, some participants mentioned that it was difficult to determine when the medication was initiated and how long the medicine should or would be continued. Another expressed challenge was the complexity of analgesia. For instance, participants reflected that intervening with OTC painkillers such as paracetamol or ibuprofen prescription are easier than controlled drugs (*e.g.,* opioids or gabapentinoids). However, the participants were aware of opioid and gabapentinoid issues, indicating dependence, tolerance, misuse, and withdrawal symptoms, and their willingness to educate patients about these issues.

> *"I think, and again there's a difficulty in terms of there's an issue with analgesia specifically about it's often not very well documented what the long-term plan is?" (CP_1)*

> *"…If someone was on either ibuprofen and I knew they were asthmatic and or if they had previous GI bleed, then that's quite an intervention that's more in my comfort zone; I can deal with that, but that's totally different if we're dealing with someone who's on like high dose morphine and it's been on that for donkey's years, and that's still analgesia, but it's just a different maybe degree of complexity" (CP_3)*

Facilitators

Health system facilitators

Participants mentioned that a patients' medical records, patient prescription, and a control drug checklist are the available resources in community pharmacies which can aid in addressing IPA. Participants considered local guidelines and literature as additional resources to verify and identify whether analgesic drugs are appropriate.

> *"… checking PMR the pharmacist will check their medical records of patient and check patient prescriptions in our pharmacy" (CP_8)*

> *"I think I think the PMR helps obviously" (CP_9)*

> *"Identify inappropriate analgesia that could be either when you check a control drug checklist or sometimes when you do check the clinical prescriptions" (CP_10)*

One participant stressed that reclassifying some analgesic drugs (*e.g.,* pregabalin and gabapentin) as schedule 3 controlled drugs under the Misuse of Drugs Regulations (2001) and Class C of the Misuse of Drugs Act (1971), helped decrease the number of inappropriate prescriptions. There was a suggestion that adding detection and identification of inappropriate prescriptions in community pharmacy should be a mandatory role of CPs and included in their job description. This was anticipated to guarantee any inappropriate prescription to be handled appropriately.

> *" I definitely have seen a decrease in prescription since gabapentin and pregabalin have reclassified." (CP_10)*

> *"… community pharmacists try to actually identify when people are suffering ill effects of medicines and I think that their role, however, is kind of limited in some way because it's not part of their contractual agreement, it needs to be part of their contract." (CP_4)*

Several participants suggested and expressed the importance of recruiting more GP pharmacists to facilitate addressing inappropriate prescriptions of analgesia. They mentioned that GP pharmacists are often seen as detectors of this issue, by re-assessing patient's pain and reviewing their medications.

> *"… as I said maybe the main responsibility will be on the pharmacists that work in general practice, because they have access to a lot more information than we have. So they'll know the patient, the medicines that patients taking. And they'll have access to the notes about when that's being used, why it's being used and, you know, patient perceptions and all the patients a little bit more than us because they make consultations with them… but maybe they are not available enough in the country. Still maybe we don't have enough pharmacists in GP practices." (CP_5)*

Patient facilitators

All participants reported that patient trust in CPs is the primary facilitator to handling IPA. They illustrated that this trust between patients and pharmacists is generally established through frequent interactions between patients and pharmacists. This rapport would help patients have confidence in their pharmacists and their recommendations, be more open about their medicines use and share their personal information.

"I think that's the value that community pharmacists have because of build long term relationships with patients and to do have that element of trust, if you're going to push the boundaries back with them about their painkiller medications." (CP_2)

"Once patients understand that you've got that knowledge and expertise that they're more trusting of you to make interventions" (CP_3)

"… trust comes with knowledge of your patients through regular visiting, and it's about an understanding of what the patient was being treated for." (CP_6)

GPs facilitators

A good relationship between GPs and CPs was considered vital to facilitate the identification and tackling IPA. Participants expressed that having good relationships helped with timely communication. Thus, as previously mentioned, participants stressed the importance of investing time in building relationships with doctors.

"It's it can be difficult, A lot of it in terms of how you work with general practice will be about relationships." (CP_6)

"I think it's pretty easy. I think, it depends on the relationships you have with the GP. So some of the GP we have very good relationships. So you know, when I email them, they will actually follow me back and they'll tell me via email because I can quickly say you know, a patient has his pain control doesn't seem inadequate, please review and then generally reply to me. We are very good relationships" (CP_9)

CPs facilitators

Participants highlighted that talking to patients helped to determine IPA. CPs often ask patients why they have been taking the medication and for how long in order to gain a deeper understanding of the situation. Participants considered this conversation is the key to collecting information about a patient's condition and their medication use.

"So first of all have a chat with the patient that would be helpful because there could be a perfectly logical explanation for it? that might be he/she tried something else that doesn't work" (CP_7)

"Okay, well, first of all talk to the patient and see what they use it for? How long?" (CP_5)

Participants agreed that a patient's regular visit to community pharmacy was a factor that aided in addressing whether the analgesic prescriptions were appropriate. Based on their experiences, participants believed understanding the full picture of a patient's case (*e.g.,* diagnosis, indication for a drug, and for how long) can be gained through regular patient contact in the community pharmacy. They also stated that new patients or patients with little or no contact with the pharmacist would limit the opportunity to gain any information about the patient.

"We'll ask them why you are taking the medication? So do you have any idea this for? Always ask the patient, to make sure that patients understand clearly what they are taking, and we can understand if there is any inappropriateness" (CP_8)

"…because you see the patient every month and it's a good opportunity for identification" (CP_1)

"Once you see a patient regularly. And they think they run this same medication, it might be sleeping tablets, it might be painkillers it might be something that you think, is it really helping them anymore? It might be gabapentin might be analgesia and you might think, oh hang on! this patient been on this so long, is it really helping?" (CP_2)

Analgesia facilitator

A new prescription of analgesia was pointed out by participants as an enabler, as it gives a starting point from which to track prescriptions. This was perceived to help in assessing for and correcting the inappropriateness. Participants also acknowledged that it is difficult to identify retrospectively inappropriate long-term analgesia in the absence of patient information and limited access to patient medical records.

"…when you look at things like postoperative analgesia where patients have started on a pain relief, but there's it's not immediately apparent to you what the plan is whether they're supposed to de-escalate the pain relief etc and that's often not communicated well to GPS, let alone community pharmacists and in those circumstances, the only thing you can do is ask and so it's quite it's a lot easier for a new analgesic." (CP_1)

Motivation

Participants stated that financial incentives and reimbursements should be offered to CPs for greater involvement in addressing IPA. Additionally, they suggested that improving the collaboration between GPs and CPs through providing direct lines of communication would promote motivation.

> *"We probably need payment for patient medicines review. Because if you want someone to do something that isn't part of their contract, you will need to include it as part of the contract, and it would need to be appropriately reimbursed…. if you really want this to happen, you'd have to establish collaboration between all health care providers to encourage community pharmacists to tackle inappropriate prescribing" (CP_4)*

5.9.1.2 Theme 2: Capability of CPs

When asking the participants about their capability to be involved in identifying inappropriate prescriptions, some participants believed that it is part of their role as a pharmacist. They described CPs as a safety net and the last defence before the wrong medication reaches the patient.

> *"I think identification of the inappropriate prescribing for sure, could be a community pharmacist responsibility" (CP_1)*

> *"So we're very much seen as like the safeguards will be involved when you know, there's a clear problem that a clear safety issue." (CP_5)*

> *"Part of your role is the safety net, so in terms of at its basic level, if you see something that's unsafe, you know that to calling it a challenge appropriately and if necessary, stop it." (CP_6)*

In addition, the participants believed their pharmacology/therapeutics background and their training meant they were well equipped to address inappropriate prescriptions. However, they emphasised that more resources (for instance, access to PMR, training on reading and writing clinical notes) were needed to support their role appropriately in addressing IPA.

> *"To be honest, yeah, that's what our job is. We don't really need any more training or skills." (CP_7)*

"Pharmacists in terms of community pharmacy don't generally get trained to make clinical notes, and therefore you're not necessarily used to interpreting clinical notes either. So having access to the system is one thing, so having access to a full patient's record is important. So many community pharmacies been asking for a long time, but continues to ask for what actually, we also need the ability to read and interpret those clinical notes. So I think that we at some point they'll be need to have additional training on it." (CP_6)

5.9.2 Stage.2 Mapping identified determinants to the TDF

As shown in the table 5.5, the codes in the two themes and subthemes were mapped to multiple TDF domains. Codes related to environmental factors (barriers, facilitators, motivation) or CPs' capability to address IPA. The theme of environmental factors was linked to seven different domains, *e.g.,* 'Environmental context and resources', 'Social influences', 'Social/professional role and identity', 'Beliefs about capabilities', 'Beliefs about Consequences', Goals, and 'Reinforcement.' Whilst the capability theme was mapped to three TDF domains: 'Social/professional role and identity', 'Skills', and 'Knowledge'. (Table 5.3)

Theme 1 **Environmental factors**		
Subtheme	Barriers	Environmental context and resources Social/professional role and identity Social influences Beliefs about capabilities Beliefs about consequences Goals
	Facilitators	Environmental context and resources Reinforcement Social influences
	Motivation	Reinforcement Environmental context and resources
Theme 2 **Capabilities of CPs**		Social/professional role and identity Skills Knowledge

Table 5-5. *Themes and subtheme mapped to eight TDF domains.*

5.9.3 Stages.3 Mapping the identified TDF domains to appropriate BCTs

The research team adopted the method previously described to map appropriate BCTs to the TDF. (367,368) Seventeen BCTs were identified that could be considered in the design of future interventions to facilitate CPs' role in addressing IPA, as presented in table 5.6.

Code	Theme	Sub theme	TDF domain	Selected BCT
Limited access to patient profile/ medical records	**Environmental factors**	**Barriers** Health system barriers	Environmental context and resources	12.1 Restructuring the physical environment 12.2 Restructuring the social environment
Confusion about who is responsible for addressing IPA			Social/professional role and identity	13.3 Incompatible beliefs
Patients' fears about stopping their medication and feeling pain		Patients barriers	Social influences	3.1 Social support (unspecified)
GPs are not receptive		GP barriers	Social influences	12.2 Restructuring the social environment
GPs are refusing to have conversation about stopping IPA				
Communication ways with GPs (prescribers)			Environmental context and resources	12.1 Restructuring the physical environment
A receptionist who is receives the identification of inappropriate medications message			Social influences	12.2 Restructuring the social environment
It is difficult to find who prescribed an inappropriate medication				
Relationships with GPs				
CPs are not comfortable to determine IPA because of lack of full history for patient		CPs barriers	Environmental context and resources	12.1 Restructuring the physical environment 12.5 Adding objects to
Time constraint				

Code	Theme	Sub theme	TDF domain	Selected BCT
Contradiction between the business and clinical responsibilities				the environment
CPs feel/ are isolated			Goals	1.2 problem solving
Lack of self-confidence Identifying IPA does not work with CPs' clinical competence			Beliefs about capabilities	15.1 Verbal persuasion about capability
Fears of taking responsibility to interfere inappropriate medications			Beliefs about Consequences	5.6 Information about emotional consequences 9.3 Comparative imagining of future outcomes
CPs focus on minor triggers *e.g.,* side effects			Skills	8.1 Behavioural practice/ rehearsal
The analgesics are not well-documented		Analgesia barriers	Environmental context and resources	12.1 Restructuring the physical environment
Complexity of analgesia			Skills	8.1 Behavioural practice/ rehearsal
Patient's prescription and PMR		**Facilitators** Health system facilitators	Environmental context and resources	12.1 Restructuring the physical environment 12.2 Restructuring the
Having conversation with patient to understand the situation				

Code	Theme	Sub theme	TDF domain	Selected BCT
Control drugs CD checklist				social environment
Benefit of reclassification (pregabalin and gabapentin)				
Providing more of GP pharmacists				
Contractual agreement to stop inappropriate prescribing as CPs' role			Reinforcement	10.1 Material incentive (behaviour) 10.2 Material reward (behaviour) 10.10 Reward (outcome)
Patient's trust in CPs to stop IPA		Patients facilitators	Social influences	12.2 Restructuring the social environment 3.1 Social support (unspecified)
Good relationships with GPs		GP facilitator	Social influences	12.2 Restructuring the social environment
Patients' regular visiting to the community pharmacy		CPs facilitators	Environmental context and resources	12.1 Restructuring the physical environment 12.2 Restructuring the social environment
New prescription of analgesics		Analgesia facilitator	Environmental context and resources	7.2 Cue signalling reward
CPs need to be incentivised *e.g.,* remuneration		**Motivation**	Reinforcement	10.1 Material

Code	Theme	Sub theme	TDF domain	Selected BCT
				incentive (behaviour) 10.2 Material reward (behaviour) 10.10 Reward (outcome)
Cooperation between healthcare professionals			Environmental context and resources	12.1 Restructuring the physical environment 12.2 Restructuring the social environment
CPs believed that tackling IPA is a part of their role as CPs	**Capability of CPs**		Social/professional role and identity	13.1. Identification of self as role model
Trained enough to identifying IPA			Skills	8.1 Behavioural practice/ rehearsal 8.3 Habit formation
Their pharmacology/therapeutics knowledge			knowledge	5.1 Information about health consequences

Table 5-6. *Inductive codes and themes mapped to the TDF domains and BCTs.*
CP: community pharmacists, IPA: inappropriately prescribed analgesia, PMR: patients' medical record.

5.10 Discussion

The findings of this Chapter identified many determinants (barriers and facilitators) from the perspectives of CPs about being involved in addressing IPA. CPs believed that the most effective way to detect inappropriate prescriptions was by having a conversation with patients about their medications and disease condition. However, the lack of access to patient's medical records was the main barrier that impacted CPs' confidence in making decisions about patients' treatment. The other four most significant barriers reported were the conflict between clinical and business responsibilities in community pharmacies, GP's resistance to pharmacists interfering with patients' treatment, patients' fear of stopping their painkillers, and professional isolation.

The study used the TDF to better understand the barriers and facilitators of tackling IPA. Mapping these to appropriate BCTs was undertaken to help design future interventions aiming to support CPs in this role. Nine TDF domains were mapped to barriers to addressing IPA in community pharmacies. Most of the barriers mapped to the 'Environmental context and resources' and 'Social influences' domains which were then linked to BCTs to address these.

A barrier significantly mentioned by CPs was the lack of adequate patient information (TDF domain 'Environmental Context and Resources') to make a decision about the appropriateness of medications. Pharmacists had little confidence in their ability and found it difficult to decide about patients' medications. An identified BCT to address this restructuring of the (physical/social) environment, could be providing a centralised system for sharing patient information between healthcare professionals. This intervention will help CPs have full medication history, improve their confidence and potential to get involved. This barrier has been identified in a previous study conducted in Ireland and was mapped to the same TDF domain 'Environmental Context and Resources'. (158)

Furthermore, another barrier listed under the 'Environmental Context and Resources' domain included conflict between the clinical and business responsibilities of community pharmacy. Consistent with this finding, the study by Korenvain *et al.* described that competing priorities between clinical responsibilities, and technical and business responsibilities interfered with the CPs' ability to complete tasks that could stop inappropriate prescriptions. (400) An intervention should target the 'Environmental Context and Resources' domain by (BCT 'adding

object to the environment') offering deprescribing guidelines for analgesic use and education (*e.g.,* lectures, toolkit, or new service) to clearly state the importance of stopping the harmful medications for patient safety. For example, an intervention has been implemented in Scotland, the Chronic Medication Service (CMS) which has been renamed as Medicines: Care and Review (MCR). This service aims to help patients with long term conditions understand their treatment and optimise the benefit of their medications. (414) This structured service prompts and motivates CPs involvement in reviewing and optimising medications.

Several studies have explored the barriers related to CPs' role in optimising opioid therapy for chronic pain and involvement in deprescribing. (158,400,415) Barriers that resonate with our study include: GPs' negative response to pharmacists involvement, patients' fears of changing or stopping their pain medications, and difficulty in identifying who prescribed inappropriate medication. (158,400,415) These barriers mapped to the 'Social influences' domain; therefore, a future intervention should address 'social support' by patients and GPs and integrate working with CPs to maximise their involvement in addressing IPA.

The facilitators to enable the identification of IPA in community pharmacies were talking to patients and patients regularly visiting the community pharmacy, which aligns with 'Environmental Context and Resources' as per previous study findings. (415) Participants emphasised that the reclassification of analgesic drugs has beneficial effects in facilitating the handling of inappropriateness. They described that there has been a notable decrease in the number of inappropriate prescriptions for analgesia since the reclassification of some painkillers (*e.g.,* pregabalin). In 2021, Kurdi assessed and compared opioid and gabapentinoid trends and found that there was a significant increase in gabapentinoids being prescribed as a safer replacement for opioids after the reclassification of tramadol in 2014 from a Schedule 4 to Schedule 3 drug. (416) As a result, risks associated with gabapentinoid misuse and abuse have increased; thereby, gabapentinoids were reclassified as class C in 2019. It is evident that reclassification can be a double-edged sword, and regular evaluation of clinical practice is necessary to prevent the diversion of the use of analgesia as a substitute for one another.

In relation to the 'Social influences' domain, CPs believed that having good relationships with doctors and patients would enable them to be involved in addressing IPA. Our findings suggest there is a need for collaborative relationships to be established between the three main actors; CPs, GPs, and patients. Similarly, the findings of Hansen *et al.* study showed that

improving collaborative relationships between healthcare providers is essential to aid CPs in tackling immediate issues of inappropriate prescriptions. (158) Another study by Keller *et al.* indicated that shared platforms for patient information are needed to increase communication between pharmacists and doctors and improve mutual professional trust between them. (417)

CPs stated that they needed incentivisation to be involved in managing the IPA ('Reinforcement' *e.g.,* remuneration for their extended role). They described that it is not easy to prioritise tackling IPA over financially compensated activities (*e.g.,* dispensing) without payment. Similarly, Alenezi *et al.* reported that the involvement in handling inappropriate opioid prescriptions is not CPs' responsibility, and they needed reimbursement for doing this service. (415) It would be reasonable to suggest an intervention that targets the 'Reinforcement', including detecting and identifying inappropriate prescriptions as a mandatory role of the CPs and making it a reimbursed service.

The capability of CPs theme identified some facilitators to tackle the IPA such as CPs' pharmacology/therapeutics knowledge 'knowledge' and trained 'Skill'. These results seem to be consistent with other research conducted in Ireland, (158) but are contrary to that of Alenezi *et al*. who found that inadequate training on pain management was a perceived barrier to CPs' involvement. (415) Some CPs expressed uncertainties about who is responsible for identifying and determining inappropriate prescriptions. On the other hand, the others had beliefs that tackling this issue was part of their job as pharmacists' Social/professional role and identity'. These results align with those of Hansen *et al.* who described that CPs were uncertain about the optimal place for identification of inappropriately prescribed medications, such as GP practice or community pharmacies. (158) It has been reported that pharmacists are reluctant to work outside of their current responsibilities and to change GP's prescribing decisions (*e.g.,* discontinuing medications). (158)

These results provide insight into the elements required for the development of an intervention designed to involve CPs in addressing IPA. There is a need to provide access to patient information through a centralised system between CPs and GPs. It has been shown that shared patient information enhances collaboration between healthcare professionals. (417) There is also a need to implement some strategies/measures that support the role of CPs in order to minimise the conflict between the business tasks and clinical responsibilities.

These strategies/measures should include radical changes for the pharmacy funding model to be focused on payment for individual patient needs (quality/patient outcomes) rather than being incentives for dispensing a high quantity of medications. Therefore, reimbursement would encourage CPs to become involved in tackling IPA. In the literature, there is an international expansion in pharmaceutical services being funded; many countries have implemented different reimbursement models, such as fee-for-service (CPs are compensated based on the quantity of the services they provide), (418) capitation (CPs will receive a fixed amount regardless of the nature or quantity of services provided, according to the number of patients assigned to them),(419) and blended funding (hybrid). (420) By utilising available remuneration and reimbursement models, pharmacy payment systems can be restructured to promote pharmacy practice and public health. Therefore, structural and organisational changes are required to permit such new services to be incorporated into the routine practice of community pharmacies. (421) The changes may include, in addition to the changes to the pharmacy funding model, hiring more clinically trained staff and providing information to patients about the services.

5.10.1 Strengths and limitations

A key strength of this study is its use of a systematic approach to conducting this research and analysing the interview data. The data analysis was done in three phases: thematic analysis to identify mediators (barriers and facilitators) that affected CPs' behaviour; linking of those mediators to TFD domains, and then mapping the theoretical domains to select potential interventions (BCTs) which are considered to be the 'active components' to be incorporated within an intervention. (422) By using the TDF and the BCTs, this study has identified core components that can be used to design interventions to support CPs' involvement in addressing IPA. Using the COM-B and TDF frameworks to develop the interview topic guide to understand the target behaviour and identify the determinants is considered another strength of this study, which has been applied successfully in previous studies. (423–425) To the researchers' knowledge, this is the first qualitative research using this approach for a behaviour change intervention for CPs to tackle inappropriate analgesic prescriptions. Two studies used theory to analyse CPs' perspectives; themes were developed deductively using

the TDF domains. However, those studies did not link findings of those domains to potential interventions (BCTs) to change the clinical practice in community pharmacies. (158,415)

This study does also include some limitations. First, a limitation of this study is that it specified barriers and facilitators from the perspective of CPs only. CPs often indicated the need to involve other healthcare providers (*e.g.,* GP doctors) in facilitating their role. Accordingly, knowing the perspective of other stakeholders is essential for a deep understanding of the factors influencing any changes in behaviour for involving CPs. Moreover, this study was mainly limited to CPs in the North East England and recruiting pharmacists from a wider geographical area is needed. Finally, we acknowledge that a convenience sampling approach does have certain limitations; this sampling technique was chosen because of the COVID-19's impact.

5.10.2 Future research

Developing a behaviour change intervention to improve the involvement of CPs in the identification and tackling of IPA is a key area for future research. Intervention development should be co-designed with patients and the healthcare professionals who will be affected by the intervention. Therefore, future work should investigate healthcare professionals' and patients' views about barriers and facilitators for tackling IPA. The results of the studies may help shape future interventions or guidelines/policies for integrating CPs to help reduce IPA. CPs expressed a desire for more support and collaboration to encourage them to be part of tackling the analgesia issue. Future work should also examine which suitable collaboration could be provided and how to motivate healthcare professionals to do so.

5.11 Conclusion

CPs expressed mixed perceptions and experiences about being involved in addressing inappropriate prescriptions as part of their daily practice, but they stated that social and environmental barriers need to be addressed to enable them to do so effectively. The study showed that providing shared platforms of patient information can promote the role of CPs in dealing with inappropriately prescribed analgesics. Previous experiences with the GPs can negatively influence CPs' expectations and may deter their involvement in identifying the

inappropriate prescriptions; therefore, the collaboration between CPs and GPs needs to be improved. The present study findings indicate that there is a need to change the current funding model in which payment is based on quantity rather than quality for greater involvement of CPs in tackling IPA.

Chapter 6 General discussion and conclusion.

6.1 Summary

This final Chapter summarises and discusses the key findings presented in the individual study Chapters. Further, it discusses limitations and future research directions that could aid in tackling the issue of gabapentinoid misuse in patients with neuropathic pain.

6.2 General Discussion

Gabapentinoids have been shown to be effective in the management of neuropathic pain. In Chapter 2 of this thesis, the efficacy outcomes of moderate or substantial pain relief were assessed. (175) It was found that gabapentin and pregabalin were more effective than placebo (≥ 30% and ≥ 50% pain intensity reduction). (426) In addition, some efficacy outcomes have been reported for the PGIC much or very much improved that revealed that gabapentinoids having a superior benefit compared to placebo. (426) Despite gabapentinoids possessing a favourable safety profile, misuse and abuse of gabapentinoids has increased significantly, putting at risk patients who need long-term treatment. This is likely caused by the practice of avoiding the prescribing of opioid analgesics that have been found to be ineffective in the management of neuropathic pain. (100) Despite extensive research focusing on gabapentinoids as effective treatments for neuropathic pain, further studies need to be conducted on their abuse and misuse potential. (427) Therefore, this thesis aims to identify the safety profile of gabapentinoids, including adverse events and abusive potential, in the management of neuropathic pain. It also investigated the potential role of the CPs in tackling this issue.

6.2.1 Summary of findings

Four categories of key findings of this thesis are outlined below.

6.2.1.1 The safety profile and the abusive potential of gabapentinoids

The systematic review and meta-analysis (Chapter 2) provided a comprehensive summary of adverse events reported during the use of gabapentinoids for the management of neuropathic pain. The analysis was conducted by categorising the adverse events in accordance with the body systems and the type of gabapentinoids administered (pregabalin or gabapentin).

Based on the findings of Chapter 2, compared to placebo, the adverse events associated with pregabalin are greater than with gabapentin. However, there have been more pregabalin studies included than gabapentin, therefore more participants were included in pregabalin studies who may have experienced more adverse events. Most of those adverse events were

related to nervous system disorders (*e.g.,* dizziness, somnolence, amnesia) or psychiatric disorders (*e.g.,* confusion). However, the subgroup analyses of gabapentinoids indicated no statistically significant differences between pregabalin and gabapentin in terms of adverse events. Compared with a placebo, gabapentinoids were associated with a high rate of patient withdrawal due to adverse events.

The misuse and abuse of gabapentinoids in the treatment of neuropathic pain is an obvious problem. In recent years, the misuse and abuse of gabapentinoids have risen rapidly and is now considered as a worldwide problem. (98,103) Even so, there is no clear evidence from Chapter 2 indicating that gabapentinoids have an abusive potential in neuropathic pain patients with no previous opioid addiction. This outcome may be due to the lack of studies that have assessed the addictive potential of gabapentinoids in patients with neuropathic pain. Therefore, there is a need for further studies to investigate the abusive potential, particularly pregabalin, in chronic pain as well as the mechanisms underlying these unwanted effects. However, the limitation of this study will be discussed in the next Section 6.2.2.1.

Several publications have reported that the misuse of pregabalin was higher than the misuse of gabapentin. (127,132,428) The experience of euphoria following treatment with these medications is one of the reported adverse effects that may explain the reason for gabapentinoid abuse. The use of pregabalin for neuropathic pain was reported to be associated with euphoria in only 21% of the included RCTs. In contrast, no gabapentin studies have reported that gabapentin may cause euphoria as an adverse event. This is consistent with a previously published meta-analysis by Zaccara *et al.* who reported euphoria adverse event with pregabalin occurred in approximately 5% of all patients. (236) Additionally, there is a most interesting finding reported by Schjerning *et al.* which was that euphoria seems to be a dose-dependently adverse event associated with using pregabalin, occurring regardless of its indication and previous abuse history. (129) The experience of euphoria may be the main trigger that leads some patients to take a high dose of pregabalin. (129) The reason behind the higher ability of pregabalin to produce euphoria can be explained by the linear pharmacokinetics of pregabalin, which implies that plasma concentrations increase with increasing dose. (239) In comparison to gabapentin, pregabalin has a 3-fold greater rate of absorption. (117) Additionally, orally administered pregabalin undergoes rapid absorption and

reaches a peak plasma concentration within 1 hour, whereas gabapentin takes up to 3 hours. (117,129)

Despite Chapter 2 reported the adverse events of gabapentinoids on the nervous system, no evidence has been found to support the possibility of gabapentinoids addiction. In light of these findings, further studies investigating the abuse potential of gabapentinoids are urgently required.

6.2.1.2 Interaction between gabapentinoids and opioids

However, there is a growing body of evidence suggesting that gabapentinoids are misused by patients using the drug concurrently with opioids where opioids are being misused. (98,128,429) Patients with opioid addictions were more likely to abuse pregabalin (3-68%) than gabapentin (15-22%). (98) According to the findings from Chapter 2, no study in the meta-analysis allowed concomitant opioid use during the study period; therefore, the effect of the opioid and gabapentinoid combination could not be evaluated.

The self-administration experiment is considered the "gold standard" animal model for studying drug addiction as it represents human behaviour of drug seeking and addiction. (248,249) Thus, the *in-vivo* pregabalin self-administration study (Chapter 3), was conducted to examine whether pregabalin has a reinforcing effect following exposure to the self-administration of morphine. It is interesting to note that reinstatement data (n=4) showed a significant difference between active and inactive lever presses, suggesting that pregabalin was able to maintain self-administration behaviour when substituted for morphine. It is evident from this study that pregabalin may have reinforcing properties, particularly when opioid abuse is present. However, this conclusion is based on an experiment on *naïve* rats only.

A recent study was conducted on patients with neuropathic pain associated with spinal cord injury who did not have a history of substance abuse and reported that gabapentinoids were misused. (245) It was found that pregabalin was more misused (81.9%) than gabapentin (66.69%). (245) Therefore, there was a plan to conduct a neuropathic pain model to investigate the notion of whether gabapentinoids are misused due to neuropathic pain.

Unfortunately, it was not possible to conduct the neuropathic pain model in this thesis due to a technical issue related to the used equipment.

6.2.1.3 Analgesia misuse and CP-led interventions

It is important to understand the approach taken by CPs to deal with the issue of the misuse of gabapentinoids. It was decided to conduct a state-of-the-art review and narrative synthesis of current evidence investigating CP-led interventions in this regard. However, there have been no studies in the literature that explore the misuse of gabapentinoids and pharmacist-led interventions. Consequently, the second review (Chapter 4) was conducted to examine analgesic misuse in general. This review found six research studies investigating CP-led interventions to address the misuse and abuse of analgesic medications. These studies were undertaken in the USA and Northern Ireland; therefore, the findings may not be representative of or transferable elsewhere.

The BCW was used in Chapter 4 to provide a conceptual framework for understanding interventions and determining their implications, especially in the absence of detailed information about the intervention. Therefore, the reported interventions were coded to the BCW components from the perspective of changing the behaviours of pharmacists and patients. This approach provides researchers and decision-makers with some evidence and strategies related to intervention design and implementation that can be developed and refined to be studied in other healthcare settings in the future.

From Chapter 4, the common aim of the provided interventions was the identification of potential abusers and misusers of prescribed analgesics, with other roles involving patient education, long-term management, prevention, and referrals. However, insufficient description of these interventions limits their evaluability, contribution to the evidence base, and potential future adoption. Despite this, most reported interventions included elements of "education" for: pharmacists to prepare them to be involved and patients to learn about the analgesia misuse. As an example of an education intervention, the PROvider of Continuing Education for Medical Professionals (ProCE) launched the Opioid Stewardship® programme in 2020 to tackle the opioid misuse crisis. (430) The Opioid Stewardship® programme targets all healthcare professionals, including pharmacists, nurses, and physicians. (430) The programme aims to develop a strong understanding of opioids, pain management, opioid use disorder,

and skills to influence the appropriate use of opioids in healthcare or within a community. Furthermore, Opioid Stewardship® focuses on the importance of patient education to enhance their awareness about adverse events and potential opioid abuse. The second example for a patient education intervention is the EMPOWER (Eliminating Medications through Patient Ownership of End Results), a patient-educational booklet to empower and encourage community-dwelling older adults to discontinue inappropriate benzodiazepine prescriptions. (431) By providing evidence-based information, they can make a more informed decision regarding whether medication overuse is safe and effective. (431) It is possible to reduce analgesic misuse through interventions such as these that educate both healthcare professionals and patients.

Another intervention function featured highly across the reported interventions was “environmental restructuring” which aimed to change the pharmacist's and/or the patient's behaviour. In this regard, pharmacists' experiences in addiction care have been evaluated, and pharmacists have expressed the need for better relationships and collaboration between health professionals working in this field. (314) Another study showed that CPs' siloed work limits their clinical capabilities. (147)

There is no disputing the importance of better integration with other healthcare services, and future interventions should be developed based on the healthcare system rather than isolated community pharmacy sectors. In doing so, the role of a pharmacist can be designed into an intervention in a more realistic, feasible and appropriate manner by engaging all stakeholders, including physicians, and patients. Using appropriate implementation strategies and theories to facilitate this multidisciplinary approach is also essential. For example, an intervention for improving appropriate polypharmacy in the elderly has been developed using TDF and BCTs, where the authors involved physicians and pharmacists in designing this intervention. (315,316) Therefore, interventions to address this analgesia misuse should be based on a multifaceted approach that targets the behaviours of pharmacists and patients. It is also essential to address the issue more effectively by developing a framework that can facilitate the design of evidence-based and theoretically based interventions.

6.2.1.4 The involvement of CPs in addressing IPA

Patients with chronic pain, particularly those with neuropathic pain, are more likely to misuse analgesic drugs as a result of inadequate pain management. (308) As a first step toward improving analgesia use and reducing their harm, is the identification and determination of IPA. Pharmacists are in a unique position to help handle medication-related problems, such as IPA, since they are the last line of defence before medications reach a patient. There is an acknowledgement that pharmacist-led interventions were limited and not fully described; (338) this indicates that the role played by pharmacists in reducing IPA remains unknown. The role of pharmacists in addressing IPA can be better understood by understanding their opinion regarding barriers and facilitators in their involvement to tackle IPA.

In Chapter 5, the TDF was employed as a “theoretical lens” where the main feature of the TDF is to provide comprehensive theoretical coverage of potential influences on behaviour. (339,432) It has been found that TDF-based data collection approaches elicited beliefs not identified in studies without a theoretical underpinning. (339) The TDF domains have been developed mainly to identify the barriers and enablers of professional behaviour change. (302) Using the TDF has successfully identified the determinants of various health behaviours assessed through interviews and focus groups. (363,364) However, the application of the TDF for analysing the data could lead to making the study restrictive to TDF domains, and the important influences and determinants that do not fit within these domains could be neglected. The inductive thematic analysis, therefore, was used to ensure that the identification of other factors not related to the TDF are not omitted. (432) The analysis approach used in the qualitative study (Chapter 5) provides a more comprehensive understanding of barriers and facilitators for tackling IPA in the community pharmacy setting, which in turn allows researchers to develop evidence-based interventions based on a theoretical understanding of the targeted behaviour.

CPs interviewed in Chapter 5 mentioned that talking to patients about their medications was the most efficient way of identifying inappropriate prescriptions. Nevertheless, CPs reported numerous barriers that affect their experience and perspective of tackling IPA. The main barrier cited by CPs was the lack of access to patients' medical records. Insufficient patient information played a vital barrier in CPs' confidence in making decisions about the

appropriateness of patients' medications. CPs believed this barrier made them uncomfortable for interfering with patients' pain medications in an isolated environment. The identified BCT to address this (the restructuring of the “physical/social” environment) suggests implementing a centralised data-sharing system for healthcare professionals. By using this centralised system, healthcare professionals can ensure that patient data is kept updated regularly, providing an effective means of seamless sharing and collaboration.

In 2014, the German Federal States of Saxony and Thuringia launched ARMIN (Arzneimittelinitiative Sachsen-Thüringen) at a regional level. The ARMIN is an interprofessional, electronically supported project for tackling polypharmacy and its consequences. (433) Several datasets have been developed and integrated into local software, and a technical infrastructure has been developed to facilitate the electronic exchange of medication information between physicians and community pharmacies. (433) Despite the fact that this intervention is implemented in some areas, it can provide the CPs with the needed information to facilitate their decision regarding the appropriateness of prescribed medication. In the UK, it has been recommended that there is a need to make changes to improve the system to combat overprescribing issues. (434) This includes improving access to patients' medical records for all healthcare professionals across care settings. It has been pointed out that centralised systems seem to be hard to build as ineffective secure ways to share information. (435) Recently, the UK has had a national movement toward granting community pharmacists access to GP records. (436) It is anticipated that CPs will be able to access and add to patient medical records currently maintained by GPs by the end of 2023. (436) GPs and CPs must cooperate more closely to support this initiative, which includes sharing patient records between the two professions. As part of the new funding and to make sure patients receive the best care possible, the NHS will invest substantially in improving the digital infrastructure between GPs and community pharmacies in order to make this possible. The plan stated that "*the NHS England will work with community pharmacy suppliers and general practice IT suppliers to develop and deliver interoperable digital solutions*.". (437) Doing so will facilitate referrals and allow additional access to patient's clinical information from the GP record. In addition, it added that pharmacists will be able to "*share structured updates quickly and efficiently following a pharmacy consultation back into the GP patient record*." (437) However, it is essential to ensure that patient safety and confidentiality remain

a priority when implementing the plan for sharing medical records between GPs and community pharmacies. (437) Patient satisfaction and experiences with the NHS are expected to be improved by removing the need to repeat the same information to multiple healthcare professionals due to sharing records, as every professional involved in the patient's care will have access to allergy, medication, and diagnosis information.

Another barrier that made CPs reluctant was the conflict between the clinical and business responsibilities in community pharmacy. Most CPs stated patients' best interests were connected to activities associated with providing patient care, such as reviewing and checking medication safety before dispensing them. In contrast, business responsibilities were connected to generating revenue. In light of this, they felt that involving community pharmacies in addressing inappropriate prescriptions would put them in a paradoxical position when considering recommendations for stopping any medication. This barrier has been reported by Korenvain *et al.* where the conflict between clinical and business responsibilities affected the CPs ability to stop inappropriate prescriptions. (400) Therefore, an intervention (BCT 'adding object to the environment') needs to provide deprescribing guidelines for analgesic drugs and education (*e.g.,* lectures, toolkits, or new services) to clarify the importance of stopping harmful medications for patient safety. The RPS in Scotland recommended in 2021 that the existing services in community pharmacy (*e.g.,* new medications/high risk medication services) should be expanded to include drugs with potential dependence and misuse so that education can begin at the point of prescribing and dispensing processes. (153) This recommendation has been raised to emphasise the role that can be played by CPs to decrease harm and prevent drug-related deaths. (153) By providing this intervention, CPs will be able to contribute effectively to addressing analgesic misuse. The MCR is also an intervention that has been provided in Scotland. The MCR has been implemented to assist patients with long-term conditions in understanding their medications and optimising their benefits. (414) This structured service encourages the involvement of CPs in reviewing and optimising medications for those patients.

Furthermore, there are other barriers identified by CPs, including the refusal from the GPs to pharmacist involvement, patients' fears, and the difficulty of identifying who prescribed IPA. For these barriers to be overcome, a future intervention should focus on collaboration between patients, GPs, and CPs. By doing so, the maximum benefit from the involvement of

CPs in addressing IPA will be achieved. There is not yet an effective method for collaborating and understanding each other's roles. However, an excellent example of an intervention which includes better collaboration between GPs and community pharmacies is the Discharge Medicines Service (DMS). The DMS has been commenced in February 2021 as a new essential service for community pharmacies by NHS England and NHS improvement. (438) This service is intended to improve effective communication and collaboration between secondary and primary care regarding any changes made to a patient's medication in the hospital, resulting in better patient care and reduced readmissions to the hospital. (438) Despite this, there is no dedicated IT system developed for this service where the referrals to community pharmacies should be made using any secure electronic platform (*e.g.,* PharmOutcomes, Refer to Pharmacy, or NHS email). (439) It is, therefore, recommended that the IT systems need to be interoperable between hospital and community settings for better seamless work. (439) Interestingly, this service will be provided to patients who use potentially abusive medications, such as opioids. This service will enable those patients to take their medications more responsibly and safely through a confidential discussion regarding the condition being treated, the prescribed medication regimen, and how the medication can be administered in order to maximise benefits and minimise side effects.

Having good relations with doctors and patients enabled CPs to be involved in addressing IPA. Accordingly, CPs stated that it is important and worthwhile to invest time in building relationships with primary care physicians. Chapter 5 findings suggest that there is a need for a collaborative relationship between the three principal factors; CPs, GPs, and patients. It was found that by Hansen *et al*. it is necessary to improve collaborative relationships with healthcare providers in order to help CPs address immediate issues resulting from inappropriate prescriptions. (158) CPs also expressed a need for incentives so that they would be more motivated to participate in addressing IPA. In the same vein, Alenezi *et al.* cited that pharmacists require reimbursement for their involvement in inappropriate opioid prescriptions service. (415) As identified in this study, it is challenging to prioritise IPA over financially compensated activities when no compensation is received. An intervention targeted at the “Reinforcement” of prescriptions would be reasonable, including identifying and detecting inappropriate prescriptions as one of the mandatory roles of CPs and doing it as a reimbursed service. In 2018, a systemic review was conducted about GPs' perception of

extended community pharmacy services and pharmacists' roles in the UK. (440) This review demonstrated the need to promote collaboration between CPs and GPs to improve integration between primary care. (440) It was found that GPs tended to be more cautious and that the collaboration between CPs and GPs remained poor despite expanding services, which required additional communication. (440) Also, it has been reported existing remuneration models will need to be revised to incentivise service quality and the alignment of outcome measures used for GP and community pharmacy contractual arrangements. This will provide better integration of GP and community pharmacy services. (440) In addition, CPs expressed enthusiasm towards the extended services; however, their responsibilities were unclear to both patients and GPs due to the absence of clearly defined roles, which allowed for services to be considered as crossing the boundaries of GPs. (440)

When asking the CPs about their capability to participate in identifying IPA, they indicated that they have pharmacology/therapeutics knowledge and are well-trained; therefore, they are capable to handle the IPA effectively. Interestingly, these findings are consistent with other research conducted in Ireland (158). In contrast, Alenezi *et al.* found that inadequate training on pain management was perceived as a barrier to CPs participation. (415) Alenezi *et al.* highlighted an important point, which is a lack of pain management education provided to medical students. (415) Therefore, training curricula need to be reviewed to meet the NHS's goal of allowing pharmacists to play a productive role in patient-centred care. The General Pharmaceutical Council has addressed this issue by revising the initial education and training standards for pharmacists in 2021. (441) A key goal of this revision was to make sure that pharmacy services users received high-quality care. The revision introduced a new set of learning outcomes encompassing five years of education and training. The main change features involved the application of the science behind pharmacy in clinical practice, focusing on the required skills for current and future roles (*e.g.,* clinical judgement, management of risk, and diagnostic and consultation skills). (441) Besides strengthening supervision support, a collaboration between higher education institutions, statutory educational bodies, and employers has been added. (441) By meeting these new learning outcomes, newly qualified pharmacists will be equipped with the skills and confidence to deliver the clinical services that patients and the NHS expect and work in a multidisciplinary manner. Additionally, pharmacists

can become independent prescribers upon registration. Doing so will enable future pharmacists to contribute significantly to patients' clinical care.

A noteworthy finding is that the reclassification of some analgesic drugs contributes to the reduction of inappropriate prescriptions. As a result of the reclassification of certain painkillers (*e.g.,* pregabalin and gabapentin), the number of inappropriate prescriptions for analgesia has decreased significantly. A study published in 2021 examined and compared opioid and gabapentoid trends, had found that gabapentinoids have become safer alternatives to opioids since tramadol was reclassified as a Schedule 3 drug in 2014. (416) This has increased the risk of gabapentinoids being misused and abused; as a result, gabapentinoids were reclassified in 2019 as class C. Reclassification action can be a double-edged sword; therefore, regular evaluation of clinical practice is essential to avoid the diversion of the use of analgesia as a substitute for one another.

6.2.2 Study limitations

With any PhD project, there are several limitations related to design, time, resources, as well as the impact of lockdowns during the COVID-19 pandemic. Each of these factors had an impact on this thesis in some way and must be taken into consideration.

6.2.2.1 The impact of COVID-19 and public lockdown

It was not possible to complete some studies that were intended to contribute to this thesis because of the restrictions imposed by the lockdowns due to the COVID-19 pandemic. There has been an unprecedented impact on academic research because of this pandemic. It has resulted in libraries closing, field sites not being accessible, productivity being reduced, morale being low, priorities being rearranged, and entire research projects being questioned. As a PhD researcher during this period, these changes had a profound impact on my research.

1- ***In-vivo* study:** Consequently, 12 rats were culled in March 2020 after the restrictions and lockdowns, and the next experiment was delayed by six months.
2- **Clinical study:** There was a plan to conduct a retrospective review of general practice computer records of patients who had been prescribed gabapentinoids to manage

neuropathic pain. In light of the COVID-19 outbreak, GPs were extremely busy and overloaded; thus, this research was changed.

A qualitative study was also planned to explore the perspectives of prescribers on deprescribing IPA. The study was approved ethically, but due to the pandemic and a poor response from the GPs, it was not possible to complete it. Currently, these studies are being considered for future directions.

6.2.2.2 The systematic review and meta-analysis (Chapter 2)

The outcomes of this review are solely based on the analysis of data retrieved from RCTs. In spite of the ethical requirement to report adverse events during RCTs, these results indicate that RCTs may not be sufficiently powered to detect adverse events; therefore, cannot provide solid evidence to support the safety of gabapentinoids. It is important to note that the included RCTs were relatively short in duration (maximum 20 weeks), which may have limited the possible occurrence of relatively rare adverse events (*e.g.,* addiction and misuse disorders). Additionally, no subgroup analysis was performed to assess the risk at different doses of gabapentinoids or in various types of neuropathic pain, as the primary aim was to evaluate the comprehensive tolerability and safety profile of gabapentinoids. Finally, this review was limited to English-language papers, so non-English-language articles might have been overlooked.

6.2.2.3 The *in-vivo* experiment (Chapter3)

The main limitation of this Chapter's findings is that it is limited to *naïve* rats. The second experiment (self-administration with the neuropathic model) was not conducted due to the loss of self-administration equipment that had been transferred to another institution outside of the UK before starting the neuropathic experiment. It would have been ideal to compare the findings of the self-administration experiment in *naïve* rats with the neuropathic pain model and correlate the findings of the extinction phase, but the loss of equipment, unfortunately, prevented such a comparison. It should also be noted that only a few rats acquired drug-seeking behaviour, thus requiring further studies with a larger number of animals.

6.2.2.4 State-of-the-art review of CP-led interventions (Chapter 4)

It is worthwhile to mention that there is a limited number of studies included in the review, and no studies about pharmacist-led interventions in the UK have been found. Additionally, there are a variety of pharmacist-led interventions that are neither adequately described nor evaluated. This means that these interventions cannot be evaluated, they contribute little to the evidence base, and they have limited potential for adoption.

6.2.2.5 The qualitative study (Chapter 5)

A limitation of this study is that it focused solely on barriers and facilitators experienced by CPs. Further, this study was mainly limited to CPs in North East England in the UK and recruiting pharmacists from a broader geographical area is needed. CPs suggest involving other healthcare providers (*e.g.,* GP physicians) to facilitate their role. In this regard, knowing the perspective of other stakeholders is essential for a thorough understanding of the factors impacting the involvement of CPs in addressing analgesia misuse issues. It must be acknowledged that convenience sampling has certain limitations; however, this sampling approach was chosen because of the COVID-19 impact.

6.3 Conclusion

Patients with neuropathic pain who are managed with gabapentinoids might suffer some adverse events which were mild to moderate in severity. There was no evidence that gabapentinoids led to addiction in RCTs despite the adverse events of gabapentinoids on the nervous system. The only reported adverse events that may be associated with the abusive potential of gabapentinoids was euphoria which was reported at the therapeutic dose range for pregabalin, but not gabapentin. The *in-vivo* study resulted that pregabalin might have reinforcing properties when substituted for morphine in *naïve* rats.

Due to the limited evidence of community pharmacy-led interventions to address medication misuse, the perspectives and experiences of CPs in identifying IPA were explored. CPs expressed mixed perceptions and experiences about being involved in tackling this issue as part of their daily practice. To better involve CPs in addressing IPA, this work suggests that there has to be a shift in the reimbursement model that focuses on payment for individual patient needs rather than incentives for dispensing a high quantity of items. Collaboration between healthcare professionals is also believed to be easier if patient medical information is shared.

6.3.1 Future research

This thesis provides an evidence base to inform future research that aims to investigate the interaction between gabapentinoids and opioids in the management of neuropathic pain, as well as enhance the role of CPs in tackling the misuse of analgesia with chronic pain.

Pre-clinical studies

There is no doubt that the drug self-administration model is one of the most powerful experiments used to study drug addiction and drug-taking behaviour (reinforcing efficacy). (248,249) This model, in comparison with other addictive models, has excellent face validity and is capable of producing the most direct point-to-point correspondence with addictive behaviour experienced in the natural environment.

The key finding from Chapter 3 demonstrates that pregabalin may have a reinforcing efficacy when substituted for self-administered morphine in *naïve* rats. Furthermore, there is evidence that gabapentinoids are misused in patients with neuropathic pain associated with spinal cord

injury who have no history of substance abuse. (245) Therefore, in the future, the pregabalin self-administration experiment will be conducted on *naïve* rats and neuropathic pain model to test the role of neuropathic pain in drug-seeking behaviour.

Clinical studies

It is important to mention that the meta-analysis findings (Chapter 2) in this thesis were limited to RCTs. This indicates that the included RCTs are not sufficiently long and powerful to detect relatively rare adverse effects, such as addition or gabapentinoids misuse. Therefore, it would be reasonable to suggest conducting large-high-quality trials to confirm the abusive potential of gabapentinoids in patients with neuropathic pain. In spite of this, the available observational evidence concerning the misuse of gabapentinoids does not specifically address neuropathic pain. (132,335) It may be worthwhile to conduct observational studies since they are longer in duration and more closely related to clinical practice than RCTs.

Developing a behaviour change intervention to improve the involvement of CPs in addressing and tackling of IPA would be a key focus of future research. Therefore, the presented work (Chapter 4 and 5) will be helpful in identifying CP-led interventions to handle IPA. To gain a better understanding of this topic, future research should examine barriers and facilitators from the perspective of healthcare professionals and patients. The development of an intervention should be co-designed with patients and healthcare professionals who will be affected by this intervention. Patient involvement in the design process and planning phase has been recommended by the Design Council of the UK. (442) This is a first step toward developing future interventions with the involvement of those impacted by it. It is essential to highlight that community pharmacists' involvement in addressing analgesia misuse needs action relies on higher authority due to the need to invest in staffing and resources, so co-designing with patients is a crucial first step that will shape and develop subsequent actions. Additionally, further studies are needed to explore the perspectives of commissioners and policymakers to determine the feasibility of the quality payment structure proposed by the thesis findings. The findings of this work may help shape future interventions or guidelines/policies for integrating CPs to help decrease IPA.

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REVIEW ARTICLE

The safety and efficacy of gabapentinoids in the management of neuropathic pain: a systematic review with meta-analysis of randomised controlled trials

Jawza Meaadi[1,2,3] · Ilona Obara[1,2] · Sam Eldabe[4] · Hamde Nazar[1,5]

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Abstract

Background There are increasing concerns regarding the abusive potential of gabapentinoids putting at risk patients with neuropathic pain requiring long-term pain management. The evidence to support this is rather inconcusive.

Aim This systematic review aimed to evaluate the safety and efficacy of gabapentinoids in the management of neuropathic pain with a focus on randomised controlled trials (RCTs) and categorising the side effects according to the body systems they were affecting.

Method Searches were conducted in MEDLINE (PubMed), EMBASE, Web of Science, PsycoINFO, and CINAHL (EBSCO), and included RCTs to identify and critically appraise studies investigating safety and therapeutic effects of gabapentionoids in adults with neuropathic pain. Data extraction was conducted using an established Cochrane form and the risk-of-bias tool was used in the assessment of quality.

Results 50 studies (12,398 participants) were included. The majority of adverse events pertained to the nervous system (7 effects) or psychiatric (3 effects) disorders. There were more adverse effects reported with pregabalin (36 effects) than with gabapentin (22 effects). Six pregabalin studies reported euphoria as a side effect, while no studies reported euphoria with gabapentin. This was the only side effect that may correlate with addictive potential. Gabapentioids were reported to significantly reduce pain compared to placebo.

Conclusion Despite RCTs documenting the adverse events of gabapentionoids on the nervous system, there was no evidence of gabapentinoid use leading to addiction, suggesting an urgent need to design studies investigating their abusive potential.

Keywords Gabapentin · Meta-analysis · Neuralgia · Neuropathic pain · Pregabalin · Systematic review

Impact statements

- This systematic review and meta-analysis identified, for the first time, that the majority of adverse events with gabapentinoids were associated with their effect on the nervous system.
- Based on included RCT outcomes, there is no evidence of gabapentinoid use (maximum 20 weeks) leading to addiction, suggesting the need to design studies investigating their abusive potential.
- Critical appraisal of included RCTs indicated that gabapentinoids are effective in reducing neuropathic pain in adults.

✉ Ilona Obara
ilona.obara@ncl.ac.uk

1 School of Pharmacy, Faculty of Medical Sciences, Newcastle University, King George VI Building, Newcastle-Upon-Tyne NE1 7RU, UK

2 Translational and Clinical Research Institute, Newcastle University, Newcastle-Upon-Tyne, UK

3 King Saud Medical City, Riyadh, Kingdom of Saudi Arabia

4 Department of Pain and Anaesthesia, James Cook Hospital, Middlesbrough, UK

5 Population Health Sciences Institute, Newcastle University, Newcastle-Upon-Tyne, UK

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Introduction

The Neuropathic Pain Special Interest Group (NeuPSIG) has recommended antiepileptic drugs to manage neuropathic pain [1]. Accordingly, the United States (US) Food and Drug Administration (FDA) has permitted gabapentin treatment for postherpetic neuralgia, while pregabalin is approved for postherpetic neuralgia, neuropathic pain associated with diabetes or spinal cord injury, and fibromyalgia [2]. In the United Kingdom (UK), gabapentin and pregabalin are approved for the treatment of peripheral (both) and central (pregabalin only) neuropathic pain in adults [3, 4]. Gabapentinoids, a collective term for these drugs, have a similar structure and mechanism of action. They target α-2-δ subunit of voltage-gated calcium (Ca^{2+}) channels leading to decreasing Ca^{2+} influx, subsequent neurotransmitter release (e.g., glutamate) that affects pain sensation, and results in a reduction of neuropathic pain [4, 5]. Recently, Goodman and Brett reflected that the rapid increase in prescribing of these therapeutics suggests that these are effective pain medications that are also promoted as alternatives to reduce opioid prescribing [6].

Associated with the rise in gabapentinoid use is a growing conjecture of the abuse liability. However, while there is a lack of convincing or sufficiently powerful evidence to support claims of addictive power in patients with no prior abuse history [7], it is recommended that gabapentinoid use be avoided or used in caution in patients with current or previous substance use disorders [7–9]. There has also been an increase in deaths linked to gabapentinoids which has prompted the Advisory Council on the Misuse of Drugs and the UK government to reclassify gabapentinoids as class C drugs [10–12].

Aim

This systematic review aimed to critically appraise the evidence from randomised controlled trials (RTCs) about the safety, including addictive potential and adverse events, and analgesic efficacy of gabapentinoids to control neuropathic pain in adults. For the first time, the analysis is conducted with a focus on categorising the side effects according to the body systems and the type of the gabapentinoid administered, therefore providing a better understanding of how and which gabapentionoid affects, and potentially compromise, the therapeutic potential and safety of the medication. Our approach has been underpinned by the principles that: (1) RCTs are conventionally considered the 'gold standard' for evidence based medicine, (2) there is an ethical requirement to report adverse effects during RCTs, and (3) RCTs provide quantitative data that are suitable for meta-analysis to provide objective evidence.

Method

Search strategy

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. Protocol methodology was registered as PROSPERO: CRD42019123869. MEDLINE (PubMed), EMBASE, Web of Science, PsycoINFO, and the Cumulative Index to Nursing and Allied Health Literature (EBSCO) were searched up to 28th June 2022. Hand searches through reference lists of key articles were also undertaken. Search terms entered into Web of Science were #1 = ("neuropathic pain" OR neuropath* OR neuralgi* OR "nerve pain"), #2 = (Gabapentin* OR Pregabalin* OR Neurontin OR Lyrica), #3 = (cancer OR neoplasm*), #4 = #1 AND #2, #5 = #4 NOT #3. The keywords used for the other databases included (pregabalin) OR (gabapentin) OR (gabapentinoids) and (neuropathic pain). The search was restricted to the English language, and there was no limitation by date.

Study eligibility

Inclusion criteria

As outlined in Table 1, inclusion criteria were adopted using the PICOS [14] and focused on safety of gabapentinoids to control neuropathic pain.

Table 1 The PICOS elements that framed the inclusion criteria

Participants (P)	Adult patients with neuropathic pain
Intervention (I)	Gabapentinoids (pregabalin or gabapentin) to detail dose, strength, tapering procedure, concomitant medication use, length of exposure, and prior exposure to opioids
Comparison (C)	Placebos or active controls to control neuropathic pain
Outcomes (O)	*Primary outcomes:* Studies were included if they assessed the safety of gabapentinoids to control neuropathic pain *Secondary outcomes:* Analgesic effect of gabapentinoids (≥ 30 or 50% pain intensity reduction) and patient global impression of change (PGIC; much improved and very much or much improved)
Study Design (S)	Randomised controlled trials

Exclusion criteria

Studies that focused on animal or in-vitro studies, or paediatric patients alone were excluded.

Types of outcome measures

Primary outcomes

- Participants who experienced any adverse event especially affecting the central nervous system.
- Withdrawals due to adverse events.
- Serious adverse events.
- Abuse and gabapentinoid misuse disorder.

Secondary outcomes

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) definitions for moderate and substantial benefit in chronic pain studies was followed [15]. These were defined as the proportion of patients who:

- Achieved ≥ 50% pain reduction (substantial).
- Achieved ≥ 30% pain reduction (moderate).
- Reported patient global impression of clinical change (PGIC) as much or very much improved (moderate).
- Reported PGIC as very much improved (substantial).

Study selection

All titles retrieved were reviewed by one author (JM). Two authors (JM and HN) then independently assessed the abstracts against the inclusion criteria. Papers considered as relevant were requested and assessed independently by the two authors for their suitability for inclusion and differences were resolved by discussion with a third author (IO).

Data extraction

Data were extracted into a piloted data extraction form adapted from an established Cochrane version [16]. Two authors (JM and HN) extracted data independently and checked for agreement or discrepancies. A third author (IO) was consulted for additional review where appropriate.

Assessment of methodological quality

The methodological quality of included studies was independently assessed by two authors (JM and HN) as recommended in the Cochrane Handbook for Systematic Reviews of Intervention [17]. The risk-of-bias tool was used for RCTs and applied by both assessors with discrepancies resolved by a third (IO).

Statistical analysis

Meta-analysis was performed to compare the safety and efficacy of pregabalin and gabapentin *vs*. placebo. All the statistical analysis was performed using Review Manager (RevMan) [computer program; version 5.4, The Cochrane Collaboration, 2020].

Statistical heterogeneity among studies was assessed by graphically examining forest plots, and then evaluating the heterogeneity using a chi-square and I^2 tests, with an $I^2 > 70\%$ indicating heterogeneity [18]. The funnel plots were generated to assess the potential impact of publication bias in analyses of ≥ 10 studies [19].

The primary and secondary outcomes were pooled using the Mantel–Haenszel method within a random-effects model and presented as risk ratios (RRs) with the corresponding 95% confidence intervals (95% CIs). Number needed to harm (NNH) and number needed to treat (NNT) were calculated with the corresponding 95% CI to assess the clinical impact of the beneficial or harmful effect of the treatment. NNHs and NNTs were calculated only when the risk ratio was statistically significant.

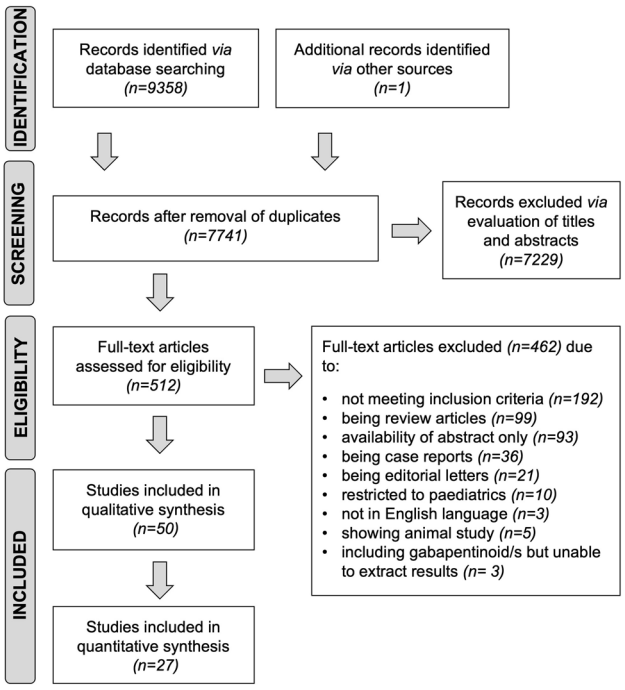

Fig. 1 The PRISMA flow diagram detailing the search results and subsequent stages of screening

Results

Literature search

A total of 9359 titles were identified from the literature search which yielded 512 potentially relevant studies. Further assessment of the abstracts and hand searches led to 50 studies meeting the inclusion criteria (Fig. 1).

Study characteristics

Out of the selected 50 controlled trials, 29 investigated pregabalin [2, 20–47], 16 gabapentin [48–63], and 5 studies assessed pregabalin and gabapentin compared to placebo-controlled trials [64–68]. Half of the included studies were undertaken in USA [29, 33, 35, 36, 39, 42–48, 50–52, 55, 57–60, 62–66]. Smaller numbers of studies were undertaken in India (n = 3) [30, 41, 53], China (n = 3) [2, 21, 23], UK (n = 2) [28, 56], Turkey (n = 2) [67, 68] and Japan (n = 2) [27, 31]. The review also included 1 study from Canada, Netherlands, Iran, Europe, Germany, Australia and Pakistan [20, 24, 38, 53, 61]. Nine studies were international multicentre [22, 25, 26, 32, 34, 37, 40, 49] (Supplementary material Table 1 and 2).

In total, these studies included 12,398 patients randomised to receive gabapentinoids, a placebo or a combination of drugs as comparators. Study sizes ranged from 14 to 804 participants, and the duration of the trials was 4–20 weeks.

As summarised in Fig. 2, pregabalin was used at doses of 150, 300, 450 or 600 mg daily and was titrated from 75 mg daily up to the maximum dose of 300 or 600 mg daily, with titration periods between 1 and 4 weeks.

As summarised in Fig. 3, gabapentin was used at doses of 1200, 1800, 2400 or 3600 mg daily, with titration periods from 1 to 8 weeks.

Additional details of included trials are shown in Supplementary material Table 1 and 2.

Quality assessment of included studies

The quality of studies is illustrated in supplementary material Table 3. Twenty-seven studies appeared to have an unclear risk of bias, while the remaining 23 studies were considered as having a high risk of bias. These studies were excluded from the meta-analysis as has been summarised in the Supplementary material Table 4. There was no clear observable evidence of publication bias among all included studies.

Primary outcomes (safety)

Reported adverse events

Most reported adverse effects pertained to a nervous system (7 effects) or psychiatric (3 effects) disorder. There were more adverse events associated with pregabalin (36 effects) than with gabapentin (22 effects) (Supplementary material Table 5). As shown in Table 2, 18 of 36 (50%) adverse events were statistically significantly associated with the pregabalin group compared to the placebo group, and 4 of 22 (18%) adverse events were significant with gabapentin treatment compared to the placebo. The highest RR (95%

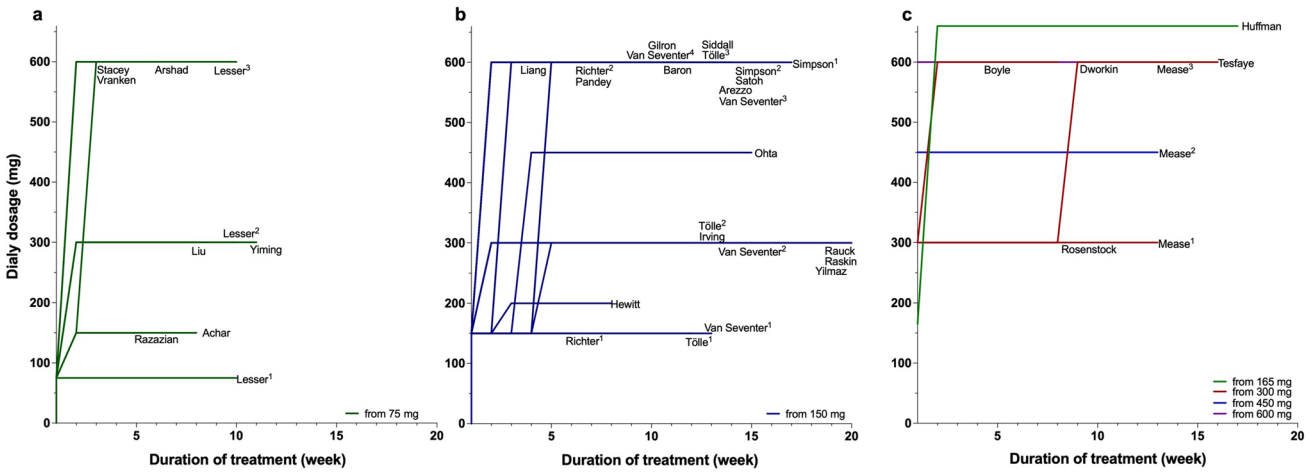

Fig. 2 Starting dose, dose escalation and maximum daily dose achieved in selected studies for pregabalin. **a** Presents data collected for starting dose, dose escalation and duration of treatment from 75 mg. **b** Presents data collected for starting dose, dose escalation and duration of treatment from 150 mg. **c** Presents data collected for starting dose, dose escalation and duration of treatment from 165, 300, 450 or 600 mg. Superscript number 1, 2 or 3 next to the name refers to the arms in the selected study. mg; milligram

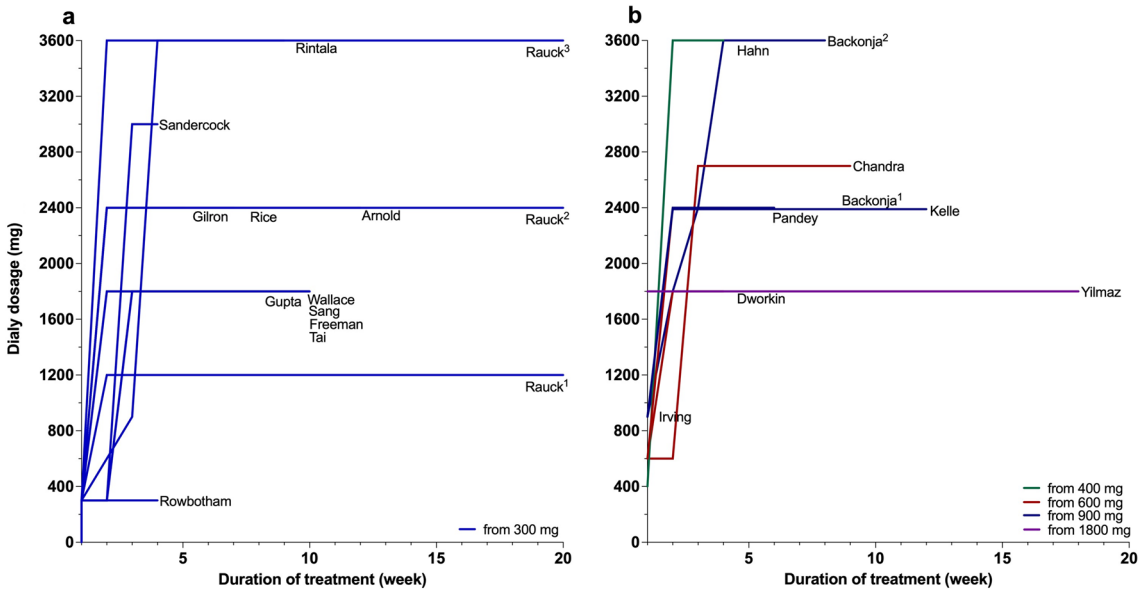

Fig. 3 Starting dose, dose escalation and maximum daily dose achieved in selected studies for gabapentin. **a** Presents data collected for starting dose, dose escalation and duration of treatment from 300 mg. **b** Presents data collected for starting dose, dose escalation and duration of treatment from 400, 600, 900 or 1800 mg. Superscript number 1, 2 or 3 next to the name refers to the arms in the selected study. mg; milligram

CI) with pregabalin treatment was found with incoordination (RR 7.21; 95% CI 1.36, 38.25), followed by abnormal gait (RR 6.71; 95% CI 1.57, 28.71), ataxia (RR 6.02: 95% CI 2.31, 31.15), euphoria (RR 6.01; 95% CI 3.02, 11.97), and increased weight (RR 4.97; 95% CI 3.08, 8.00). While gabapentin treatment had the highest RR (95% CI) with increased weight (RR 5.61; 95% CI1.04, 30.22), followed by dizziness (RR 3.33; 95% CI 2.39, 4.65), peripheral oedema (RR 3.06; 95% CI 1.25, 7.48), and somnolence (RR 2.91; 95% CI 2.10, 4.03). Analysis of adverse events data showed no evidence of heterogeneity across the studies (Supplementary material Table 5 and Figure 1).

Withdrawal due to adverse events

The majority of adverse events were mild to moderate in severity. The proportion of participants who withdrew due to adverse events was not reported in all the included studies. There were some studies that reported the proportion of withdrawal due to adverse events: 18 pregabalin studies [2, 21, 23, 28, 31, 37, 39, 46, 47] and 10 gabapentin studies [24, 34, 35, 45–49, 52, 61]. Adverse event withdrawals were more common with pregabalin with 314 out of 3173 participants (10%) reporting these compared to 130 out 2352 participants (6%) on placebo (RR 1.71; 95% CI 1.28, 2.29) ($I^2 = 41\%$; $P = 0.0003$) (NNH = 23; 95% CI 17.4, 33.6). Similarly, the proportion of participants who withdrew due to gabapentin adverse events (166/1378) (12%) were more than those participants taking the placebo (77/981) (8%) (RR 1.47; 95% CI 1.08, 2.00) ($I^2 = 21\%$; $P = 0.01$) (NNH = 24; 95% CI 15.1, 55.8).

Serious adverse events

The included studies reported that all serious adverse events were not relevant to pregabalin or gabapentin interventions and findings were not analysed.

Abuse and gabapentinoid misuse disorder

None of the studies assessed abuse and gabapentinoid misuse disorder.

Secondary outcomes (efficacy)

Proportion of participants who achieved at least 50% pain reduction

The outcome was reported in 15 of pregabalin [21, 27, 29, 31–34, 36, 38, 39, 41–43, 46, 64] and 6 of gabapentin studies [48, 49, 51, 56, 59, 64] and the pooled results showed that pregabalin and gabapentin groups were significantly better than the placebo as presented in Table 3 (Supplementary material Figure 2).

Table 2 A summary of adverse events related to pregabalin and gabapentin use

Outcome	Intervention	Comparator	Studies	N	Random-effect RR (95%CI)	*P* value	I^2 (%)	NNH (95%CI)
Nervous system disorder								
Dizziness	Pregabalin	Placebo	27	5702	3.56 (2.91, 4.36)	< 0.00001	25	6 (4.90, 5.90)
Somnolence	Pregabalin	Placebo	18	5666	3.28 (2.62, 4.11)	< 0.00001	25	7 (6.20, 7.80)
Ataxia	Pregabalin	Placebo	5	1793	6.02 (2.31, 15.68)	0.0002	0	20 (15.6, 27.0)
Amnesia	Pregabalin	Placebo	3	652	3.38 (1.08, 10.62)	0.04	0	34 (19.3, 201.6)
Abnormal gait	Pregabalin	Placebo	3	719	6.71 (1.57, 28.71)	0.01	0	29 (18.7, 63.6)
Incoordination	Pregabalin	Placebo	3	1294	7.21 (1.36, 38.25)	0.02	0	31 (22.7, 47.4)
Asthenia	Pregabalin	Placebo	8	2544	2.00 (1.28, 3.70)	0.002	0	33 (21.3, 68.5)
Psychiatric disorder								
Confusion	Pregabalin	Placebo	4	1056	4.01 (1.42, 11.34)	0.002	0	30 (19.5, 62.2)
Euphoria	Pregabalin	Placebo	6	1548	6.01 (3.02, 11.97)	< 0.00001	0	16 (12.1, 22.4)
Abnormal thinking	Pregabalin	Placebo	4	1420	5.46 (2.09, 14.32)	0.0003	0	20 (14.8, 30.3)
Eye disorder								
Amblyopia	Pregabalin	Placebo	7	2155	2.90 (1.39, 6.03)	0.005	33	25 (17.2, 40.2)
Blurred vision	Pregabalin	Placebo	4	1306	2.59 (1.25, 5.39)	0.01	0	39 (22.5, 138.6)
Gastro-intestinal disorder								
Constipation	Pregabalin	Placebo	12	3838	2.49 (1.75, 3.54)	< 0.00001	0	25 (18.6, 36.0)
Dry mouth	Pregabalin	Placebo	12	3307	3.08 (2.05, 4.62)	< 0.00001	0	18 (14.0, 23.7)
General disorder and administration site condition								
Oedema	Pregabalin	Placebo	5	1381	2.82 (1.39, 4.74)	0.004	0	24 (16.4, 44.3)
Peripheral oedema	Pregabalin	Placebo	17	5529	2.83 (1.92, 4.17)	< 0.00001	44	22 (17.3, 29.3)
Endocrine disorder								
Increase weight	Pregabalin	Placebo	9	3161	4.97 (3.08, 8.00)	< 0.00001	0	16 (11.8, 17.7)
Musculoskeletal disorder								
Fatigue	Pregabalin	Placebo	4	838	2.00 (1.08, 3.70)	0.03	0	25 (14.0, 105.2)
Nervous system disorder								
Dizziness	Gabapentin	Placebo	9	2258	3.33 (2.39, 4.65)	< 0.00001	21	8 (5.90, 8.50)
Somnolence	Gabapentin	Placebo	9	2258	2.91 (2.10, 4.03)	< 0.00001	0	13 (9.50, 16.6)
General disorder and administration site condition								
Peripheral oedema	Gabapentin	Placebo	5	1770	3.06 (1.25, 7.48)	0.01	31	28 (19.0, 47.4)
Endocrine disorder								
Increase weight	Gabapentin	Placebo	2	504	5.61 (1.04, 30.22)	0.004	0	28 (16.3, 80.5)

NNH number needed to harm

Table 3 Secondary outcomes reported for pregabalin and gabapentin use

Outcome	Intervention	Comparator	Studies	N	Random-effect RR (95%CI)	*P* value	I^2 (%)	NNT
Secondary outcomes								
≥ 50% pain intensity reduction	Pregabalin	Placebo	15	4247	1.72 (1.37–2.16)	< 0.00001	73	10 (6.70, 10.50)
	Gabapentin	Placebo	6	1851	1.76 (1.34–2.32)	< 0.0001	54	8 (5.80, 10.80)
≥ 30% pain intensity reduction	Pregabalin	Placebo	12	3926	1.56 (1.29–1.88)	< 0.00001	79	8 (6.10, 9.80)
	Gabapentin	Placebo	7	1769	1.53 (1.25–1.88)	< 0.0001	59	7 (5.20, 9.80)
PGIC much or very much improved	Pregabalin	Placebo	13	4188	1.53 (1.28–1.83)	< 0.00001	82	9 (6.50, 10.60)
	Gabapentin	Placebo	7	1825	1.70 (1.27–2.28)	0.0004	71	7 (5.10, 9.20)
PGIC very much improved	Pregabalin	Placebo	4	1795	1.40 (1.01–1.92)	0.04	22	25 (13.8, 81.9)
	Gabapentin	Placebo	3	728	2.47 (1.79–3.41)	< 0.00001	0	6 (3.90, 7.30)

NNT number needed to treat, *PGIC* patient global impression of change

Proportion of participants who achieved at least 30% pain reduction

The proportion of participants who achieved at least a 30% pain reduction were reported in 12 of pregabalin [2, 21, 27, 29, 32, 36, 38, 42, 43, 46, 47, 64] and 7 of gabapentin studies [48, 49, 51, 52, 55, 59, 64] and the pooled results were significantly better than the placebo; but there was significant heterogeneity across the trials (Table 3).

Much or very much global pain improvement scale (PGIC)

The improvement in PGIC was reported in 13 of pregabalin [2, 25, 27, 29, 33, 34, 36, 39, 41, 43, 46, 47, 64] and 7 studies [48, 49, 51, 52, 56, 59, 63] comparing gabapentin against a placebo, and the pooled results indicated that pregabalin and gabapentin groups were significantly better than the placebo group but significant heterogeneity was found across the trials (Table 3).

Very much global pain improvement scale (PGIC)

The very much improved was reported in 4 studies with pregabalin [27, 29, 36, 47] and only 3 gabapentin studies [56, 59, 63] compared to the placebo and the pooled results demonstrated that the proportion of participants with this result was higher in pregabalin and gabapentin groups than the placebo group (Table 3).

Withdrawal due to lack of efficacy

Withdrawals due to lack of efficacy occurred in significantly fewer patients (3%) taking pregabalin than placebo (7%) (RR 0.41; 95% CI 0.31–0.54) ($I^2 = 4\%$; $P < 0.00001$) while there was no difference between those taking gabapentin compared to those on placebo (3.6%) (RR 0.59; 95% CI 0.33–1.04) ($I^2 = 0\%$; $P = 0.07$).

Statistical heterogeneity was noticed in some of the meta-analyses for the secondary outcomes ($I^2 \geq 70\%$), this heterogeneity might be due to the included studies examining gabapentnoids with different types of neuropathic pain (i.e., postherpetic neuralgia, peripheral diabetic neuropathy, and fibromyalgia).

Discussion

In this study, for the first time, the analysis was conducted with a focus on categorising the adverse effects according to the body systems they were affecting to better understand the safety profile associated with the use of gabapentinoinds in neuropathic pain. We identified that the majority of documented adverse events pertained to the nervous system or psychiatric disorders. Specifically, 12 of 18 (65%) adverse events were related to cognition/coordination; of these 7 pertained to a nervous system disorder (dizziness, somnolence, ataxia, amnesia, abnormal gait, incoordination, and asthenia), whereas 3 were related to a psychiatric disorder (confusion, euphoria, and abnormal thinking) and 2 to an eye disorder (amblyopia and blurred vision). This observation is in line with Perucca et al. who found that adverse events associated with the use of gabapentinoids were related to cognition/coordination and were, importantly, also the main issues impairing health-related quality of life for patients who used these medications [69]. In addition, Zaccara et al. reported that the adverse events with the highest RRs in the use of pregabalin were related to cognition/coordination [70]. This also corroborates our findings for pregabalin with the highest RRs between 3.33 and 7.20 for cognition/coordination adverse events.

Based on the included RCT outcomes, we did not detect clear indication about the abusive potential of gabapentinoids. One of the reported adverse effects that may suggest abusive potential could be euphoria resulting from the treatment with this medication. While we found 6 of 29 pregabalin studies reporting euphoria as an adverse event, no gabapentin studies reported euphoria as an adverse event. In addition, in a recently published systematic review about the abuse potential of pregabalin from 102 RCTs, euphoria was reported in 14 RCTs as an adverse event with rates between 1–10%, but 1 study reported a rate as high as 26% [71]. The reason behind the ability for pregabalin to produce euphoria, in contrast to gabapentin, may lay in the fact that the peak plasma concentration for pregabalin is achieved after 1 h of oral administration, whereas it takes between 4 and 5 h for gabapentin to reach the peak plasma concentration. This may suggest that pregabalin has rapid absorption and very high bioavailability compared to gabapentin (> 90% for pregabalin vs. 33–66% for gabapentin) [72] hence pregabalin may have higher abuse liability than gabapentin.

Even though our study design did not focus on opioid and gabapentinoid drug combination, it should be noted that gabapentinoid misuse is significantly higher in patients taking the drug in combination with an opioid analgesic where that opioid is being misused [54, 73]. Indeed, gabapentinoids have GABA-mimetic properties that may lead to drug dependence, especially in patients with a history of opioid abuse [8, 28, 54] and patients, showing long-term opioid tolerance, may desire the euphoric effect resulting from treatment with pregabalin [75]. In line with this, it has been found that the prevalence of abuse of gabapentinoids in patients with opioid use disorders was higher in pregabalin users [8, 76, 77]. However, it seems as RCTs included in this systematic review did not allow for concomitant treatment with opioids during

the study period and therefore the effect of opioid and gabapentinoid drug combination would not be possible to be assessed.

We assessed the efficacy outcomes of moderate or substantial pain relief, as defined by the IMMPACT group [15]. We found that pregabalin and gabapentin were more efficacious than placebo (≥ 30% and ≥ 50% pain intensity reduction). The NNTs of pregabalin were 8 and 10, whereas gabapentin's NNTs were 7 and 8. These findings are consistent with Finnerup et al. reporting NNT of 7.7 and 7.2 for pregabalin and gabapentin, respectively [78]. In addition, some efficacy outcomes have been reported for the PGIC much or very much improved that revealed that gabapentinoids having a superior benefit compared to placebo.

The main limitation of this study is that our outcomes are based on the analysis of data retrieved from RCTs only. While there is an ethical requirement to report adverse effects during RCTs, our outcomes suggest that RCTs may not be sufficiently powered to detect adverse effects and therefore provide solid evidence to support the safety of gabapentinoids. Moreover, included RCTs were relatively short in duration (maximum 20 weeks) and this potentially limited the possible occurence of relatively rare side effects, such as addiction and misuse disorders. In addition, subgroup analysis was not undertaken to assess the risk at different doses of gabapentinoids or in different types of neuropathic pain because the main aim was to focus on the comprehensive tolerability and safety profile of gabapentinoids.

Conclusion

This meta-analysis presents the evidence from RCTs that confirms analgesic effectiveness of gabapentionoids in adults with neuropathic pain. However, despite RCTs documenting the adverse events of gabapentionoids on the nervous system, there was no evidence of gabapentinoid use leading to addiction and misuse disorders. The only reported side effect that may be associated with the abusive potential of gabapentionoids was euphoria that was observed at the therapeutic doses range for pregabalin, but not gabapentin. Given that our outcomes were limited to RCTs only, our work suggests that RCTs assessing effectiveness of gabapentionoids are not sufficiently long in duration and not sufficiently powered to detect relatively rare side effects, such as addiction and misuse disorders. Thus, there is a critical need to improve study design or new approaches to confirm the abusive potential of gabapentinoids, to better inform and educate patients and clinicians.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-022-01528-y.

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Conflicts of interest None declared.

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We excluded 23 studies at high risk from this meta-analysis and reasons for exclusion were:

- Non-placebo-controlled trials.
- Different study design (crossover and Enriched enrolment with randomised withdrawal EERW).
- Acute pain.
- Integrated data.
- Flexible dose.
- Did not meet the study criteria.

Study	Reason for exclusion
Arshad, 2018	Missing data and active comparator
Pandey *et al.*, 20215	Did not meet study criteria
Freeman *et al*., 201	Integrated data from 2 included studies
Liang *et al.*, 2015	Acute pain
Razazian *et al*., 2014	Active comparators
Irving *et al.,* 2014	Open label trial (non-randomised)
Boyle *et al.,* 2012	Active comparators
Achar *et al.,* 2010	Active comparators
Chandra *et al.,* 2006	Active comparators and small sample size
Vranken *et al.,* 2008	Active comparators and small sample size
Baron *et al.,* 2010	EERW
Tesfaye *et al.,* 2013	Flexible dose and small sample size
Hewitt *et al.,* 2011	EERW
Dworkin *et al.,* 2009	Active comparator, EERW, small sample size
Tai *et al.,* 2002	Crossover design, acute pain
Yilmaz *et al.,* 2005	Crossover design, small sample size
Gilron *et al.*, 2005	Crossover design, small sample size
Kelle *et al.*, 2012	Did not meet the study criteria, small sample size
Rintala *et al.*, 2007	Did not meet the study criteria, crossover
Gupta and Li, 2013	Integrated data from 2 included studies, did not meet the study criteria
Huffman *et al.*, 2017	EERW
Raskin *et al.*, 2013	EERW
Gilron *et al.*, 2011	EERW

Table A-1. *Characteristics of excluded studies.*

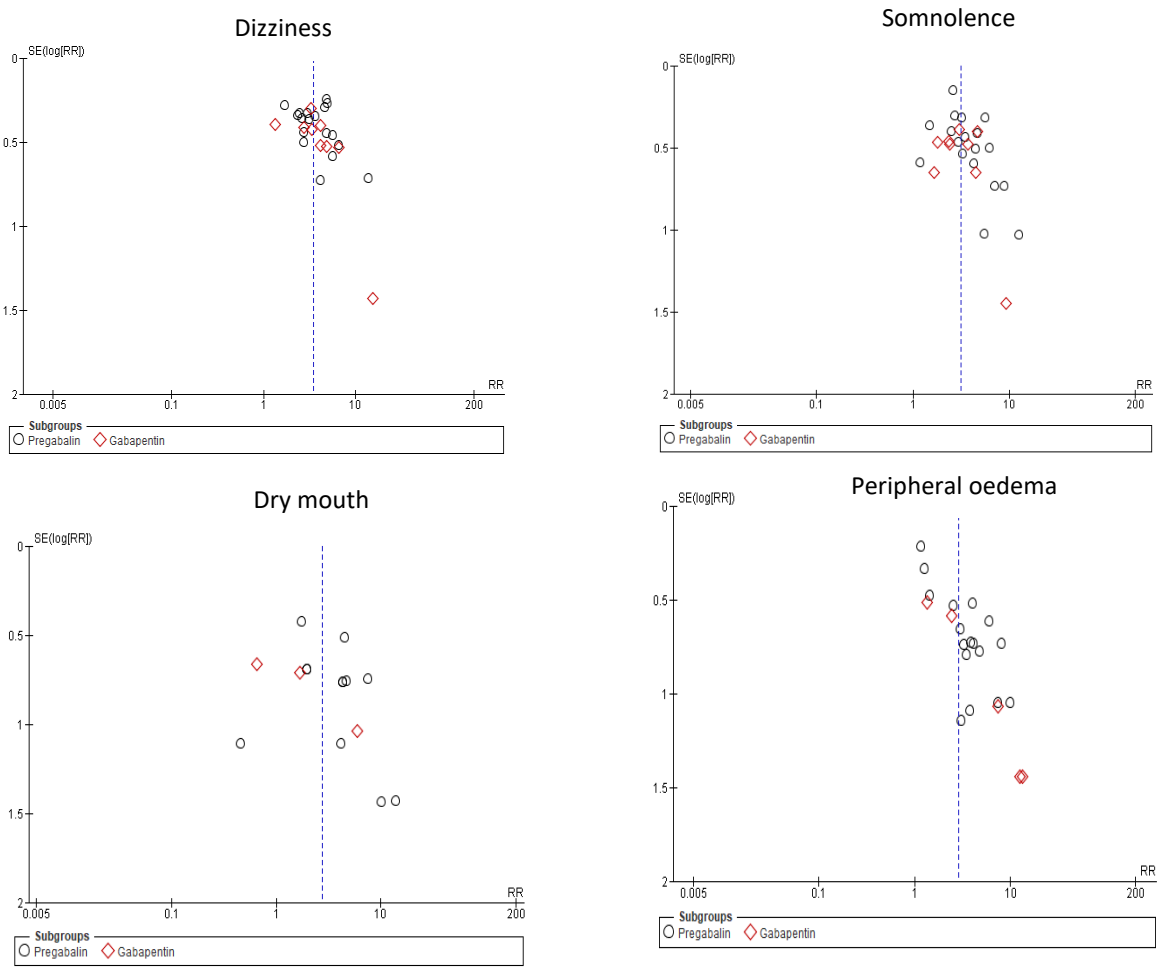


Figure A-1. *Funnel plots for safety and tolerability of gabapentinoids.*

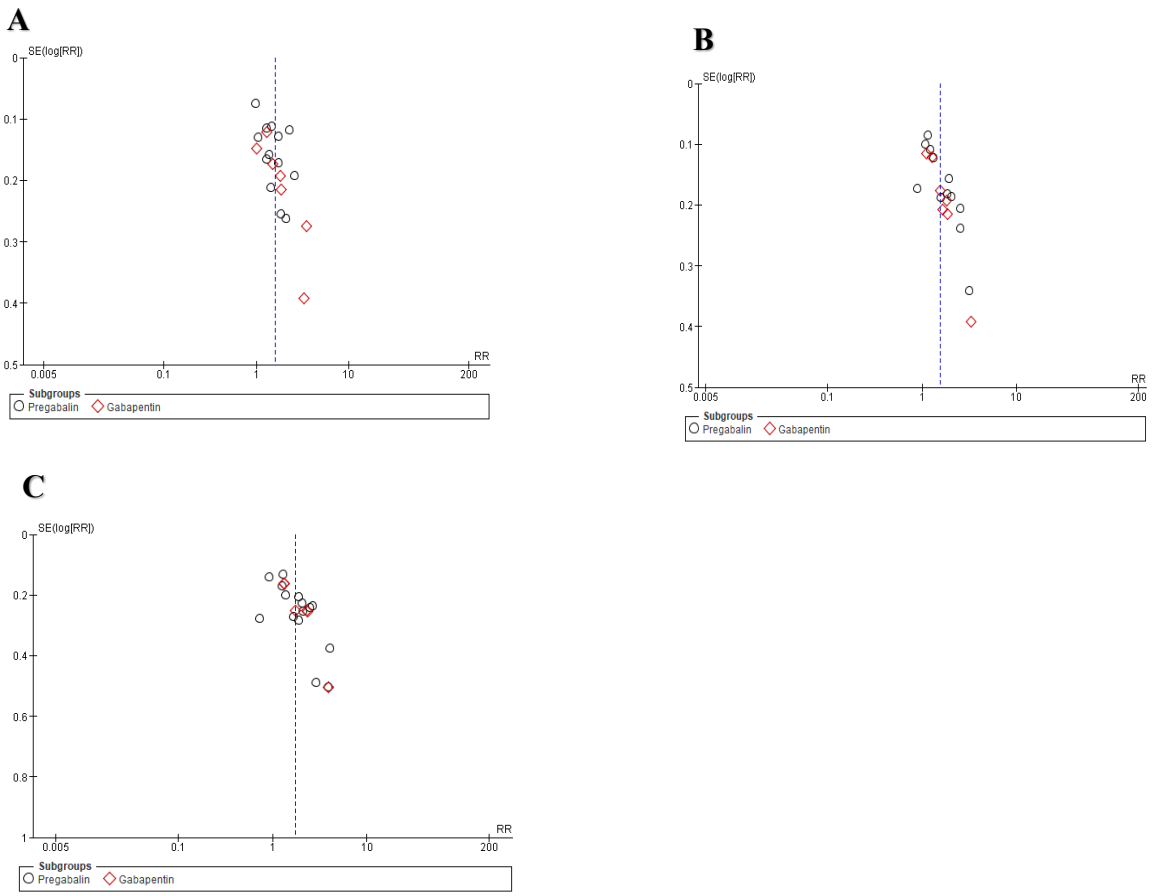


Figure A-2. *Funnel plots of comparison for the secondary outcomes:*
A: Efficacy of gabapentinoids versus placebo: Proportion of patients with a 50% or greater reduction.
B: Efficacy of gabapentinoids versus placebo: Proportion of patients with a 30% or greater reduction.
C: Efficacy of gabapentinoid versus placebo: Proportion of patients with Improvement on PGIC scale.

Appendix B Home-made catheter preparation: materials for assembly IV catheter for rat.

Ingredients:

- Micro-Renathane® Implantation Tubing (.033" x.014" (12) 3 ft. lengths)
- Terumo Agani Needle 21Gx1.5 ‘’0.8x38mm
- Wire heating element Ø1.2mm, 2:1 ratio (RS 170-6355)
- Plastic Screws (nylon)
- General purpose 33-gauge wire (approximately 10 cm lengths)
- Toluene
- Superglue
- Silicone

Catheter building

Stage 1

Prepare green needles:

1. Break the Terumo Agani Needle from the green plastic, and also break off the sharp end of the needle.
2. Using a dremmel and the bits, grind down the sharp edges of the needle. The resulting length of the needle should be between 3-4cm long.
3. Bend the needle to a 90° angle.

‘’ It was connected to an L-shaped connector (made in house) and mounted with dental acrylic and screws embedded in the skull’’

Prepare nylon screw:

1. A plastic Mount screw fixed on platform
2. Drill a hole through the middle of the screw
3. Create a notch on the screw

Cut tubing & heat shrink tubes:

1. The tubing should be cut to approximately 15cm long
2. Cut the heat shrink tubes to approximately 11-12mm

Disinfect the tubing:

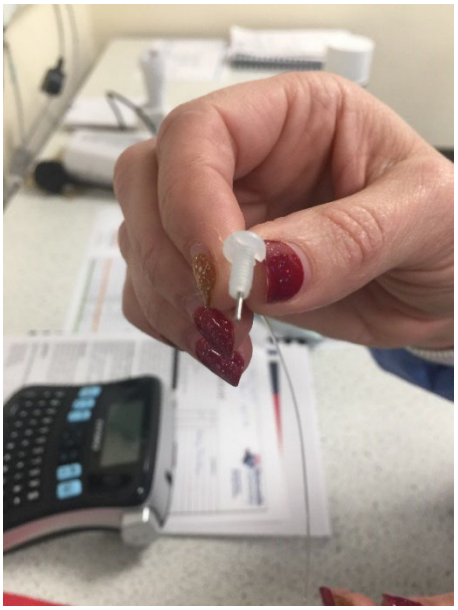
- Clean the screw and needle using toluene. Make sure that you are doing this step in a well-ventilated area. Ideally under a fumehood (or an equivalent).

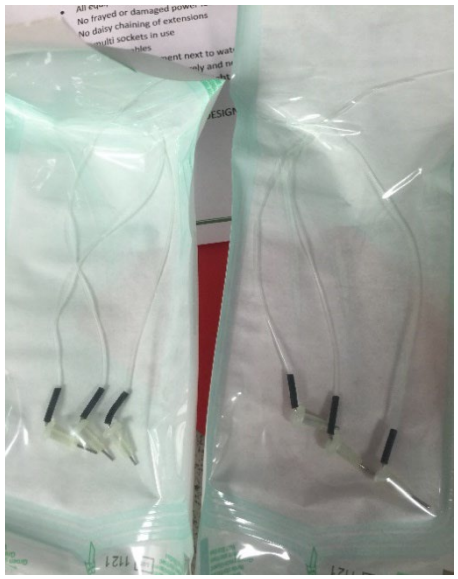
- Assemble the catheter by first connecting the tube to one end of the needle, and then securing the screw to the other end of the needle using superglue.

- Allow the superglue to completely dry before proceeding to the next step.

- Once the superglue is dry, the heat shrink tube can now be placed around the area where the tube wraps around the needle. Make sure the heatshrink tube is as close as possible to the nylon.
- *This is important because if the heatshrink tubing is too far away from the needle, it may end up constricting the tubing during autoclave, resulting in blockage*

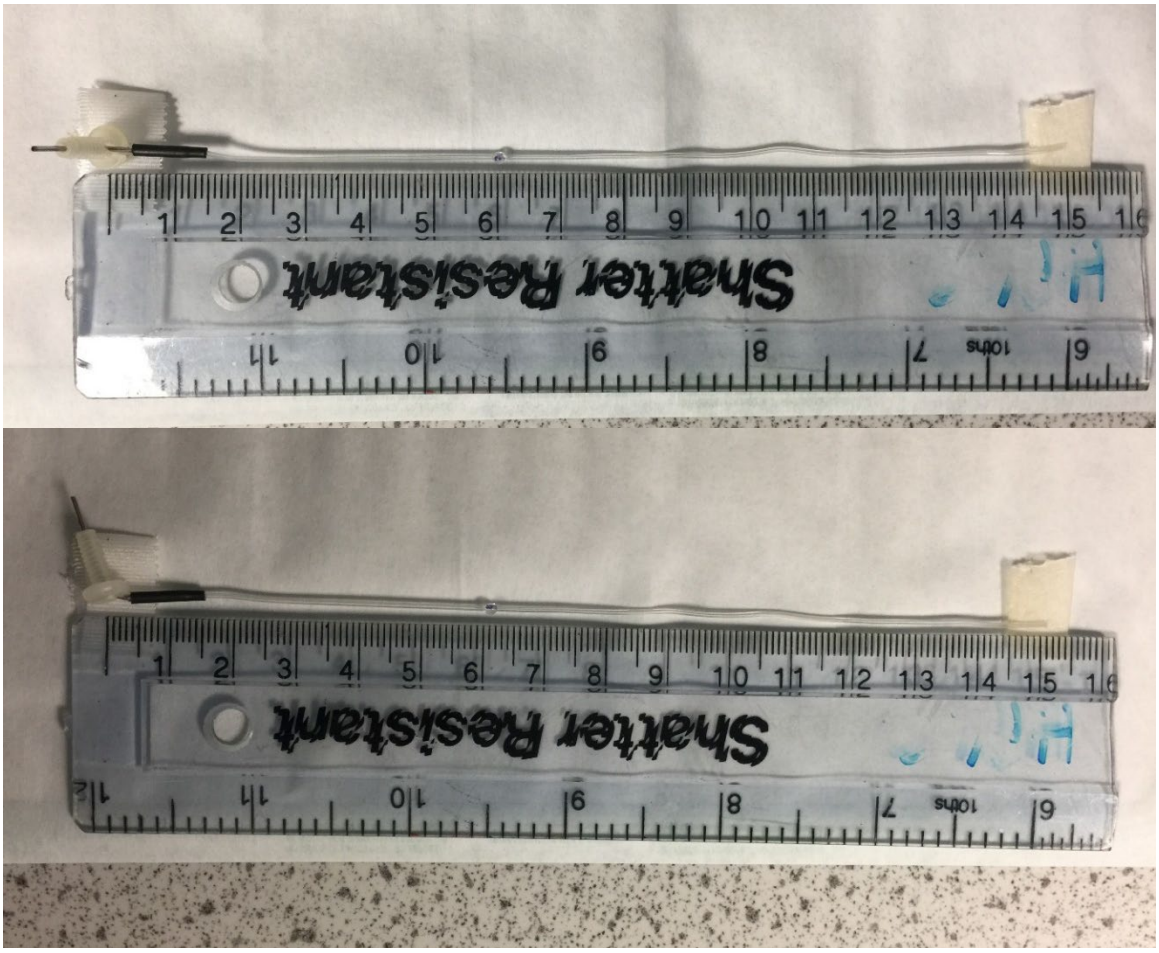
- Place the catheters in 3s into an autoclave bag (20x6cm), making sure that the catheters are as straight as possible, and autoclave the bags UPRIGHT. You must make sure again that the heatshrink tubes are as close to the needle bend as possible.





Stage 2

- After the IV catheters have been autoclaved, they need to be inspected, to make sure that the heat shrink tubes are in the right position.
- Then using a flusher (green needle with tubing and 1ml syringe filled with sterile water), pressure test the catheters. Make sure that there are no leaks and blocks.
- Using a ruler, make a mark of 6cm on the tubing from the bend of the needle. The mark is where a small silicone ball should be placed.
- Once complete, place the catheter flat on a container with several lengths of tape across it, and let the silicone dry for 24-48 hours.
- Once the silicone is dry, pressure test the IV catheter once more.
- Place pairs of IV catheter in small autoclave bags, autoclave them, and they should be ready for surgery.



INSTITUTE OF NEUROSCIENCE

PAIN & DISTRESS SCORING SYSTEM/POST-OPERATIVE CARE CHART

RAT NO: **DATE OF SURGERY:** **PRE-OP WEIGHT:**

LICENSEE: **PROJECT LICENSE:**

	VARIABLE	POINTS	Day 1 (pm)	Day 2 (am)	Day 2 (pm)	Day 3 (am)	Day 3 (pm)
0	Weight (grams)						
1	Weight Loss: ≤5% >5% >10% >20%	 0 1 2 4					
2	Impaired eating or drinking	2					
3	Abnormal faeces or urine	2					
4	Lack of grooming or movement, abnormal posture (e.g. hunched), excessive restless activity, scratching of surgical wounds	4					
5	Piloerection, eye/nose discharge, or abnormal respiration	4					
6	Self-injury, (scores of 0 or 4 only)	4					
7	Fitting (scores of 0 or 4 only are allowed)	4					
8	Squeal/withdrawal/bite/violent movement if touched	4					
	Total for Items 1-8	**Max=28**					
	Score item 9 only if total for 1-8 > 4						
9	'Tenting' of skin (dehydration)	3					
	Total for Items 8-10	**Max=3**					
	Overall total score	**Max=31**					
10	**Injections** **Initials**						

POST-OP DAY	4	5	6	7	8	9	10
General Condition							
Weight (g)							
Eating/Drinking							
Urine/Faeces							
Movement							
Discharges							
Injections							
Comments							
Initials							

Appendix C Publication (2)

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Review Article

IJPP International Journal of Pharmacy Practice

OXFORD

A review and narrative synthesis of community pharmacist-led interventions to tackle medicines for pain that are misused

Verity G. Mills[1], Jawza Meaadi[1,2,3], Hamde Nazar[1,*] and Ilona Obara[1,2]

[1]School of Pharmacy, Newcastle University, Newcastle upon Tyne, UK
[2]Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK
[3]King Saud Medical City, Riyadh, Kingdom of Saudi Arabia

[*]Correspondence: Hamde Nazar, School of Pharmacy, King George VI building, Newcastle University, Newcastle upon Tyne, NE1 7RU, UK. Tel: 0191-2082361; Email: Hamde.nazar@newcastle.ac.uk

Abstract

Objectives To undertake a state-of-the-art review and narrative synthesis of current evidence investigating community pharmacist-led interventions addressing analgesic medication misuse. To achieve the objective, a systematic database search was undertaken during October and November 2020 across Embase, Medline, Web of Science and Scopus. Community pharmacy interventions were mapped to the Behaviour Change Wheel to investigate the pharmacist and patient behaviours addressed by the interventions. Outcomes about process and effects were extracted. A risk of bias assessment was undertaken.

Key findings Five studies undertaken in the USA and Northern Ireland were included. Brief Motivational Interviewing and Medication Therapy Management and the Opioid and Naloxone Education programme demonstrated positive process outcomes and feasibility in delivery. Intervention functions addressing patient and pharmacist behaviours across the studies included education, training, environmental restructuring and enablement. Restrictions were an additional intervention function targeting patient behaviour incorporated in one study. Pharmacist roles involved the identification of potential misusers/abusers, patient education, long-term management, prevention and referral. Low study numbers, non-experimental designs, high risk of bias, incomplete reporting of interventions and heterogeneous outcome measures limited evidence synthesis.

Summary There is limited evidence of pharmacy interventions and their well-tested impact on pharmacists and patients. There is clinical and methodological heterogeneity across studies. It is pragmatic to suggest that a systems-thinking approach is adopted to investigate the potential role of community pharmacists and engage all stakeholders in the design of a theory-informed intervention. More high-quality studies including larger population sizes undertaken for longer periods of time that are rigorously reported are needed to improve the evidence base.

Keywords: community pharmacy; clinical topics; drug misuse; patient safety; systematic review

Introduction

Chronic pain affects approximately 37% of individuals in developed countries, specifically in the UK between 33% and 50% of the population are experiencing chronic pain at any one time.[1, 2] Globally, it is estimated that 1 in 10 people are newly diagnosed with chronic pain each year. In 2016, pain-related disorders, including lower back pain, were the leading cause of disease impact worldwide, related to years lived with disability.[3]

Generally, healthcare professionals implement a stepwise, individualised treatment plan when initiating pharmacotherapies for chronic pain. The list of which is extensive (e.g. opioid and non-opioid analgesics, anticonvulsants and antidepressants).[4, 5] Treatment responses, however, differ significantly between individuals due to the multifactorial nature of chronic pain and the physiological differences between chronic pain conditions.[4, 6] In 2020, the National Institute for Health and Care Excellence (NICE) in the UK published a draft guidance for public consultation regarding chronic pain management to reflect the ongoing challenges associated with chronic pain control.[7] Contradictory to previous chronic pain recommendations, opioids are now not recommended by any route, even though this group of medications remain the gold standard for acute pain management. This amendment reflects the minimal evidence demonstrating that these medications improved patients' pain, psychological distress or quality of life, alongside increasing evidence of medication-related harms (e.g. risk of tolerance, addiction and dependence, opioid-induced hyperalgesia and intolerable side effects).[8]

Other concerns associated with opioid use are the devastating global opioid crisis and the severe health consequences and fatalities when the medicine is misused for illicit and medicinal purposes.

Pharmacists are, in most cases, the last healthcare professional a patient will interact with before obtaining medicines, either via prescription or when purchased over the counter (OTC). This means that they are in a unique position to identify

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medicines-related problems such as misuse and potentially intervene.[9] Also, in the UK, pharmacists are among the most readily available healthcare professionals in primary care. It has been estimated that 89.2% of the UK population live within a 20-min walk of a community pharmacy.[10] Community pharmacist roles in substance misuse management have generally focussed on the dispensation of opioid substitution therapy and needle exchange services. Other community pharmacy-led informal interventions undertaken in the UK have included refusing sales, referring patients elsewhere, limiting the quantity of products sold or moving products out of sight.[11] There has been a recent increased interest in community pharmacists contributing to reducing the use of potentially inappropriate medications (PIMs),[12] like the inappropriate use of analgesics. The specific role of the community pharmacist is not yet clear as much of this research is ongoing. This review will focus on community pharmacist interventions that have aimed to identify and manage misuse of analgesic medicines. A behaviour change lens has been employed to categorise the components of the interventions. This will make transparent the active ingredients of the interventions, which future intervention designers, commissioners and implementers will find helpful in exploring patterns of successes and failures. The objectives are to investigate what roles community pharmacists have played, what were the intervention components and strategies to change behaviours and what evidence exists to demonstrate impact.

Methods

This state-of-the-art review aims to identify and critically appraise the evidence for community pharmacists delivering interventions to identify and address misuse and/or abuse of analgesic medications. A systematic approach was used; however, as no funding was in place to support the work, the steps of the review were not undertaken independently in duplicate. Apart from this omission, the review followed all steps of a systematic review procedure.

Search strategy

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist[13] was used to frame the reporting of this review. Eligibility criteria were defined using 'Population, Intervention, Comparison, Outcomes' components[14] and the details of which are included in Supplementary File 1. The inclusion and exclusion criteria are detailed in Table 1.

The search was applied to Embase (search strategy is included in Supplementary File 2) and adapted for Medline, Web of Science and Scopus using keywords and database-specific medical subject headings (MeSH) where applicable. Search terms focussing on 'community pharmacy' and 'analgesic medications' were used. The keywords and MeSH headings relating to specific analgesics were informed by draft NICE guidelines on chronic pain in over 16 year olds.[6] The literature search strategy was developed in consultation with a subject librarian and reviewed by two further researchers. The final search was undertaken during October and November 2020 with no publication date restrictions applied.

Study selection and data collection

Upon exporting all references into the referencing software Endnote, duplicates were removed; titles and abstracts were screened for topic relevance by applying the inclusion and exclusion criteria, and full texts were obtained for all relevant articles published in English. Reference lists of these articles were scanned for additional studies.

A data extraction sheet was developed using the Cochrane Consumers and Communication Review Group's data extraction template[15] as a basis. The application of the exclusion criteria, screening of full-text articles and data extraction was undertaken by two researchers.

The information extracted is presented in Box 1.

Table 1 Inclusion and exclusion criteria for the search strategy

Inclusion criteria	• Any study implementing community pharmacist-led interventions to address analgesic misuse. • Studies whose study population included patients at risk of analgesic misuse or actively misusing analgesic medications. • Studies reporting 'drug misuse' and/or 'drug abuse' of analgesics. • Analgesic medications included those for chronic pain, which are commonly misused such as opioids (e.g. morphine, codeine and tramadol) and gabapentinoids (e.g. gabapentin and pregabalin). • Studies reporting qualitative outcomes (e.g. pharmacist attitudes towards feasibility and acceptability of the intervention) and/or quantitative outcomes (e.g. patient outcomes). • All types of study design. • All peer-reviewed articles reported in English with no publication status or date restrictions imposed.
Exclusion criteria	• Interventions facilitated by healthcare professionals other than community pharmacists. • Interventions involving the supply/dispensation of pharmacy-based naloxone for the prevention of opioid overdose without counselling to address analgesic misuse. • Opioid substitution therapy interventions, if the study population used analgesics for illicit purposes or if the purpose for misuse was undefined. • Non-peer-reviewed and non-English-language studies. • Study protocols or articles with research in progress.

Categorising and coding the interventions

The interventions were categorised as to whether they included components of patient identification, patient education, long-term management, active intervention to prevent misuse or referral for onward or additional support. The component parts were interpreted or directly understood from study descriptions.

Behaviour change theories and frameworks can be used to examine and understand what strategies have been tried and tested and understand their effects. The Behaviour Change Wheel (BCW) has been produced from the evaluation and critical compilation of 19 behaviour change frameworks.[16] It comprises a central hub: the behaviour system that includes capability (C), opportunity (O) and motivation (M). Each of the three components (C, O and M) is divided heuristically

Box 1 Data extracted from included studies.

- Publication details [including author name(s), publication date and region of study],
- Type of study (including study design and methods)
- Characteristics of participants (including target populations/patients receiving the intervention)
- Analgesic(s) misused (including drug classification/drug name and the measure of misuse/abuse if applicable)
- Type of intervention implemented
- Type of outcome measure(s) (including qualitative and quantitative outcomes)
- Key findings (including qualitative and quantitative findings).

into two subcomponents – capability: psychological (Ps) and physical (Ph); opportunity: physical (Ph) or social (So); and motivation: reflective (Re) or automatic (Au). Surrounding the central hub are intervention functions that aim to address deficits in one or more of these behavioural components. The outer layer comprises seven categories of policy that facilitate the intervention. The BCW was employed in this study as it provides a conceptual framework to categorise and understand the content of interventions and their potential implications, particularly where in-depth detail about the intervention may not be available.[16]

The interventions were coded using the COM components and subcomponents, and the intervention functions (education, persuasion, coercion, incentivisation, training, restriction, environmental restructuring, modelling and enablement). The interventions were coded from the perspective of changing the pharmacists' behaviours and changing the patients' behaviours to explore:

1. How pharmacists were prepared and engaged to implement and deliver the patient interventions, and
2. What aspects of patient behaviour were being targeted with the intervention.

This mapping process was conducted by two researchers independently and then discussed to reach consensus.

Categorisation of outcomes

All reported qualitative and quantitative outcomes were categorised in terms of three principal summary measures: (1) process outcomes, (2) satisfaction and attitudinal outcomes and (3) clinical outcomes.

Due to the range of studies design and outcomes reported, meta-analysis was not appropriate and no a priori frameworks were adopted to frame the results. Instead, a narrative synthesis was undertaken.

Risk of bias

The critical appraisal tools from the Joanna Briggs Institute such as analytical cross-sectional studies, case reports, qualitative research and randomised controlled trial (RCT) checklists were used to ascertain the risk of bias.[17] This was undertaken by one researcher and reviewed by two further researchers to reach consensus.

Results

A total of 2712 titles were identified from the literature search. Figure 1 illustrates the steps involved in the search and selection process to yield the final five relevant studies included in the review. Characteristics and details of the studies are included in Table 2.

Study characteristics

One study was conducted in Northern Ireland[18] and four studies in the USA.[19–22] Three studies were analytical cross-sectional designs,[18, 20, 21] one a case report[19] and one small-scale RCT.[22]

Study participants

Across the studies, 934 pharmacists working within the community pharmacy sector were included,[18–22] with a range of 2 to 852 involved across the studies. A total of 2144 patients were involved and who were either misusing opioid prescriptions,[22] suspected of OTC misuse or abuse,[18] at varying degrees of risk of misusing opioid prescriptions and accidental overdose,[19, 20] or in treatment for substance misuse at a drug treatment agency.[21] The patient number across the studies varied from 2 to 1685.

Study interventions

Four studies assessed complex/multiple component community pharmacy-led interventions including the Harm Minimisation Model (HMM) for the treatment of OTC drug abuse,[18] Standard Medication Counselling (SMC) and Brief Motivational Interviewing and Medication Therapy Management (BMI-MTM),[22] the Opioid Misuse Risk Prevention Toolkit (ORT)[19] and the Opioid and Naloxone Education (ONE-Rx) programme,[20] based on the preliminary findings of the pilot Opioid Misuse Risk Prevention Toolkit.[19] One study measured the acceptability of five single component prescription opioid misuse interventions including:

1. Pharmacist-led counselling about the risk of misuse, abuse, addiction and overdose associated with prescription opioids,
2. Pharmacist referral of patients with suspected medication misuse, abuse and addiction to local treatment services,
3. The use of prescription drug monitoring programs (PDMP) to identify illegitimate prescriptions,
4. Naloxone provision by pharmacists with opioid prescriptions, and
5. Pharmacists selling OTC naloxone.[21]

The RCT was the only investigation to use a control group that included participants who received SMC as opposed to BMI-MTM.[22]

Two of the interventions incorporated intervention functions: education, training, environmental restructuring and enablement, to address pharmacist behaviours.[18, 22] One study also incorporated education, training and enablement,[19, 20] and Riley and Alemagno did not describe any strategies to address pharmacist behaviour.[21]

The BMI-MTM involved more intervention functions to target patient behaviour, including education, training, environmental restructuring and enablement,[22] whereas the HMM was similar but deficient in the training function.[18] The One (Rx) only incorporated education and restrictions,[19, 20] and the five interventions discussed by Riley and Alemagno each only involved a maximum of one intervention function (mainly environmental restructuring)[21] (Table 3).

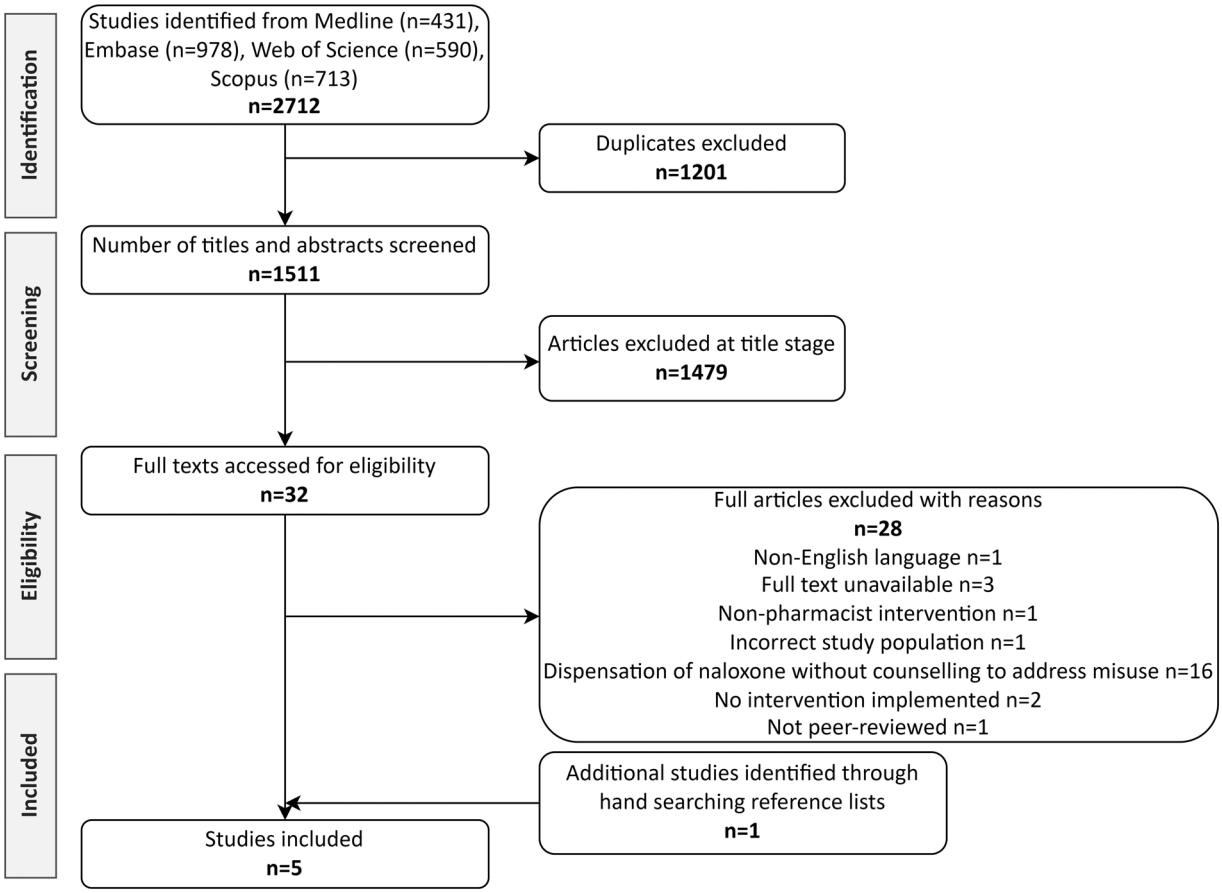

Figure 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram to illustrate the search strategy.

Study outcomes

Process outcomes

Four studies assessed the reach of community pharmacist-led interventions.[18–20, 22] This was variable across all the studies, ranging from 100%[22] to 35.7%.[18]

Adoption, implementation and maintenance of the One-Rx programme were reported by Strand *et al*. as organisational measures.[20] About 45% (n = 67) of eligible community pharmacies enrolled in the One-Rx programme. Of those community pharmacies that enrolled, only 44.8% (n = 30) achieved implementation of the programme by providing at least five patient screenings. Moreover, it was reported that 80% (n = 24) of implementing pharmacies achieved maintenance by completing at least one screening 3 months after the initial provision.[20]

Satisfaction and attitudinal outcomes

Outcome measures included pharmacist feasibility of using the opioid risk tool (ORT),[19] pharmacist perceptions of the HMM,[19] patient acceptability and feasibility of BMI-MTM[22] and acceptability of five specific pharmacy-based prescription opioid misuse interventions among pharmacists and patients.[21]

Strand *et al*. found that pharmacists valued having an objective measurement of potential opioid misuse, rather than relying exclusively on professional judgement. Pharmacists reported an increased ability to identify patients at risk of opioid medication misuse by use of the ORT, which improved conversations with the patients and subsequent patient care. The screening tool was perceived to be simple to incorporate into workflow and required minimal time to collect relevant information.[19]

Wazaify *et al*. reported that the training provided for the HMM allowed pharmacists to improve their communication skills and professional development.[18] Pharmacists participating in the HMM opined that their communication with neighbouring pharmacies improved and that there was raised awareness of the misuse of OTC medicines within the pharmacy team. However, respondents shared that clients were generally reluctant to talk about misuse and unreceptive to advice. Also, time pressures within community pharmacy meant that data collection and recording were challenging. More training and greater participation within the sector were suggested as future recommendations for intervention sustainability.[18]

Riley and Alemagno reported that pharmacists were generally favourable to provide counselling on the addictive potential of prescription opioids (98%, n = 670) and refer patients to local drug treatment services (67.3%, n = 460).[21] Patients largely agreed for these interventions to be provided by pharmacists. The sale of naloxone OTC received moderate support (33.7%, n = 231), but the provision of naloxone with opioid prescriptions generated sizable opposition from pharmacists (approximately 41%, n = 280). Patients, conversely, preferred the latter intervention over the former showing a statistically significant level of disagreement with pharmacists about these interventions.[21]

The majority of BMI-MTM participants reported high level of satisfaction with the pharmacy portion of the intervention.

Table 2 The study details, methods used, description of the intervention, the outcomes measured and key findings

Study details (author, year)	Region and type of study	Methods	Analgesic(s) misused/ measure of misuse	Intervention(s)	Outcomes measured	Key findings
Cochran *et al.* (2019)[22]	Pennsylvania, USA Single-blinded RCT	32 participants randomly assigned (1:1 ratio) to BMI-MTM (n = 15) or SMC (n = 17) conditions. Assessments were conducted at baseline, 2 months [upon patient navigation (PN) completion for BMI-MTM recipients] and 3 months.	Analgesic(s) misused: Prescription opioids. Measure of misuse: Prescription Opioid Misuse Index, urine toxicology.	*BMI-MTM* (15 months): Integrated model comprising a pharmacist-led: (1) medication therapy management (MTM), (2) brief motivational interviewing (BMI), (3) PN and (4) naloxone training and referral. *SMC (control)*: (1) offer medication counselling, (2) document counselling has been offered, (3) document patient refusal of counselling, (4) discuss possible generic substitutions and (5) provide information about the medication.	Process outcomes: Reach. Satisfaction and attitudinal outcomes: Feasibility and patient acceptability of BMI-MTM. Clinical outcomes: Mitigation of opioid medication misuse, opiate toxicology, pain, depression.	Process outcomes: 100% of BMI-MTM recipients received the pharmacist intervention. Satisfaction and attitudinal outcomes:13 BMI-MTM recipients agreed/strongly agreed that the pharmacist actively listened to their concerns, increased their confidence when managing medications and ensured safety. One patient would not recommend the pharmacist to family/friends. Clinical outcomes: BMI-MTM recipients were less likely than SMC patients to report continued opioid misuse at 3 months. For BMI-MTM recipients, there was a non-significant decrease in positive opiate toxicology screens over the study duration. Greater improvements in BMI-MTM recipients' mean scores for pain and depression were demonstrated over time compared with SMC recipients. There was a non-significant improvement in pain compared with SMC recipients.
Riley and Alemagno (2019)[21]	Ohio, USA Cross-sectional	Surveys for pharmacists and patients in treatment for substance use disorders examining five specific pharmacy-interventions using a Likert scale to measure acceptability. Pharmacist and patient acceptance of the interventions was compared using Cohen's Kappa and using the Altman Benchmark Scale.	Analgesic(s) misused: Prescription Opioids, Illicit Opiates. Measure of misuse: Patients in treatment for substance misuse disorder.	Five pharmacy-based opioid misuse interventions: 1. Pharmacists providing patients with counselling on the risk of misuse, abuse, addiction and overdose associated with prescription opioids. 2. Referring patients suspected of misuse to local treatment services. 3. Use of Prescription Drug Monitoring Programs (PDMP) to identify illegitimate prescriptions. 4. Providing naloxone with opioid prescriptions 5. Selling naloxone OTC	Satisfaction and attitudinal outcomes: Acceptability of interventions among pharmacists and patients, level of agreement or disagreement when comparing the opinions of each group.	Satisfaction and attitudinal outcomes: PDMP use and patient counselling were the most acceptable interventions among pharmacists with 85.8% of pharmacists supporting counselling and 97.9% supporting PDMP use. PDMP use and OTC availability of naloxone were the most acceptable interventions among patients with 71% of patients supporting PDMP use and 83.7% supporting OTC naloxone.
Strand *et al.* (2019)[19]	North Dakota, USA Case report	Pharmacists trained to use the screening toolkit. Following each patient encounter, pharmacists completed a summary of care worksheet. After 6 weeks, each pharmacist completed a Pilot Project Process Evaluation Survey and focus group.	Analgesic(s) misused: Prescription Opioids, Measure of misuse: ORT.	Opioid Misuse Risk Prevention Toolkit (6 weeks): Pharmacists assigned a score to the patient's screening questionnaire. If the ORT score was ≥4, the pharmacist evaluated the patient for red flags indicative of misuse via review of PDMP or professional judgment. If red flags were raised, pharmacists contacted the prescriber. Patients then offered all/some of the following services: prescribe, dispense and counsel on naloxone; counsel patient on substance misuse and community support services available; counsel patient on partial fills and safe disposal of unused medication.	Process outcomes: Reach. Satisfaction and attitudinal outcomes: Feasibility of ORT by pharmacist feedback.	Process outcomes: All patients with ORT ≥ 4 received all the pharmacy services. Feasibility of ORT: Pharmacists valued having an objective measurement of opioid misuse, rather than relying exclusively on professional judgement. Pharmacists reported an increased capacity to identify eligible misuse patients by use of ORT.

Table 2. Continued

Study details (author, year)	Region and type of study	Methods	Analgesic(s) misused/ measure of misuse	Intervention(s)	Outcomes measured	Key findings
Strand *et al.* (2020)[20]	North Dakota, USA Cross-sectional	ONE-Rx implemented in 63 community pharmacies. The five domains of the RE-AIM (Reach, Efficacy, Adoption, Implementation, Maintenance) Model were used to evaluate ONE-Rx.	Analgesic(s) misused: Prescription Opioids. Measure of misuse: ORT.	ONE-Rx (9 months): Each patient was screened for risk of accidental overdose and opioid misuse using the ORT. Based on screening results, pharmacists provided interventions using a clinical decision-making tool; medication take-back, opioid prescription partially filled, critical Interventions for At-Risk Individuals, discussed community support services, explained benefits of or dispensed naloxone, contacted provider, discussed opioid use disorder and accidental overdose.	Process outcomes: RE-AIM.	Process outcomes: Reach/Efficacy: 16.9% of all patients receiving opioid prescriptions were screened for risk of opioid misuse and/or accidental overdose; 97.1% of eligible patients were delivered the pharmacy interventions. Adoption: 45% of eligible community pharmacies enrolled in ONE-Rx. Implementation: 44.8% of adopting pharmacies successfully implemented ONE-Rx. Maintenance: 80% of implementing pharmacies achieved maintenance by completing at least one screening 3 months after the initial provision.
Wazaify *et al.* (2006)[18]	Greater Belfast Cross-sectional	Six pharmacists volunteered to participate in the 6-month study. All pharmacists participated in semi-structured interviews to explore their views and experiences of the study. No client proceeded to completion of the follow-up phase (e.g. health-related quality of life).	Analgesic(s) misused: OTC opioid-containing products. An ibuprofen–codeine combination product was the third highest product associated with misuse/abuse (n = 22). Measure of misuse: Professional judgement	Harm minimisation model (6 months): Client identification and recruitment (cases of misuse/abuse), treatment and referrals and data collection and outcome measurement. Treatment by pharmacists alone (information provided on management of condition, alternative products suggested, follow-up visits arranged) or referrals to general practitioner or community addiction team (CAT) are outlined in the treatment algorithm. The treatment path chosen depends on the product involved and if the product is being abused or misused.	Process outcomes: Reach. Satisfaction and attitudinal outcomes: Pharmacist perceptions of the intervention. Clinical outcomes: Success of the intervention.	Process outcomes: Of the 196 identified patients, the subject of inappropriate OTC use was raised with 70 (27 misuse/43 abuse cases). Satisfaction and attitudinal outcomes: Some pharmacists thought that training was difficult and non-relevant. Pharmacists agreed that time pressures made data collection difficult. All pharmacists agreed that the study positively impacted their practice; however, further training and greater participation by all pharmacies in a geographical area were advocated. Clinical outcomes: Success was achieved with 12 misuse and 2 abuse cases.

Table 3 The intervention aim, components and how they are coded by the BCW

Study details (author, year)	Intervention name	Intervention functions to change pharmacist behaviour (components of COM-B targeted)	Intervention aim	Intervention components	Intervention functions to change patient behaviour (components of COM-B targeted)
Cochran *et al.* 2019[22]	BMI-MTM	Education Training Environmental restructuring Enablement (C-Ps, C-Ph, O-Ph, O-So, M-Re, M-Au)	1.Identification 2.Education 3.Long-term management 4.Prevention 5.Referral	Prescription Opioid Misuse Index (POMI) 1.Medication therapy management: improving adherence to opioid medication as prescribed and resolving barriers: -Review opioids and identify interactions -Speak about misuse and how to identify -Identify targets for adherence improvement 2.Brief motivational interviewing 3.Patient navigation around holistic care 4.Naloxone training and referral	Education Training Environmental restructuring Enablement (C-Ps, C-Ph, O-Ph, M-Re, M-Au)
Wazaify *et al.* (2006)[18]	Harm minimisation model	Education Training Environmental restructuring Enablement (C-Ps, C-Ph, O-Ph, O-So, M-Re, M-Au)	1.Identification 2.Education 3.Long-term management 4.Prevention 5.Referral	(Based on Transtheoretical change model) 1. Client identification and recruitment (non-standardised or validated) 2.Treatment and referral to General Practitioner (GP) or community addiction team 3.Follow-up data collection and outcome measurements	Education Environmental restructuring Enablement (C-Ps, O-Ph, M-Re, M-Au)
Strand *et al.* (2019) and Strand *et al.* 2020 [19,20]	One (Rx)	Education Training Enablement (C-Ps, C-Ph, O-Ph, O-So, M-Re, M-Au)	1.Identification 2.Education 3.Long-term management 4.Prevention	Opioid Risk Tool (ORT) screening tool Pathways that include: -Prescribe, dispense and counsel on naloxone -Counsel patient on potential for substance use disorder and community support -Counsel on opioid prescription pearls, such as the possibility of a partial fill and safe disposal of unused medication.	Education Restrictions (C-Ps, O-Ph, O-So, M-Re)
Riley and Alemagno (2019)[21]	Five individual interventions		1.Identification 2.Education	Pharmacists providing patients with counselling on the risk of misuse, abuse, addiction and overdose associated with prescription opioids	Education (C-Ps, M-Re)
			1.Identification 2.Referral	Pharmacists referring patients suspected of misuse, abuse and addiction to local treatment services	Environmental restructuring (O-Ph, O-So, M-Au)
			1.Identification	The use of prescription drug monitoring programmes to identify illegitimate prescriptions	
			1.Identification 2Prevention	Pharmacists providing naloxone with opioid prescriptions	Environmental restructuring (O-Ph, O-So, M-Au)
			1. Prevention	Pharmacists selling naloxone OTC	Environmental restructuring (O-Ph, O-So, M-Au)

Specifically, 13 BMI-MTM participants agreed that the pharmacist actively listened to their concerns, increased their confidence when managing medications and ensured safety.[22]

Effectiveness outcomes

Of the 70 clients (27 misuse and 43 abuse cases) who received the HMM, success was reported in 12 misuse cases and 2 abuse cases equating to 44.4% of misusers and 4.7% of abusers agreeing to stop using the products and/or try a safer alternative.[18]

In terms of unadjusted changes in opioid medication misuse across time, Cochran *et al*. observed greater improvements in participants who received the BMI-MTM intervention compared with SMC patients.[22] BMI-MTM participants were less likely to report continued opioid misuse at 2- and 3-month follow-up assessments. Moreover, a promising but non-significant trend for decreases in positive opiate toxicology screens for BMI-MTM recipients was observed over the study duration.[22] This RCT also demonstrated improvements in mean pain and depression scores for both groups over the study duration, with greater improvements for BMI-MTM recipients compared with SMC recipients (all $P > 0.05$).[22]

Quality assessment

Across the cross-sectional studies, confounding factors were neither identified nor addressed. In all studies, pharmacists had the choice whether they wanted to participate in the study. It is possible that those who chose to participate were more positive about the intervention. Consequently, a wider sample of pharmacists not recruited by self-selection would reduce this bias.[23] The validity and reliability of the measure of exposure were an issue across all studies. Relatively low response rates of 5.9%[21] and 4.1%[18] were obtained in two studies. The full quality assessment of the studies is included in Supplementary File 3.

Discussion

This review provides an overview of pharmaceutical care interventions provided by community pharmacists in response to the misuse and abuse of analgesic medications, specifically opioids. The interventions are not fully described, and there is little use of experimental research designs. This limits the interventions' evaluability, contribution to the evidence base and thereby potential future adoption in practice. However, the majority of these interventions included aspects of education: for the pharmacists to prepare them to engage and for the patients to address analgesic misuse. Functions of environmental restructuring also featured highly across the interventions aiming to change behaviour of the pharmacist and/or the patient.

It is apparent that the interventions are complex, aiming to address pharmacist and patient behaviours. In accordance with the guidance on the development and evaluation of complex interventions,[24] comprehensive experimental research designs are warranted with nested process evaluations. This will not only allow the better capture of what is working, or not, but also provide information on the how and why.

The initial study identification through database searching was undertaken by only one researcher. The inclusion criteria only incorporated study populations at risk of analgesic misuse or actively misusing analgesics; studies implementing interventions for patients prescribed analgesic medicines with abusive potential were discarded. The included studies were all undertaken in the USA or Northern Ireland; hence, the findings may not be representative of or transferable to other countries. However, the identification of the intervention components and coding to the BCW provide researchers and decision-makers with some evidence and strategies about intervention design and implementation that can be refined and/or tailored to be tested within other healthcare settings.

From the included studies, the identification of patients who may be potentially misusing/abusing analgesics appears to be a common aim of interventions, with other roles including providing patient education, long-term management, prevention and referral. Understanding the distinct role that can be played by a community pharmacist may be a pragmatic place to start in addressing the problem. Murphy *et al*. evaluated the experiences of community pharmacists in addiction care, where pharmacists expressed the desire for better relationships and the necessity for additional communication and collaboration between healthcare professionals in this area.[25] Other research has cited that the silo working of community pharmacists challenges their capacity to provide clinical services. Formal referral pathways and integrated working have previously been recommended to improve this situation.[26] The reference to better integration with other care and support services cannot be ignored and, therefore, suggests future interventions would be best designed considering the local healthcare system rather than the isolated community pharmacy setting. By engaging with all stakeholders (e.g. pharmacists, patients and doctors), a more realistic, feasible and appropriate role for a pharmacist can be designed into an intervention. This holistic, system-level approach can be facilitated with the use of appropriate implementation frameworks and theories. An example is illustrated in studies by Cadogan *et al*., where authors described an intervention to improve appropriate polypharmacy in older adults using the Theoretical Domains Framework and behaviour change techniques. Authors engaged with both doctors and pharmacists in the design of this intervention that crosses care settings.[27, 28]

The need for further evidence in this area also means that planning how interventions are assessed for effectiveness requires significant attention. The Health Foundation suggests a 'balanced scorecard' approach, which assesses process and clinical outcomes alongside patient experience and the cost of the service.[29] Cochran *et al*. successfully evaluated process, attitudinal and clinical outcomes of BMI-MTM.[22] Future RCTs should consider this multifaceted approach with the addition of assessing pharmacists' experiences of implementing interventions. Validated objective outcome measures should be used, where possible and service evaluations that monitor performance are crucial for community pharmacists to demonstrate their ability to deliver interventions.[30]

Moreover, evaluations should be undertaken at a time to allow for potential substance relapse to be captured and to predict long-term health outcomes (e.g. emergency department admissions or incidence of opioid use disorder). Ramo and Brown found that 100% of adults experienced a relapse in the first 18 months following initial substance misuse and psychiatric treatment.[31]

There is current relevant research in progress at Keele University's Institute for Primary Care and Health Sciences

in the UK. In 2019, the research team began to develop PROMPPT, a Proactive clinical Review of patients taking Opioid Medicines long-term for persistent Pain led by clinical Pharmacists in primary care Teams, where clinical pharmacists address overprescribing of opioid analgesics to prevent subsequent addiction and overdose.[32] If the results of this preventative intervention prove successful, proactive measures within general practices should be expanded to directly tackle the source of the problem. Additionally, this would reduce the need for measures, which simply react to the problems of opioid medication misuse at the community pharmacy level. Most likely, preventative measures will be required alongside reactive measures to challenge the opioid epidemic and improve health outcomes for all chronic pain patients including those prescribed opioids and those actively misusing opioids.

Conclusions

There is limited evidence in this emerging area of research. Roles for community pharmacists are being researched; however, the interventions are diverse and poorly described and/or evaluated. As such, no significant deductions or recommendations can be made to inform future intervention design and implementation.

Interventions are generally multi-faceted in nature, targeting both pharmacist and patient behaviour. However, given the complexity of the problem that is not isolated to the community pharmacy setting, and the issues around silo working, adopting a framework to facilitate evidence-based, theoretically informed intervention design is warranted to better address the problem.

Further studies are required to test this suggestion by adopting experimental designs, involving larger study populations for a sufficient evaluation period to contribute more significantly to the evidence base.

Supplementary Material

Supplementary data are available at *International Journal of Pharmacy Practice* online.

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Author Contributions

H.N. and I.O. conceived the study. V.G.M. undertook data collection. Data were analysed by V.M. and checked and verified by H.N., I.O. and J.M. V.G.M., H.N., I.O. and J.M. all wrote the final manuscript and approved it before submission.

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None to declare.

Conflict of Interest

None declared.

Data Availability Statement

Original data from the searches are available from the authors upon reasonable request.

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The following search strategy was used for EMBASE (OVID):

1. analgesic agent/ or gabapentin/ or pregabalin/
2. codeine/ or codeine phosphate/ or morphine/ or morphine sulphate/ or opiate/ or tramadol/
3. gabapentinoid*.mp.
4. opioid*.mp.
5. 1 or 2 or 3 or 4
6. community pharmacist/
7. "pharmacy (shop)"/
8. community pharmac*.mp.
9. 6 or 7 or 8
10. 5 and 9

The following search strategy was used for MEDLINE (OVID):

11. 1. analgesics/ or gabapentin/ or pregabalin/
12. 2. analgesics, opioid/ or codeine/ or morphine/ or tramadol/
13. 3. gabapentinoid*.mp.
14. 4. opiate*.mp.
15. 5. 1 or 2 or 3 or 4
16. 6. Pharmacies/
17. 7. Pharmacists/
18. 8. Community Pharmacy Services/
19. 9. community pharmac*.mp.
20. 10. 6 or 7 or 8 or 9
21. 11. 5 and 10

The following search strategy was used for the Web of Science:

#1. TS=analgesic*
#2. TS=opioid*
#3. TS=gabapentin*
#4. TS=opiate*
#5. TS=pregabalin
#6. TS=codeine
#7. TS=morphine
#8. TS=tramadol
#9. TS= "community pharmac*"
#10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#11. #10 AND #9

The following search strategy was used for SCOPUS:

1. TITLE-ABS-KEY (analgesic*)
2. TITLE-ABS-KEY (opioid*)
3. TITLE-ABS-KEY (opiate*)
4. TITLE-ABS-KEY (gabapentin*)
5. TITLE-ABS-KEY (pregabalin)
6. TITLE-ABS-KEY (codeine)

7. TITLE-ABS-KEY (morphine)
8. TITLE-ABS-KEY (tramadol)
9. TITLE-ABS-KEY (“community pharmac*”)
10. (TITLE-ABS-KEY (analgesic*)) (TITLE-ABS-KEY (opioid*)) OR (TITLE-ABS-KEY (opiate*)) OR (TITLE-ABS-KEY (gabapentin*)) OR (TITLE-ABS-KEY (pregabalin)) OR (TITLE-ABS-KEY (codiene)) OR (TITLE-ABS-KEY (morphine)) OR (TITLE-ABS-KEY (tramadol))
11. ((TITLE-ABS-KEY (analgesic*)) (TITLE-ABS-KEY (opioid*)) OR (TITLE-ABS-KEY (opiate*)) OR (TITLE-ABS-KEY (gabapentin*)) OR (TITLE-ABS-KEY (pregabalin)) OR (TITLE-ABS-KEY (codiene)) OR (TITLE-ABS-KEY (morphine)) OR (TITLE-ABS-KEY (tramadol))) AND (TITLE-ABS-KEY ("community pharmac*"))

Appendix D

Jawza Alotaibi BSc, MSc, PhD researcher
School of Pharmacy
Faculty of Medical Sciences
Newcastle University
King George VI Building
Newcastle upon Tyne
NE1 7RU UK

Dear participant,

I am a PhD researcher who study at Newcastle University and I would like to talk to community pharmacists who have been working in community pharmacy for more than 1 year. I would like to invite you to take part in our research study entitled:

"A study to investigate interventions to tackle inappropriately prescribed medications, specifically analgesics, in community pharmacy''

In this study, I would like to explore your views of inappropriate prescribing of medications, specifically analgesics, and your approach in identifying and managing inappropriate prescribing for patients and your perception of the barriers and facilitators to achieving appropriate treatment.

It is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. If anything is not clear or if you would like more information about anything, please ask. Your participation is entirely voluntary. Please note this is a discussion study only, there will be no interventions made to patients' medications as a result of participating. Further details are provided in the attached participant information sheet.

I would like to conduct an interview with you lasting for a maximum of one hour. I'd like to conduct this via Zoom at a time that is convenient for you. Before you take part in the study, you must sign a consent form. There is one provided for you to complete if you choose to take part. If you're interested in taking part, please read the enclosed participant information sheet and sign the attached 'Consent Form' before'. After I receive your consent form, I will get in contact with you to arrange the interview.

If you do not wish to take part, simply do not respond to this e-mail or invitation.

Thank you.

Printed name: …… Electronic signature: …….

Why we are doing the study?

The aim of this study is to explore your views of inappropriate prescribing of medications, specifically analgesics, in community pharmacy. We would like to explore your approach in identifying and managing inappropriate prescribing for patients and your perception of the barriers and facilitators to achieving appropriate treatment.

Do I have to take part?

No. Taking part is entirely voluntary. It is completely up to you to decide whether or not to take part.

Why have I been asked to take part?

You have been asked to participate in an interview via Zoom where you will be asked some questions about your experience in community pharmacy, and explore your views about interventions to address inappropriate medications in community pharmacy. You can give as much or as little information as you like.

What will happen if I take part?

If you agree to take part, you will be asked to provide some suitable times for the interview via Zoom. All the questions will be about your experience and opinion about addressing inappropriate prescribing in community pharmacy.

What will happen during the study?

The interview will take a one-hour maximum. This will be recorded using an audio recorder and/or online Zoom recording. If you have any questions or need any explanation or would like anything clarified, please feel free to stop me at any time.

What happens after the study?

We will transcribe the audio recording of our discussion and will keep all information about you safe and secure. We will use the information from our discussion for this study and only the research team will access this information. The recordings will be destroyed after completing the study. This study will be included in Newcastle University data and confidentiality policies that apply to personal data being kept only for as long as we need it for the purposes of the study.

What are the possible risks of taking part?

It is very unlikely you will come to any harm from taking part in the study. We will only ask about what you know about interventions to tackle inappropriate prescribing medications through your experience in the community pharmacy. You are free to leave from the study at any time, without giving a reason, by informing the researcher Jawza Alotaibi on J.alotaibi2@newcastle.ac.uk

What are the possible benefits of taking part?

Although there will be no direct benefit to you by taking part in this study, you will be helping the research team to investigate interventions to tackle inappropriately prescribed medications, specifically analgesics.

Who is checking what you are doing is right?

This study was approved by the Faculty of Medical Sciences Research Ethics Committee, part of Newcastle University's Research Ethics Committee. This committee contains members who are internal to the Faculty, as well as one external member. This study was reviewed by members of the committee, who must provide impartial advice and avoid significant conflicts of interests.

What do I do now?

If you want to take part in this study please fill the 'Electronic Participant Consent Form' and we will contact you to arrange the interview.

Further information

If you have any concerns or other questions about this study, please contact the chief investigator:

Jawza Alotaibi BSc MSc PhD researcher

School of Pharmacy
Faculty of Medical Sciences
Newcastle University

Interview questions

Aim:

The aim of this interview is to explore your views of inappropriate prescribing of medications, specifically analgesics, in community pharmacy, your approach in identifying and managing inappropriate prescribing for patients and your perception of the barriers and facilitators to achieving appropriate treatment.

Prior to starting:

Thank you so much for making the time to talk to me.

- Today we are looking for you to discuss some of your thoughts and ideas about identifying and managing inappropriate prescribing in community pharmacy.
- I will be recording the interview to focus on what you are saying without the need to write down lots of notes and distract you.
- It is important to know that there are no right and wrong answers, just be yourself and answer the questions honestly.
- All the discussion in this meeting will be treated confidentially, your responses will be stored in an anonymous format, and so your names will not appear in any report.
- Have you had a chance to read through the information sheet that was sent out to you?

Question	Probes (TDF domain number)
1. **If I say the words "inappropriate prescribing," what comes to mind? How do you define it? What about inappropriate prescribing of analgesics?**	What is the first thing that come into your head? Is this something that you have experience seeing and managing in practice? **(2,3)**
2. What are your thoughts and ideas about identifying inappropriate prescribing of analgesics in community pharmacy?	• What helps one identify inappropriate prescribing of analgesics? **(5)**
3. What are your thoughts and ideas about managing inappropriate prescribing of analgesics in community pharmacy?	• At what point is inappropriate prescribing addressed? When would you like it to happen? **(11)** • Who do you think is best placed to do this? **(6)** • What do you think is your role as a pharmacist in stopping inappropriate prescribing of analgesics? **(1)**
4. **What do you think is your role as a pharmacist to address inappropriate prescribing of analgesics?**	How difficult or easy is it for you get involved in this? And why? (Barriers) **(8)**
5. What do you think is needed to help in the identification and management of inappropriate prescribing of analgesics in community pharmacy? (Facilitators)	• What additional resources do you require? (access to computers, more time etc.) **(4)** • What additional skills/training do you require? **(1, 2)** • What is the role of other healthcare professionals in addressing inappropriate prescribing of analgesics? **(6)**
6. A patient is currently on an analgesic medication that you feel they should NOT be taking. Tell me what may have contributed to you identifying this? How do you think you might tackle this?	
7. **At this time, how ready do you think community pharmacists are in identifying and addressing inappropriate prescribing of analgesics?**	
8. We are finished with the formal questions for the interview. **Do you have any additional comments or thoughts on this topic of stopping medications that we have not had a chance to discuss?**	

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A qualitative study to investigate community pharmacists' perceptions about identifying and addressing inappropriately prescribed analgesia

Jawza Meaadi[1,2,3,*], Ilona Obara[1,2] and Hamde Nazar[1,4]

[1]School of Pharmacy, Newcastle University, Newcastle upon Tyne, UK
[2]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[3]King Saud Medical City, Riyadh, Kingdom of Saudi Arabia
[4]Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK

*Correspondence: Jawza Meaadi, Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle-Upon-Tyne, NE1 7RU, UK. Email: J.alotaibi2@newcastle.ac.uk

Abstract

Objectives Inappropriate prescribing, particularly for analgesia, is a recognised global problem. This leads to increased morbidity and mortality and presents a significant challenge for patients and the healthcare system. There is a need to identify strategies that best identify inappropriately prescribed analgesia (IPA). This study aims to explore the perspectives and experiences of community pharmacists (CPs) about addressing IPA.

Methods Semi-structured interviews informed by the Behaviour Change Wheel model and the Theoretical Domains Framework (TDF) were conducted with consenting community pharmacists. Transcripts were coded using a capability, opportunity, motivation model of behaviour (COM-B) model. The COM-B components were mapped to the TDF and behaviour change techniques (BCTs) were identified to address these.

Key findings A total of 12 pharmacists who work in community pharmacies in England were interviewed between March and May 2021. COM-B components were identified through analysis and mapped to nine TDF domains. Component 1 referred to 'Capability' of CPs to be involved in addressing IPA (knowledge). Component 2 pertained to 'Opportunity' to identify IPA (e.g. social influence). The 'Motivation' component linked to five TDF domains (e.g. goals). Seventeen BCTs were identified to support CPs in addressing IPA (e.g. environmental context and resources domain mapped to 2 BCTs 'restructuring the physical and social environment').

Conclusions CPs expressed mixed perceptions about their involvement in the deprescribing of IPA as part of their daily practice, but they stated that social and environmental barriers needed to be addressed to facilitate their involvement. The identified BCTs provide evidence-based strategies to help the involvement of CPs to identify IPA.

Introduction

Medications can be difficult to stop once they have been started. Healthcare professionals have a responsibility to reassess medication usage among patients with multi-morbidities to identify clinical appropriateness, effectiveness and safety.[1] Inappropriate medications can be defined as medications that are used when their risks outweigh their benefits.[2] Therefore, the inappropriate use of medications (IUM) refers to (1) the use of medication without indication (misuse), and (2) incorrect choice of medication, incorrect dose or duration.[1, 2] The IUM is associated with adverse events, mortality, hospitalisation and death.[2] A recent report from the Office for National Statistics revealed that the death rate related to drug misuse in England and Wales was 52.3 per million people.[3] However, the issue of inappropriate prescriptions can be addressed by examining the prescribing process and reviewing and optimising the patient medication regimen.

The IUM is a widespread problem among patients with chronic pain because of insufficient pain management.[4] Therefore, healthcare professionals are faced with the significant challenge of distinguishing legitimate prescriptions for analgesics from illicit prescriptions.[5] Since many analgesic abusers obtain inappropriate drugs directly from healthcare professionals in different ways: fabricating pain symptoms, forging prescriptions, and engaging in doctor and pharmacy shopping (e.g. receiving multiple prescriptions from different doctors or multiple pharmacies). Eventually, they have multiple prescriptions from multiple providers.[6] In the USA, opioid analgesics alone or in combination with other analgesics (e.g. gabapentinoids or benzodiazepine) accounted for nearly half of the drug overdose deaths and more than 75% of prescription drug-related emergency department visits in 2009 [6]. In the UK, 13% of adults had one or more opioid analgesic prescriptions dispensed from 2017 to 2018 [7]. In 2018, the death rate due to opioid misuse increased from 34.9 to 38.7 deaths per million people.[8]

The World Health Organization launched a third global patient safety challenge in March 2017, Medications without

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Harm, whose objective was to decrease severe avoidable medication-related harm by 50% over a five-year period.[9] Addressing inappropriate prescriptions can be the first step to improve the use of medications and thereby reduce harm. This can be considered a multistep process that includes assessing the therapeutic plan, agreeing on a plan between healthcare providers and patients which could include decreasing or stopping medications, and monitoring the outcomes.

Studies have reported many barriers to prescribers addressing IUM at the point of prescribing, these are varied and complex.[10–12] Pharmacists, downstream from the prescribing process, are the last defence before a patient receives a supply of medication which means they are in a potential position to address medicines-related problems such as IUM.[13] In the UK, informal community pharmacy-led interventions are employed to decrease medication misuse, including refusing to sell items, restricting the number of products sold, or moving products out of sight.[14] However, the specific role of community pharmacists (CPs) in reducing inappropriately prescribed analgesia (IPA) is currently unclear.[13]

It is essential to understand the process underlying a target behaviour to change traditional practice. Thus, it is fundamental to understand the determinants (barriers and facilitators) for the involvement of CPs in addressing IPA. It has been demonstrated that theory-based approaches to identify barriers to behaviour change and designing targeted interventions to address those barriers are more effective than non-theory-based approaches in changing behaviour.[15, 16] There is no theory-driven behaviour change strategy specific to addressing IPA, this study applied the Theoretical Domains Framework (TDF) to address this gap. The TDF works as a 'theoretical lens' through which specific determinants of the target behaviour can be recognised for targeting with a behaviour change intervention.[17, 18] The TDF has a unique advantage in that it is linked to the Behaviour Change Techniques (BCTs) taxonomy version 1 (BCTTv1).[19] This helps researchers progress from a theoretical understanding of the behaviour to develop an evidence-based intervention.[19]

Existing research has examined different ways to assess the interventions targeted to prevent inappropriate prescriptions in hospital care settings.[20] In contrast, little research is being carried out in primary care.[10] As yet, little attention has been given to CPs' views on tackling IPA. Accordingly, this study has used the TDF to understand the determinants impacting if/how the CPs identify IPA when consulting with a patient and find appropriate BCTs to include in a theoretically informed intervention to facilitate their involvement in addressing IPA.

Methods

Study design

A qualitative study using semi-structured interviews to investigate CPs' views and experiences about addressing IPA. The consolidated criteria for reporting qualitative research (COREQ) 32 checklist was used of reporting this qualitative study (Supplementary Material S1).[21]

Ethical approval

Ethical approval was obtained from the Newcastle University Faculty of Medical Sciences Ethics Committee (2116/11765).

Sampling and recruitment

Convenience sampling was used to recruit CPs who had experience of more than 1 year.[22] CPs were invited to participate via email that was sent by the Local Pharmaceutical Committee chair (as the gatekeeper) to all community pharmacies in the North East of England. Because the initial recruitment strategy did not yield many participants, possibly because of the COVID-19 pandemic, social media platforms (e.g. Twitter, LinkedIn) were used to widen the recruitment of UK-based CPs. CPs received a formal email including a participant information sheet and consent form which they signed and returned to the researcher if they agreed to take part.

Topic guide

An interview topic guide was developed based on previous studies using COM-B Model which is linked to the Behaviour Change Wheel and the TDF (Supplementary Material S2).[22, 23] By doing so, the topic guide allowed for a more thorough investigation of behavioural determinants. The interview topic guide was refined through consultation with the research team J.M., I.O. and H.N. (who have academic and experience in community pharmacy practice).

Data collection

Semi-structured interviews were conducted between March and May 2021 by J.M. Consenting participants were offered to undertake the interview at a convenient time and place (e.g. virtually, telephone, or face-to-face). The interviews were audio-recorded, transcribed verbatim, and then coded anonymously. The interviews were conducted until inductive thematic saturation was reached (no further codes were generated).[24]

Data analysis

All interviews were transcribed verbatim and then double-checked for accuracy (J.M.). Interview data were imported into QSR NVivo Version 12 Pro software to aid data analysis which went through the following three stages: (1) theoretical framework analysis approach using COM-B as the a priori framework to identify determinants of addressing IPA,[25, 26] (2) mapping the identified determinants to the TDF domains and (3) linking the identified TDF domains to appropriate BCTs.[27]

Stage 1: COM-B framework coding

Collected data were analysed using the COM-B Model.[25, 26] Transcripts were coded deductively using the COM-B components (J.M.) and reviewed by two researchers (I.O. and H.N.). Disagreements were resolved through discussion. CP quotations were extracted to be used as illustrative quotes.

Stage 2: Mapping COM-B components and subcomponents to the TDF domains

All codes from stage 1 were mapped to the TDF domains independently by two researchers (J.M. and H.N.). The mapping was compared, and any disagreement was discussed within the research team until consensus was achieved.

Stages 3: Mapping the identified TDF domains to appropriate BCTs

The researchers completed online training in BCTTv1 prior to the mapping process. Identified TDF domains were mapped onto appropriate BCTs independently by two researchers (J.M. and H.N.). This was reviewed and

discussed within the wider team until consensus was achieved.

Reflexivity

This study is a part of J.M.'s PhD thesis (pharmacist and a PhD researcher who completed training in qualitative research).

J.M. has professional experience as a pharmacist and is therefore clinically aware of the complexity of treatment for chronic pain and the issues arising when patients use analgesia long term. J.M. believes that community pharmacists have a role to play in identifying and addressing IPA due to the growing recognition and wider implementation of pharmacist-led medicines optimisation and clinical reviews.

Results

Sample

Twelve individuals came forward for interview and all provided consent to participate. The characteristics of the participants are given in Table 1. All CPs except for one worked for a large chain community pharmacy and there was a range in level of experience from 1–5 to > 10 years of experience. The mean (±SD) interview duration was 25 (±10) minutes. The interviews were coded using the COM-B framework, which includes three main components and six subcomponents. On reviewing the data relating to these components, more explanative themes were generated (Figure 1).

Stage 1: COM-B framework coding

Figure 1 shows COM-B themes and their subthemes. These highlighted the determinants of addressing IPA and illustrative quotes are given below as appropriate.

Theme 1. Capability (physical/psychological)

CP training

This capability refers to the competencies pharmacists possess that enable them to tackle IPA. The CPs believed that their training meant they were well equipped to address IPA. However, they emphasised that more resources (e.g. access to patient's information, training on reading clinical notes) were needed.

> To be honest, that's what our job is. We don't need any more training or skills (CP_7)

CP knowledge

When asking the CPs about their capability, they reported that their pharmacology/therapeutics background facilitates identifying IPA during their daily practice.

Theme 2. Opportunity (physical/social)

Access to medical records

CPs raised that the main barrier preventing them from identifying IPA was the lack of access to patients' medical records. This barrier impacts CPs' confidence in decision-making and making intervention recommendations. For instance, the lack of patient information (e.g. medication indication) meant CPs were unable to decide whether or not the analgesia was appropriate.

> I guess some of the challenges you don't have access to patient records. So, in the initial review of a prescription comes to you, you don't have any background information that would help you to decide is this appropriate? (CP_1)

Patient fears and experiences

All CPs agreed that some patients have fears about interventions relating to their pain medications. CPs further stated that they believed this attitude was influenced by the patient's personal experiences with pain. There was a belief that chronic pain patients were scared of increased pain if they changed their medications or stopped taking painkillers.

> Patients might be scared about you moving their medicines around because they rely on them for pain relief (CP_5)

GP resistance and communication

CPs described their experience that doctors were resistant to interference with patients' medications. They also expressed

Table 1 Interview participants' characteristics

ID Code	Gender	Age (years)	No. of years experience and location	Qualification(s)	Interview format	City
CP_1	Male	25–30	1–5 (Chain)	Master degree	Video-call	Cardiff
CP_2	Female	25–30	6–10 (Chain)	Master degree; Postgraduate diploma	Video-call	Newcastle
CP_3	Female	25–30	1–5 (Chain)	PhD; Master degree	Video-call	Glasgow
CP_4	Male	>45	>10 (Independent)	Bachelor degree	Video-call	Middlesbrough
CP_5	Male	41–45	>10 (Chain)	Master degree	Video-call	Sunderland
CP_6	Male	41–45	>10 (Chain)	Bachelor degree	Telephone	Kent
CP_7	Male	31–35	6–10 (Chain)	Bachelor degree; Postgraduate diploma	Face-to-face	Glasgow
CP_8	Male	36–40	>10 (Chain)	Master degree	Face-to-face	Leeds
CP_9	Male	25–30	1–5 (Chain)	Master degree	Face-to-face	Newcastle
CP_10	Female	31–35	6–10 (Chain)	Master degree	Face-to-face	Newcastle
CP_11	Male	41–45	>10 (Chain)	Master degree	Face-to-face	Newcastle
CP_12	Male	>45	>10 (Chain)	Bachelor degree	Face-to-face	Newcastle

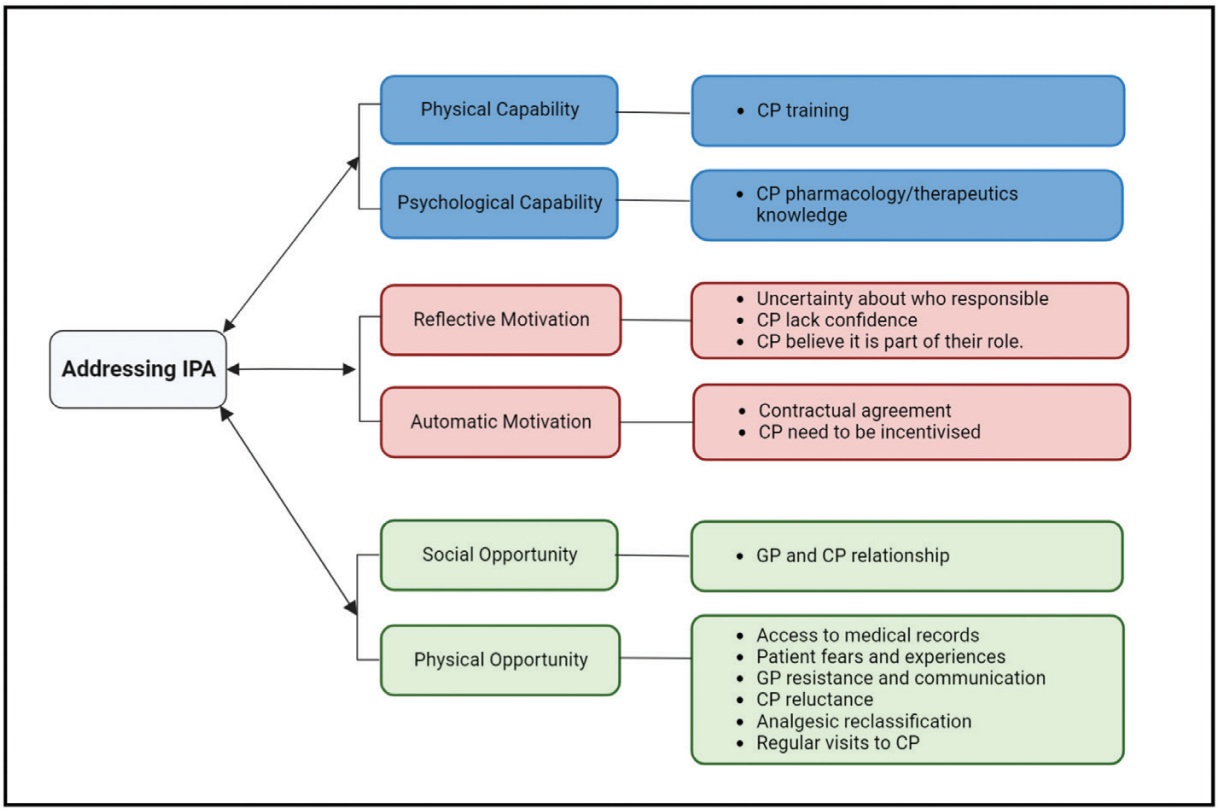

Figure 1. COM-B themes and subthemes identified from the interviews with community pharmacists. Created with BioRender.com.

concern regarding the GP refusal to speak with them about the IPA.

> The challenge is that the GP are not receptive. They respond quite defensively in quite negatively (CP2)

Another challenge was the several possible modes of communication to reach GP, such as telephone or NHS email. CPs assured that the lack of a straightforward method to contact the prescriber is also a barrier to tackling IPA.

> What's best with the GP isn't a phone call or email by NHS mail? understanding the way of working out the GP and with the background of how urgent this is to resolve for the patient? (CP_6)

CP reluctance

CPs are not involved in the communications between the doctor and patient about the rationale for using these medications. Due to this isolation, CPs were reluctant to take on the task of changing a patient's pain medication. Also, they emphasised the conflicting priorities facing them within their practice: business responsibilities and championing the interests of patients. Most CPs linked patients' best interests to activities associated with delivering patient care through checking the safety of medications before dispensing them, while the business responsibilities of CPs were connected to revenue generation.

> I think the biggest barrier it is a liability; I don't want to be liable for stuff in someone's pain medicines or changing them (CP_2)

> There's always been the sort of contradiction between the business and the sort of patient's best interest, especially when it comes to deprescribing that there's actually a disincentive to deprescribing community pharmacy because you'd get less payment prescriptions (CP_1)

Difficulty to find who prescribed IPA

Some reported that it has been difficult to identify which doctor prescribed an inappropriate medication. They struggled to contact the right person to discuss the appropriateness, especially with the limited access to patient information.

> …so I think finding the person who initiated the prescription is going to be really difficult (CP_3)

Analgesic reclassification

One participant stressed that reclassifying some analgesic drugs (e.g. gabapentinoids) as schedule 3 controlled drugs under the Misuse of Drugs Regulations (2001) and Class C of the Misuse of Drugs Act (1971), helped decrease the number of inappropriate prescriptions. There was a suggestion to add the identification of IPA as a mandatory role in community pharmacy and that it should be included in pharmacist's job description.

> I definitely have seen a decrease in prescription since gabapentin and pregabalin have reclassified (CP_10)

GP and CP relationship

A good relationship between GPs and CPs was considered vital to facilitate the identification and tackling of IPA. CPs expressed that having good relationships helped with

timely communication. Thus, CPs stressed the importance of investing time in building relationships with doctors.

> It's it can be difficult, a lot of it in terms of how you work with GP will be about relationships (CP_6)

Regular visits to CP

CPs agreed that a patient's regular visit to the community pharmacy was a factor that aided in addressing whether the analgesic prescriptions were appropriate. Based on their experiences, CPs believed understanding the full picture of a patient's case (e.g. diagnosis or indication) can be gained through regular patient contact in the community pharmacy.

> We'll ask why you are taking the medication? we can understand if there is any inappropriateness (CP_8)

Theme 3. Motivation (reflective/automatic)

Remuneration

CPs stated that financial incentives and reimbursements should be offered to CPs for greater involvement in addressing IPA. Additionally, they suggested that improving the collaboration between GPs and CPs through providing direct lines of communication would promote motivation.

> We need payment for patient medicines review and it would need to be appropriately reimbursed, if you really want this to happen, you'd have to establish collaboration between all healthcare providers to encourage pharmacists to tackle it (CP_4)

CP believed it is part of their role

Some CPs believed that it is part of their role as a pharmacist. They described CPs as a safety net and the last defence before the wrong medication reaches the patient.

> Part of your role is the safety net, if you see something that's unsafe, you know that to calling it a challenge appropriately and if necessary, stop it (CP_6)

Stage 2: Mapping COM-B components and subcomponents to the TDF domains

Themes and subthemes were mapped to multiple TDF domains. The theme of capability was linked to two different domains; the opportunity theme was mapped to two domains, and the motivation was linked to five TDF domains (Table 2).

Stages 3: Mapping the identified TDF domains to appropriate BCTs

The research team adopted the method previously described to map appropriate BCTs to the TDF.[28, 29] Seventeen BCTs were identified that could be considered in the design of future interventions to facilitate the CPs' role in identifying IPA (Table 2).

Discussion

This is the first qualitative study using a theoretical framework to investigate CPs' perceptions about the barriers and facilitators that influence the identification of IPA behaviour. This study showed that nine TDF domains represented barriers to addressing IPA. Most of the barriers mapped to the

Table 2 Deductive themes and subthemes mapped to the TDF domains and BCTs

COM-B		Subtheme	TDF domain	Selected BCT
Capability	Physical	CP training	Skills	8.1 Behavioural practice/rehearsal 8.3 Habit formation
	Psychological	CP pharmacology/therapeutics knowledge	knowledge	5.1 Information about health consequences
Opportunity	Physical	Limited access to medical records Cooperation between healthcare professionals Analgesic reclassification Conversation with patient Regular visiting to CP	Environmental context and resources	12.1 Restructuring the physical environment 12.2 Restructuring the social environment
		Communication ways with GP Analgesia is not well-documented		12.1 Restructuring the physical environment
		Contradiction between the business and clinical responsibilities		12.1 Restructuring the physical environment 12.5 Adding objects to the environment
	Social	Patient fears and experiences	Social influences	3.1 Social support (unspecified)
		Relationships with GPs GP resistance Difficulty to find who prescribed IPA		12.2 Restructuring the social environment
Motivation	Reflective	CPs believed IPA is a part of their role as CP Confusion about who is responsible for addressing IPA	Social/professional role and identity	13.3 Incompatible beliefs
		Lack of confidence to make a decision	Beliefs about capabilities	15.1 Verbal persuasion about capability
		Fears of taking responsibility to interfere with prescribed pain medications	Beliefs about Consequences	5.6 Information about emotional consequences 9.3 Comparative imagining of future outcomes
		Professional isolation	Goals	1.2 problem solving
	Automatic	Contractual agreement to stop IPA as CP role. Remuneration	Reinforcement	10.1 Material incentive (behaviour) 10.2 Material reward (behaviour) 10.10 Reward (outcome)

'Environmental context and resources' and 'Social influences' domains. Most of the BCTs which were identified as potential intervention ingredients were related to the 'Environmental context and resources' and 'Social influences' domains, suggesting that this area is appropriate for developing an intervention (BCTs 'restructuring the (physical/social) environment' and 'social support') (Table 2).

A key strength of this study is its use of a systematic approach to conducting the research and analysing the interview data. The researchers used the COM-B and TDF frameworks to develop the interview guide to understand the target behaviour and identify the determinants which have been applied successfully in previous studies.[30–32] Two studies used theory to report the analysis of CPs' perspectives; themes were developed deductively using the TDF domains. However, those studies did not link the findings of those domains to potential interventions (BCTs) to change the clinical practice in community pharmacies.[33, 34]

This study does also include some limitations. First, this study identified determinants from the perspective of CPs only. Accordingly, knowing other stakeholders' views is essential for a deep understanding of the factors influencing any changes in behaviour for the involvement of CPs. Moreover, this study was mainly limited to CPs from chain pharmacies in the North East England and recruiting pharmacists from a wider geographical area and from different types of pharmacies (i.e. independent pharmacy) is needed. Finally, we acknowledged that a convenience sampling approach does have certain limitations; this sampling technique was chosen because of the COVID-19 impact.

The study findings have identified that a broad range of determinants impact the CPs' experience and perceptions of tackling IPA. Some of these barriers have been identified by the limited evidence currently available, such as CPs lacking access to patient information to make a decision about the appropriateness of the medications, a contradiction between the business and clinical responsibilities, isolated setting (TDF domain 'Environmental Context and Resources'), GPs resisting interference with patients' treatment, and patients being afraid to change their pain medications ('Social influences').[33, 35] This consensus suggests that an intervention targeting 'Environmental Context and Resources' and 'Social influences' would be pragmatic to involve CPs in addressing IPA. For example, there is a need to provide access to patients' information through a centralised system between CPs and GPs. In relation to the 'Social influences' domain, an intervention should facilitate a collaborative relationship to be established between the three main actors; CPs, GPs, and patients. It has been indicated that shared platforms for patient information are needed to increase communication between pharmacists and doctors and improve mutual professional trust between them.[36]

The facilitators to identify IPA including talking to patients, and regular visits to the pharmacy ('Environmental Context and Resources') align with previous study findings.[33] Additionally, CPs described that a notable decrease in the number of inappropriate prescriptions of analgesia since the reclassification of some painkillers (e.g. pregabalin). In 2021, Kurdi compared opioid and gabapentinoid trends and found that there was a significant increase in gabapentinoids prescribed as a safer replacement for opioids after the reclassification of tramadol in 2014 from a Schedule 4 to Schedule 3 drug.[37] Consequently, risks associated with gabapentinoid misuse increased; thereby, gabapentinoids were reclassified as class C in 2019. It is evident that reclassification can be a double-edged sword, and regular evaluation of clinical practice is necessary to prevent the diversion of the use of analgesia as a substitute for one another.

The capability theme identified some facilitators to tackle IPA, such as CPs' pharmacology/therapeutics knowledge ('knowledge') and training ('Skill'). These results seem to be consistent with other research conducted in Ireland,[34] but are contrary to that of Alenezi *et al.* who found that inadequate training on pain management was a perceived barrier to CPs' involvement.[33]

Policy, practice and research implications

In order for CPs to be more involved in addressing IPA, we suggest that there has to be a shift in the model of reimbursement that focuses on payment for individual patient needs rather than incentives for dispensing a high quantity of items. We also believe patient information must also be shared to make collaboration easier between healthcare professionals.

We anticipate that these findings are informative internationally as we have highlighted some key barriers and facilitators to the involvement of CPs in identifying and addressing IPAs. Policy makers and practitioners can consider their respective contexts to assess the relevance and appropriateness of these towards improving practice (e.g. in a context where there are already shared records between CP, GP and the patient, policy makers can assess if/how this is improving practice in this area).

Developing a behaviour change intervention to facilitate the involvement of CPs in identifying IPA is a key area for future research. Intervention development should be co-designed with patients and the healthcare professionals who will be affected by the intervention. Therefore, future work should investigate wider healthcare professionals' and patients' views about determinants for tackling IPA. The results of such studies would be valuable for future interventions or guidelines/policies for involving CPs in reducing IPA.

Conclusion

CPs expressed mixed perceptions and experiences about being involved in identifying and addressing IPA as part of their daily practice, but they stated that social and environmental barriers need to be addressed to enable them to do so effectively. The study showed that providing shared platforms of patient information can promote the role of CPs in dealing with IPA since this allows them to access patients' clinical records (BCT 12.1. Restructuring the physical environment). Previous experiences with the GPs can negatively influence CPs' expectations and may deter their involvement in identifying and tackling the inappropriate prescriptions; therefore, improvements in collaborative working between CPs and GPs are needed (BCT 12.2. Restructuring the social environment). The present study findings indicate that there is a need to change the current funding model in which payment is based on quantity rather than quality for greater involvement of CPs in tackling IPA.

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Conflicts of interest

The author(s) declare that there are no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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know. But as I said that just the history of the patient is not complete in the pharmacy.

Access medical record

CP_11: The first thing we should do is not dispense this medication to the patient's stop it for a while, phone the GP practice. Maybe ask to speak to the doctor.

Stop dispensing
Contact prescriber

Encourage patient to go to GP

CP_12: To get quite busy? It's very hard to find your time and then there's no system is that should be that a system linked to the GP that they should I think they you should have like you should follow that guideline for analgesia, and then obviously review it and see, you know what I'm trying to know but then you need to know how long patients on the what they taking for ,you know at what time should be reduced? If you can do to talk to your patients

Time constraint
Access medical file

CP_10: for analgesia? particularly. Probably not that common. And I definitely have seen a decrease in prescription since gabapentin and pregabalin have reclassified. So that's probably a good thing. So I'm

Benefit of reclassification

CP_2: Well, again, just sort of safeguarding and double checking clinically, prescriptions appropriate? And so we always whenever we do clinical check, it's always checking the dose is appropriate, the items appropriate against the age of the patient duration of treatment, you know what it's

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